Case 1: Polymorphous Low-Grade Adenocarcinoma of Minor Salivary Gland Origin

Polymorphous low-grade adenocarcinoma (PLGA) of minor salivary gland origin is a malignant epithelial neoplasm arising from the minor salivary glands, characterized by a varied architecture (polymorphous), bland cytomorphology, infiltrative growth and indolent biologic behavior. Synonyms include lobular carcinoma and terminal duct carcinoma. Lobular carcinoma was used because PLGA demonstrated areas of an infiltrative “Indian-file” growth pattern identical to that of the lobular carcinoma of the breast. Terminal duct carcinoma was used to emphasize the proposed histogenesis of the tumor, thought to be the progenitor cell of the distal or terminal duct portions of the salivary gland unit, that is, the intercalated duct reserve cell.

Clinical

PLGA is considered an uncommon type of salivary gland malignant tumor but is becoming more widely recognized. PLGA affects women more than men; occurs over a wide age range but is most frequently seen in the 7th decade of life. PLGA is predominantly a tumor of minor salivary glands and is almost exclusively identified in the oral cavity where the palate represents the most frequent site of occurrence. In descending order of frequency the other intraoral sites include: buccal mucosa > lip > retromolar pad > cheek > tongue > maxillary area > mandibular mucosal area > posterior trigone region. Involvement of non-oral minor salivary gland sites is rare and includes the nasal cavity and nasopharynx. Until recently, PLGA had not been identified in major salivary glands except as the malignant epithelial component in a carcinoma ex pleomorphic adenoma. However, over the last few years there are reports identifying PLGA in major salivary glands. The most common symptom is a painless mass or swelling occasionally associated with bleeding, increase in size or discomfort. Other less frequently identified symptoms include otalgia, odynophagia, tinnitus and airway obstruction. The duration of symptoms is quite variable ranging from as short as 2 weeks to a 20 to 30 year history of a mass lesion. There may be a predilection for PLGA to occur in blacks. There are no known predisposing factors associated with this neoplasm.

Pathology

The tumors are polypoid or raised, round to oval, mucosal-covered masses ranging in size from 1.0 to 6.0 cm in greatest dimension. In general, the mucosa remains intact; however, scattered surface ulceration may occur.

The histologic appearance is that of a well-circumscribed but unencapsulated tumor characterized by morphologic diversity, cytologic uniformity and infiltrative growth. The polymorphic nature of these lesions refers to the variety of growth patterns that include solid, trabecular, glandular, ductular, and tubular; cribriform and cystic patterns can be seen but generally do not predominate. These patterns may be identified within the same lesion and...
from lesion to lesion. The presence of small tubular structures with a distinct central lumen lined by a single layer of cuboidal cells is a characteristic feature. A pattern of cell growth in which the cells are arranged in a single row termed "Indian-file" can be seen and is often located at the periphery of the tumor. A focal papillary pattern can be identified. There has been some controversy in the literature relative to the presence and importance of a prominent papillary component. Some authorities feel that PLGA does not demonstrate a predominant papillary growth and would consider tumors with prominent papillary growth as papillary cystadenocarcinomas. This is also based on the differences in biologic behavior with papillary cystadenocarcinomas associated with local recurrence, regional cervical lymph node metastases, distant (visceral) metastases, and mortality, all findings that are unusual for PLGA. However, other authorities believe in a papillary and non-papillary variants of PLGA with the papillary variant associated with a more aggressive biologic behavior than the non-papillary counterpart. Recently, Evans and Luna reported 40 cases of PLGA and evaluated for the importance of tumors with prominent papillary areas. These authors found that those PLGA with “papillary areas of more than focal extent” (17 cases) showed a statistically significant relationship with regional lymph node metastasis and between positive or unknown surgical margins and local recurrence. However, there was no statistical significance with patient survival. As such, focal or more extensive papillary growth occurs in PLGA but those tumors with a predominate or exclusive papillary pattern and do not show other characteristics of PLGA, are best classified as papillary cystadenocarcinomas or another carcinoma depending on the overall features.

PLGA is composed of cuboidal to columnar isomorphic cells with indistinct cell borders, which have uniform ovoid to spindle-shaped nuclei and small and inconspicuous nucleoli. The nuclear chromatin pattern varies from vesicular to stippled but basophilic nuclei can also be identified. Scant to moderate amounts of eosinophilic to amphophilic cytoplasm can be seen, and occasionally clear cytoplasmic changes predominate. The tumor stroma varies from mucoid to hyaline to mucoid, and in some cases tumor nests are separated by a fibrovascular stroma. Neurotropism (peri- and intraneural) is found in the majority of tumors; perivascular invasion can also be seen with tumor nests often arranged in concentric fashion around these structures. In addition, the tumor may infiltrate the surface epithelium, residual minor salivary glands and/or connective tissue components (bone, cartilage, muscle, and adipose tissue). Mitotic figures are rare and necrosis is not seen. Other histologic changes that may be identified include: intratubular calcifications (psammoma-like bodies), pseudoeppitheliomatous hyperplasia of the surface epithelium and squamous metaplasia within the tumor. Squamous metaplasia can be identified following fine-needle aspiration biopsy.

Intraluminal mucin can be identified by diastase-resistant, PAS-positive material; however, only focal intracytoplasmic mucin is seen. The immunohistochemical reactive pattern for PLGA includes immunoreactivity with antibodies to cytokeratin, vimentin, muscle specific action, epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) and glial fibrillary acidic protein (GFAP). Electron microscopic findings include the presence of glandular differentiation, junctional complexes (desmosomes, tight junctions), lumina, and microvilli.

Vargas et al reported that the staining patterns with Ki-67 (MIB1), S-100 protein and BCL2 may be useful in differentiating PLGA from mixed tumor and adenoid cystic carcinoma.

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These authors found that: 1) PLGA: low Ki-67, p53 and BCL2 immunostaining but strong S-100 protein reactivity; 2) mixed tumors: low Ki-67, p53 and BCL2 immunostaining but strong S-100 protein reactivity; 3) adenoid cystic carcinomas: high Ki-67 and more intense BCL2 reactivity, the percentage of p53 staining increased with increasing histograde and less intense and less frequent S-100 protein staining as compared with PLGA and mixed tumor.

Some authors advocate that PLGA represents the low-grade or less aggressive variant of adenoid cystic carcinoma based on the morphologic similarities as well as common derivation from the intercalated duct region. However, cytologic, immunohistochemical, and biologic differences do not support this contention. Recently, high-grade transformation of PLGA characterized by a predominantly solid growth pattern, nuclear atypia with prominent nucleoli and foci of necrosis has been reported with the recommendation PLGA with these histologic features not be included under the designation of “typical PLGA”.

Treatment and Prognosis

Conservative but complete surgical excision is the treatment of choice. Depending on whether there is involvement of bone (e.g., maxilla or mandible), as may occur in palatal or retromolar tumors, en bloc resection of the involved bone may or may not be necessary. Neck dissections are unwarranted unless there is clinical evidence of cervical lymph node metastasis. Post-operative radiotherapy and chemotherapy have been used, but there is no evidence to substantiate any benefit of these modalities in conjunction with surgery. PLGA is a slow-growing, indolent malignant neoplasm that has a good prognosis following complete surgical excision. PLGA may recurrence from months to years after the diagnosis. The rate of tumor recurrence is quite variable and probably correlates with the ability to completely excise the tumor. Metastasis to regional cervical lymph nodes may occur (< 10% of patients) but distant metastasis has not been reported. Death attributable to PLGA is extremely rare but has been reported.

Differential Diagnosis includes mixed tumor (pleomorphic adenoma), monomorphic adenomas and adenoid cystic carcinoma.

Mixed Tumor (MT) or Pleomorphic Adenoma (PA) is a benign epithelial-derived tumor composed of cells demonstrating epithelial differentiation (ductal structures with associated nonductal elements) and mesenchymal differentiation (myxoid, hyaline, chondroid, and osseous areas).

Clinical

MT represents the most common neoplasm of salivary glands accounting from 40-70% of all neoplasms of the parotid, submandibular glands and minor salivary glands. MT of the sublingual glands is rare. MT affect women more than men and occurs over a wide age range but is most commonly seen in the 3rd-6th decades of life. MT is the most common salivary gland tumor in children and adolescents. The most common site of occurrence is the tail of the parotid gland but it may also occur in the deep lobe of the parotid, in the submandibular and sublingual glands, and in all minor salivary glands throughout the upper and lower respiratory tract. Involvement of minor salivary glands occurs most frequently on the palate (hard and soft) but other common sites include the upper lip and buccal mucosa. The most common site of PA in the upper respiratory tract is by far the nasal cavity.
Symptoms vary according to site but most commonly presents as a slow-growing, painless mass present for periods up to several years. Other symptoms, in particular those occurring in the minor salivary glands, may include difficulties in chewing, dysphagia, dyspnea, hoarseness and epistaxis. In the parotid, the tumor typically occurs outside of the facial nerve and facial nerve involvement typified by facial nerve paralysis is rare and, if present, should be suspicious for a malignant process. MT appears to be entirely of epithelial origin with the mesenchymal areas composed predominantly of cells that represent modified myoepithelial cells. There are no known etiologic factors.

**Pathology**

The gross appearance is that of a firm, freely-movable, unifocal mass which is encapsulated or well-demarcated, tan-white and solid in appearance and may demonstrate cystic change. Ulceration of the overlying skin does not occur. The tumors vary in size from a few centimeters up to large, disfiguring masses. Minor salivary gland tumors are polyoid or lobulated, encapsulated or well-delineated, tan-white usually measuring 1-2 cm but capable of attaining sizes of 7 cm or more. Recurrent tumors tend to be multinodular.

PA in major salivary glands are encapsulated tumors but the fibrous capsule varies in thickness and may be quite thin or even absent. Prominently myxoid tumors often have incomplete capsules and there may be juxtaposition of the tumor to the adjacent normal salivary gland. PA of minor salivary gland is generally not encapsulated but is well-demarcated. The histologic appearance includes an admixture of epithelial, myoepithelial and stromal components. Morphologic variability can be seen within a single neoplasm. The epithelial component may have a variety of growth patterns, including solid, cystic, trabecular or papillary consisting of a proliferation of duct-lining epithelial cells and myoepithelial cells. The duct-lining epithelial cells form the inner layer of acini or tubules and appear flattened, cuboidal or columnar with round to oval nuclei and a variable amount of cytoplasm appearing eosinophilic to amphophilic. The myoepithelial component forms the outer layer and is spindle-shaped in appearance with hyperchromatic nuclei and may be more than one cell layer thick. The stromal component, the product of myoepithelial cells, varies in appearance from myxoid to chondroid to myxochondroid and may also appear fibrous and vascular. Any one or all of these components may coexist in the same neoplasm. In a given tumor, any of the components may predominate so that tumors may be diagnosed as epithelial-, myoepithelial- or stromal-predominant pleomorphic adenoma. However, all components must be identified in order to diagnose a pleomorphic adenoma. Extracellular crystalloids may be identified, particularly in the nonepithelial areas. Crystalloids are more often present in MT than in any other salivary gland tumor. Other findings may include the presence of keratinization, squamous cells, mucous cells, clear cells, spindle cells, plasmacytoid cells, and sebaceous cells. Mixed tumors of the nasal cavity (particularly the septum) tend to have an increased plasmacytoid-appearing myoepithelial component. Additional features may include oncocytic metaplasia, calcification and fat.

The immunohistochemistry staining pattern seen in MT includes cytokeratin, S-100 protein, smooth muscle action (SMA), vimentin (variable), glial fibrillary acidic protein (variable) and carcinoembryonic antigen (variable).
Treatment and Prognosis

Complete surgical excision is the treatment of choice and should include an adequate margin of uninvolved tissue. Parotid gland tumors usually require lobectomy with preservation of the facial nerve. Submandibular gland tumors usually necessitate complete removal. MT of minor salivary glands require complete but conservative excision. Incomplete excision results in recurrent tumor. For recurrent parotid gland MT, the treatment includes total parotidectomy. Minor salivary gland MT are less likely to recur. The overall prognosis for MT is excellent with 5- and 10-year recurrence free rates are 97 and 94%, respectively. Complications include malignant transformation (carcinoma ex pleomorphic adenoma) and the rare occurrence of so-called "benign" metastasizing mixed tumor. Surgical complications may include nerve damage and Frey’s syndrome (gustatory sweating).

Monomorphic Adenoma

Benign tumor of salivary glands encompassing a whole group of neoplasms that are not pleomorphic adenomas. These neoplasms are characterized by a lack of the mesenchymal-like stromal component seen in pleomorphic adenomas and are composed exclusively of the epithelial component or rarely, the myoepithelial component, arranged in a variety of morphologic patterns. The World Health Organization classification of monomorphic adenomas include: 1) Warthin's tumor or papillary cystadenoma lymphomatosum, 2) oxyphilic adenoma or oncocytoma, 3) all others which include basal cell adenoma, canalicular adenoma, myoepithelioma, clear cell adenoma. It is the latter category of monomorphic adenomas, particularly the basal cell adenoma and canalicular adenoma that may present diagnostic difficulties with PLGA.

Basal Cell Adenoma (BCA): Synonyms include Membranous Adenoma; Dermal Analogue Tumor.

Clinical

BCA represent from 1.8 to 7.5% of benign salivary gland tumors. BCA are slightly more common in women than in men occurring over a wide age range but is most commonly seen in the 5th-7th decades of life. BCAs most commonly involve the parotid gland (>70% of cases) but also occurs in other major salivary glands and in minor salivary glands (upper lip). The usual presentation is that of a slow-growing, painless, freely mobile mass often involving the superficial portion of the parotid gland. May be associated with skin tumors (turban tumors) suggesting a possible genetic predisposition.

Pathology

BCA tend to be round to oval tumors usually measuring < 3 cm in greatest dimension (range 1 – 8cm). BCA may consist of multiple nodules especially when associated with cutaneous tumors. Cut section generally demonstrates a homogenous, solid appearance but a cystic component can be seen.

Like their pleomorphic counterparts, basal cell adenomas tend to be encapsulated or well-delineated and mononodular. The growth is usually expansile with compression and atrophy of the surrounding salivary gland tissue. However, these tumors may be unencapsulated, multifocal or may demonstrate extension of the tumor beyond the capsule (in particular, the membranous subtype).
Four histologic patterns based on the growth characteristics can be seen: 1. **solid** (most common), 2. **trabecular**, 3. **tubular**, and 4. **membranous**. In any given tumor one of these patterns may exclusively be seen or multiple patterns may occur. Irrespective of the growth pattern, basal cell adenomas are characterized by the presence of basaloïd cells. The basaloïd cells have two morphologic forms that are intermixed and include a small cell with a hyperchromatic round nucleus and scant cytoplasm; the other is a larger cell with an ovoid vesicular nucleus and amphophilic to eosinophilic cytoplasm. The usually pattern is that the larger cells predominate with the smaller cells identified at the periphery of the neoplastic tumor nests. Cellular pleomorphism, increased mitotic activity and invasive growth (neurotropism or vascular space invasion) are not seen. Characteristically, there is palisading of the peripherally positioned cells as well as sharp demarcation between the neoplastic cells and the surrounding connective tissue. Additional findings that may be seen include the presence of mature squamous eddies associated with prominent keratinization, and the presence of ductlike structures.

**Treatment and Prognosis**

Surgery is the treatment of choice and is generally curative. Recurrences rarely occur. The membranous basal cell adenomas are the type that are most commonly associated with recurrence. Malignant transformation of a basal cell adenoma is rare. These so-called hybrid tumors consist of basal cell adenoma and adenoid cystic carcinoma.

**Differential Diagnosis**

BCA needs to be differentiated from its malignant counterpart the **Basal Cell Adenocarcinoma (BCAd)**, which is a tumor with cytologic characteristics of a basal cell adenoma but morphologic growth patterns indicative of malignancy. BCAd represents approximately 1-4.5% of all malignant salivary gland tumors. The vast majority of BCAd occur in patients older than 50 years of age. The vast majority of BCAd involve the parotid gland (90%); submandibular gland involvement also occurs. Swelling is the principal symptom occasionally associated with pain or tenderness; typically, the enlargement occurs over one year but occasionally the salivary gland enlargement may be rapid in onset. The latter has no prognostic importance. May be associated with skin tumors (turban tumors) suggesting a possible genetic predisposition.

The general morphologic features are similar to basal cell adenoma but cytologic indices of malignancy include pleomorphism, increased mitotic figures and necrosis. However, these features may be minimal or absent. The key histologic feature in differentiating a basal cell adenoma from a basal cell adenocarcinoma is the presence of invasive growth into the adjacent salivary gland or into connective tissue (nerves, muscle, adipose tissue, lymph-vascular spaces).

Surgical excision with a wide surgical margin to ensure complete excision, including partial or total parotidectomy for parotid disease and complete submandibular gland: complete resection. Prognosis is considered good. Local recurrence may occur. Metastatic disease is uncommon but may occur to regional lymph nodes or to the lung.
Canalicular Adenoma (CA)

Clinical
CA is less common than basal cell adenoma. CAs are more common in women than in men occurring over a wide age range but with a peak incidence in the 7th decade of life. The most common site of occurrence of CA is the upper lip (>70% of cases). Other minor salivary gland sites can be affected (buccal mucosa, in particular); major salivary gland involvement is rare. The clinical presentation includes a slow-growing, painless mass. These tumors are usually nonulcerated, are freely mobile, and may impart a bluish hue to the overlying mucosa.

Pathology
CAs may be discrete and encapsulated nodules or may be circumscribed and unencapsulated. CAs have a tendency for multinodular and multifocal growth. The nodules range in size from 0.4 to 2cm in greatest dimension.

The histology of canalicular adenomas are fairly characteristic and include the presence of uniform cuboidal to columnar appearing cells with basophilic ovoid to elongated nuclei and a varying amount of eosinophilic cytoplasm. The neoplastic infiltrate generally grows in columns, cords or in a single layer; in areas, single rows of cells are arranged in parallel lines forming long "canal" with central lumens. Cellular pleomorphism, increased mitotic activity and invasive growth are not seen. The neoplastic cells show the presence of PAS-positive, diastase-sensitive granularity indicative of glycogen; large cystic spaces may be present containing papillary projections into the lumens. In these foci, psammomatoid bodies may be seen. The neoplastic epithelial cells are well-demarcated from the fibrous connective tissue stroma; the stroma is characterized by prominent vascularity and absent cellularity or fibrillarity. In those cases with a multinodular growth, the larger nodules are usually encapsulated while the smaller nodules are often unencapsulated.

Differential Diagnosis
The differential diagnosis includes cutaneous basal cell carcinoma, benign mixed tumor, adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and ameloblastoma.

Treatment and Prognosis
Surgery is curative. Recurrences rarely occur.

Adenoid Cystic Carcinoma (ACC)
ACC is a malignant epithelial salivary gland neoplasm characterized by its histologic appearance, tendency to invade nerves and its protracted but nonetheless relentless clinical course. With the recognition of new types of salivary gland tumors, including such tumors as polymorphous low-grade adenocarcinoma, a histologic simulator of adenoid cystic carcinoma, the incidence of ACC has been affected.
Clinical
ACC is felt to represent approximately 7.5 percent of all salivary gland epithelial malignancies and 4 percent of all salivary gland neoplasms. In major salivary glands, ACC primarily involve the parotid and submandibular glands. Fifty-five percent of ACC occur in these sites. ACC is the most frequently encountered malignant neoplasm of the submandibular gland. Minor salivary gland involvement may occur throughout the upper respiratory tract where it most frequently involves the palate; other intraoral sites of involvement include the tongue, lower lip, retromolar-tonsillar pillar region and the sublingual gland. ACC may also occur in ceruminal glands of the external auditory canal as well as representing 50 percent of all lacrimal gland neoplasms.

Pathology
ACCs are usually firm and tan white. Small tumors may be circumscribed but encapsulation is rare. Circumscribed tumors may be deceptive because infiltration beyond the tumor margin is often present tumor but difficult to appreciate by gross examination.

The histologic appearance of ACC is that of an unencapsulated, infiltrating neoplasm with varied growth patterns consisting of cribriform, tubular/ductular, and solid. Individual neoplasms may have a single growth but characteristically are composed of multiple patterns any one of which may predominate. The most common pattern is the cribriform type, considered the "classic" pattern demonstrating arrangement of cells in a "Swiss cheese" configuration with many oval or circular spaces. These spaces contain basophilic mucinous substance or hyalinized eosinophilic material. The tubular type has cells arranged in ducts or tubules. The ducts or tubules contain faintly eosinophilic mucinous material. Cribriform and tubular patterns often occur together. The least common pattern is the solid type, composed of neoplastic cells arranged in sheets or nests of varying size and shape. There is little tendency to form cystic spaces, tubules or ducts.

Irrespective of the growth pattern, the neoplastic components are the same consisting of fairly uniform sized cells with small, hyperchromatic round to oval to angulated nuclei, scant amphophilic to clear cytoplasm and indistinct cell borders. The nuclear to cytoplasmic ratio is about 1 to 1. The majority of the neoplastic cells are abluminal type cells of myoepithelial differentiation. The cystic spaces seen in the cribriform or classic type are pseudocysts, which are extracellular and lined by replicated basement membrane. Scattered among these abluminal cells are ductal cells, which surround small true lumens (glands). True duct like lumens are an infrequent feature of ACC but are most frequently seen in the ACC with a tubular growth. In the solid pattern, the cell population is dominated by the basaloid myoepithelial cells. The interstitial stroma, from which the epithelial component is sharply demarcated, varies in appearance from myxoid to hyalinized. Cellular and nuclear pleomorphism, necrosis and mitotic activity are limited in the cribriform and tubular patterns. However, these features are more frequently seen in the solid pattern. Common to all histologic variants is the proclivity for nerve invasion (neurotropism), including peri- and intraneural invasion, as well as invasion of adjacent issue structures can also be seen. Squamous differentiation is a decidedly uncommon feature in ACC.

The histochemical features of ACC include the presence of diastase-resistant, PAS-positive and mucicarmine positive material within the pseudocysts. Alcian blue staining is also present within the pseudocysts. Immunohistochemistry of ACC vary depending the
cellular component with the myoepithelial cells showing cytokeratin, vimentin, S-100 protein, actin (muscle specific) positivity with variable and glial fibrillary acidic protein reactivity. The ductal cells showing cytokeratin, epithelial membrane antigen (EMA) and carcinoembryonic antigen (CEA) positivity. Ultrastructural studies show the presence of cells with bidirectional differentiation, including the luminal or ductal cells, and the abluminal or myoepithelial/basal cells.

**Treatment and Prognosis**

The treatment of choice for ACC is wide local surgical excision and postoperative radiotherapy. Problems confronting the surgical removal of ACC relate to the infiltrative nature of these neoplasms with tendency to extend along nerve segments further compounded by their deceptively circumscribed macroscopic appearance. Recurrence rates are high and directly relate to inadequate surgical excision. Adenoid cystic carcinomas are radiosensitive and radiotherapy is particularly useful in controlling microscopic disease after initial surgery, in treating locally recurrent disease or as palliation management in unresectable tumors. Radiotherapy is not curative. The short term prognosis is generally good corresponding to the slow-growth leading to prolonged survivals, the long term prognosis is poor. These facts are reflected in the 5 year and 20 year survival rates of adenoid cystic carcinomas of all head and neck sites of 75 percent and 13 percent, respectively. The solid type of ACC, is felt by most authorities to have the most aggressive clinical course with early metastasis and poor 5-year survival rates. Both Szanto et al and Greiner et al found worse cumulative survival rates in patients who had ACC with greater than 30 percent solid growth. Spiro and Huvos reported that clinical staging plays a more decisive role than histologic grading in predicting prognosis in ACC. These authors report a cumulative 10-year survival of 75 percent, 43 percent and 15 percent for patients with Stage I, II, and III and IV, respectively.

**References**

**Polymorphous Low-grade Adenocarcinoma**


**Mixed Tumor or Pleomorphic Adenoma**


**Basal Cell Adenoma, Basal Cell Adenocarcinoma**


**Canalicular Adenoma**


Adenoid Cystic Carcinoma


Case 2: Sinonasal Undifferentiated Carcinoma
The most commonly encountered malignant neoplasms of the sinonasal tract are the keratinizing and nonkeratinizing types of squamous cell carcinoma. However, this complex anatomic region may represent the site of aggressive non-epithelial malignant neoplasms of varying histogenesis, which are grouped under the term "small round blue cell tumor." Frequently, these undifferentiated tumors share clinical and light microscopic features, which make differentiation one from the other virtually impossible without the use of adjunct analyses (immunohistochemistry, electron microscopy or molecular biologic studies). These tumors are aggressive and often fatal despite all attempts at controlling disease. Nevertheless, differentiating these tumors has clinical import as advances in therapeutic intervention may increase survival with good quality of life and in some instances may achieve a cure.

The group of sinonasal "small round blue cell tumors" may include squamous cell carcinoma, sinonasal undifferentiated carcinoma, small cell undifferentiated (neuroendocrine) carcinoma, mucosal malignant melanoma, rhabdomyosarcoma, hematolymphoid malignancies, and other malignant neoplasms.

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Sinonasal Undifferentiated Carcinoma

Sinonasal undifferentiated carcinomas (SNUC) is a high-grade malignant epithelial neoplasm of the nasal cavity and paranasal sinuses with or without neuroendocrine differentiation but without evidence of squamous or glandular differentiation.

Clinical

SNUC affects women more than men; occur over a wide age range including the 4th-8th decades of life. Generally present as large tumors involving multiple (sinonasal) sites and may also extend into the nasopharynx. Typically, patients present with multiple symptoms including: nasal obstruction, epistaxis, and due to invasive growth may also include proptosis, cranial nerve palsies, visual disturbances, and pain. There are no known etiologic agents. Radiographic studies demonstrate a large sinonasal mass typically with local invasive growth extending beyond its bony confines with involvement of orbital or cranial bones. Intracranial extension may occur. The histogenesis for SNUC has not been completely identified. It seems likely that SNUC arises from the Schneiderian epithelium (ectodermal derivation). However, while speculative, given overlapping clinical, light microscopic, immunohistochemical and ultrastructural features with olfactory neuroblastoma and neuroendocrine carcinoma, the cell of origin may be related to both the Schneiderian and olfactory epithelia.

Pathology

SNUC often present as a large fungating mass often invading into adjacent structures or anatomic compartments. The histologic appearance is characterized by a hypercellular proliferation with a varied growth including trabecular, sheet-like, ribbons, lobular and organoid patterns. Surface involvement may be seen (severe dysplasia or carcinoma in-situ) but often ulceration precludes evidence of epithelial derivation. The cellular infiltrate consists of polygonal cells composed of round to oval, hyperchromatic to nuclei, inconspicuous to prominent nucleoli and moderate amount of eosinophilic cytoplasm. Distinct cell borders can be seen. The nuclear to cytoplasmic ratio is high. Cellular pleomorphism, increased mitotic activity and necrosis (confluent areas and individual cell) are typically present. The tumors are invasive with vascular space invasion and neurotropism. Squamous or glandular differentiation are not evident, and neurofibrillary material and true neural rosettes are not identified. Histochemical studies are noncontributory to the diagnosis of SNUC.

The immunohistochemical antigenic pattern may vary from case to case but SNUC are consistently immunoreactive with epithelial markers, including cytokeratin and/or epithelial membrane antigen (EMA). Reactivity is often intense and diffuse. In contrast, olfactory neuroblastomas are inconsistently cytokeratin or EMA reactive and when positive, the reactive pattern is focal and of relatively weak intensity. Variable reactivity can be seen with neuron specific enolase (NSE), S-100 protein, Leu-7, chromogranin, and synaptophysin. Desmin, leukocyte common antigen, HMB-45 and Ewing's marker are absent. By electron microscopy, membrane-bound, dense core neurosecretory granules may be seen, and poorly formed desmosomes may occasionally be found.
Treatment and Prognosis

The treatment for SNUC includes intensive multimodality therapy, including surgical resection and adjuvant therapy (radiotherapy, chemotherapy). However, SNUC is a highly-aggressive neoplasm that cannot be completely eradicated by surgery nor is it responsive to radiation treatment. Frierson et al report a mean survivals of 4 months with no disease free patients. Righi et al report that of their seven patients, four died of disease with mean survival of 11.5 months none of whom were disease free; three of their patients alive with no evidence of disease over a mean period of 13.3 months. In these three patients, two had locally confined disease at presentation; the third had extensive disease that responded dramatically to combined radiotherapy and chemotherapy. Deutsch et al reported improved survival following treatment with chemotherapy (cyclophosphamide, doxorubicin, and vincristine), followed by radiotherapy and then radical surgery. These authors, as well as others recommend this treatment regimen for SNUC regardless of the extent of disease. High dose chemotherapy and autologous bone marrow transplantation have been used. Local recurrence is common and is the major cause of morbidity and mortality. Metastatic disease to bone, brain, liver and cervical lymph nodes may occur.

Differential Diagnosis

The differential diagnosis of SNUC includes poorly-differentiated squamous cell carcinoma, poorly differentiated adenocarcinoma, olfactory neuroblastoma, high-grade, small cell undifferentiated neuroendocrine carcinoma, mucosal malignant melanoma, nasal-type NK/T cell lymphoma, rhabdomyosarcoma, others.

Olfactory Neuroblastoma (ONB) is a malignant neoplasm thought to arise from the olfactory membrane of the sinonasal tract.

Clinical

ONB is an uncommon malignant neoplasm. There is slight female predominance; ages at onset range from 3 years to the ninth decade, with a bimodal peak in the second and sixth decades of life. The main presenting symptoms are unilateral nasal obstruction and epistaxis; less common manifestations include anosmia, headache, pain, excessive lacrimation and ocular disturbances. It appears that ONB take origin from the olfactory membrane located in the upper nasal cavity, which is the most common site of presentation. Included in the areas of proposed origin are Jacobson's organ (vomeronal organ), Sphenopalatine (pterygoid palate) ganglion, olfactory placode, and the ganglion of Loci (nervus terminalis). Light microscopic and ultrastructural studies support the bipolar neurons of the olfactory membrane as the cell of origin. "Ectopic" origin within one of the paranasal sinuses may occur. Radiologically, a sinonasal mass causing sinus opacification with or without bone erosion may be seen. ONB may be associated with calcifications producing a speckled pattern by radiographic analysis. Angiographic studies may disclose a hypervascular neoplasm.

There are no known etiologic agent(s). Cytogenetic abnormalities (translocation) have been seen in association with olfactory neuroblastomas. These include the 11:22 chromosomal translocation, a similar finding identified in both PNET and Ewing's sarcoma.
Based on finding this chromosomal translocation in ONB, there is speculation relative to a shared histogenesis of ONB with the group of PNETs. However, there is no unequivocal confirming data supporting the concept that ONB, SNUC or neuroendocrine carcinoma belong to PNET. The chromosomal translocation is probably a key factor in oncogenesis rather than a "marker" of histogenesis.

Pathology
The gross appearance of ONB includes a glistening, mucosal covered, soft, polypoid mass varying from a small nodule less than 1 cm to a mass filling the nasal cavity with possibly extension into adjacent pranasal sinuses and nasopharynx. The histologic appearance is divided into four grades as defined by Hyams (Table 1). Grade I is the most differentiated and includes lobular architecture with intercommunication of the neoplasm between lobules. The neoplastic cells are well-differentiated with uniform round to vesicular nuclei with or without nucleoli. The cells do not have distinct borders; rather, the nuclei are surrounded by a neurofibrillary material suggesting cytoplasmic extension. A pseudorosette pattern (Homer Wright rosettes) is frequently seen. Varying amounts of calcification may be noted. Interlobular fibrous stroma is often extremely vascular. Mitotic activity and necrosis are absent. Grade II tumors share many of the histologic features described for Grade I lesions but the neurofibrillary element is less well defined, and the neoplastic nuclei show increased pleomorphism. Scattered mitoses can be seen. Grade III tumors may retain a lobular architecture with an interstitial vascular stroma. These tumors are characterized by a hypercellular neoplastic cell proliferation composed of cells that are more anaplastic, hyperchromatic, and have increased mitotic activity as compared to Grade I or II tumors. Necrosis is seen. The neurofibrillary component may be focally present, but is much less conspicuous as compared to Grades I or II tumors. True neural rosettes (Flexner-Wintersteiner) may be seen; however, in general, these structures are uncommonly identified. Calcification is absent. Grade IV tumors may also retain the overall lobular architecture and the neoplastic element is the most undifferentiated and anaplastic of all the histologic grades. In these grade tumors, the cellular infiltrate is characterized by pleomorphic nuclei often with prominent eosinophilic nucleoli and an indistinct cytoplasm. Necrosis is commonly seen and there is increased mitotic activity, including atypical mitosis. True neural rosettes may be seen but like Grade III tumors are uncommon. The neurofibrillary component is generally absent. Calcification is absent.

In general, the lower grade ONB are readily recognizable and diagnostic by light microscopy. Adjunct studies, particularly in the higher histologic grade tumors, may assist in the diagnosis. Histochemical stains have been replaced by immunohistochemistry in the diagnosis of ONB. Nevertheless, silver stains such as Bodian, Grimelius and Churukian-Schenk may be helpful. The most consistent immunohistochemical stain in the diagnosis of ONB is the nonspecific stain neuron specific enolase (NSE). Variable reactivity is seen with S-100 protein (which typically is seen at the periphery of the neoplastic lobules), cytokeratin, glial fibrillary acidic protein (GFAP), neurofibrillary protein (NFP), beta-tubulin, microtubule-associated protein, chromogranin, synaptophysin, and Leu-7. Epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA), leucocyte common antigen (LCA), HMB-45, desmin and Ewing's marker are absent. Electron microscopy evaluation is a useful adjunct in the diagnosis and includes the presence of dense core neurosecretory granules measuring from...
80 to 250 nm in diameter). In addition, neurofilaments and neurotubules, and occasionally Schwann-like cells, can be seen.

Table 1. Hyams' Histologic Grading System for Olfactory Neuroblastoma

<table>
<thead>
<tr>
<th>Microscopic Features</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Architecture</td>
<td>Lobular</td>
<td>Lobular</td>
<td>Lobular</td>
<td>Lobular</td>
</tr>
<tr>
<td>Pleomorphism</td>
<td>Absent to Slight</td>
<td>Present</td>
<td>Prominent</td>
<td>Marked</td>
</tr>
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<td>NF matrix</td>
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<td>Present</td>
<td>May be present</td>
<td>Absent</td>
</tr>
<tr>
<td>Rosettes</td>
<td>Present*</td>
<td>Present*</td>
<td>May be present**</td>
<td>May be present**</td>
</tr>
<tr>
<td>Mitoses</td>
<td>Absent</td>
<td>Present</td>
<td>Prominent</td>
<td>Marked</td>
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<td>Prominent</td>
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<tr>
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<td>May be present</td>
<td>May be present</td>
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<tr>
<td>Calcification</td>
<td>Variable</td>
<td>Variable</td>
<td>Absent</td>
<td>Absent</td>
</tr>
</tbody>
</table>

NF-neurofibrillary; *Homer Wright rosettes (pseudorosettes); **Flexner-Wintersteiner rosettes (true neural rosettes)

Treatment and Prognosis

For ONB, complete surgical eradication is the treatment of choice followed by full course radiotherapy. Limited success using chemotherapeutic modalities has been achieved for advanced unresectable tumors and/or for disseminated disease. Clinical staging as proposed by Kadish et al correlate with 5-year survival: Stage A - tumor confined to the nasal cavity - 75 percent; Stage B (most common) - tumor involves the nasal cavity plus one or more paranasal sinuses - 68 percent; Stage C - extension of tumor beyond the sinonasal cavities - 41 percent. More recently, Eden et al reviewed the University of Virginia experience with ONB and report that the overall 5, 10 and 15 year survival were 78 percent, 71 percent and 68 percent, respectively. Mills and Frierson reported that complete tumor resection was of greater prognostic significance than the Kadish stage. The majority of tumors behave as locally aggressive lesions mainly involving adjacent structures (orbit and cranial cavity). Local recurrence and distant metastasis may occur years following the initial diagnosis. From 30 to 70 percent of patients will experience local recurrence, 20 to 40 percent will have cervical lymph node metastasis, and approximately 10 percent of patients will experience distant metastasis. The more common sites of metastatic disease include lymph nodes, lungs, and bone. All histologic grades have the capacity to metastasize.
Neuroendocrine Carcinoma

Neuroendocrine carcinoma (NEC) is a malignant neoplasm with divergent differentiation along both epithelial and neuroendocrine cell lines.

Clinical

In general, NEC is an uncommon group of neoplasms. NEC may be identified in virtually all sites of the head and neck including: larynx, sinonasal cavity, salivary glands and middle ear. NEC affects men more than women and most commonly occurs in older age groups (6th-7th decades of life).

The classification of NEC is still being debated. Some classification schemes divide these tumors into three types, including carcinoid tumor, atypical carcinoid tumor and small cell carcinoma. Other schemes propose classifying these tumors according to differentiation to include: 1) well-differentiated neuroendocrine carcinoma (equated with carcinoid tumor); 2) moderately-differentiated neuroendocrine carcinoma (equated with atypical carcinoid) and 3) poorly-differentiated neuroendocrine carcinoma (equated with small ("oat") cell undifferentiated neuroendocrine carcinoma [SCUNC]). Other authors further subdivide the small cell neuroendocrine carcinomas into small cell variant and large cell variant. Because of the time honored terminology and to minimize confusion, the terms carcinoid, atypical carcinoid and small cell carcinoma, as proposed by the World Health Organization will be used in this section. However, it should be kept in mind that the “atypical” carcinoid tumor is a fully lethal tumor and the term “atypical” should not lull the clinician into a false sense of security that this tumor is only slightly different in its behavior from the relatively indolent “classic” carcinoid tumor.

Among the group of NEC, the one that may present diagnostic difficulties in differentiating from other round cell malignancies is the small cell undifferentiated neuroendocrine carcinomas (SCUNC). SCUNC may be identified in virtually all upper aerodigestive tract sites but primarily involve the larynx, salivary glands (parotid), and sinonasal tract.

Pathology

Irrespective of the site of occurrence, the histologic appearance of SCUNC is the same. These tumors are hypercellular with varied growth, including sheets, cords or ribbons. The cells are small and hyperchromatic with oval to spindle-shaped nuclei, absent nucleoli and minimal cytoplasm. Cellular pleomorphism, increased nuclear to cytoplasmic ratio, increased mitotic activity, confluent necrotic areas and individual cell necrosis are readily apparent. Characteristically, crush artifact of the neoplastic cells are seen. Squamous cell foci may occasionally be present; glandular or ductal differentiation is rarely seen. Although uncommon, neural-like rosettes can be seen in association with SCUNC. SCUNC are infiltrative tumors frequently associated with vascular/lymphatic space and perineural invasion. SCUNC may demonstrate the presence of epithelial mucin. Argyrophilia can be seen but argentaffin staining is absent. Because of its poor differentiation, the immunohistochemical antigenic profile of SCUNC may be quite variable from case to case. Reactivity with the following antibodies may be present to a varying degree: cytokeratin, chromogranin, synaptophysin, neuron specific enolase (NSE) and S-100 protein. Cytokeratin reactivity may include a punctate paranuclear or globoid pattern. The paranuclear punctate...
staining for cytokeratin is a characteristic feature of Merkel cell carcinoma. Recently, Chan et al compared the reactive staining pattern of the epithelial marker CK20, in SCUNC of various anatomic sites versus that of Merkel cell carcinoma. Chan et al found that CK20 preferentially reacted with Merkel cell carcinomas. Further, those tumors diagnosed as SCUNC of salivary gland origin, including a paranuclear punctate staining pattern for cytokeratin, reacted with CK20. These results suggested that the purported salivary gland SCUNC were in fact Merkel cell carcinomas arising from a cutaneous site with secondary involvement of the parotid gland or originated within the parotid gland. Calcitonin is rarely present. Leucocyte common antigen (LCA), CK-20, HMB-45 and HBA-71 (Ewing's marker) are absent. Ultrastructural studies may show the presence of neurosecretory granules (when identified measure from 50-200nm). Cellular junctional complexes including desmosomes and tonofilaments are scanty, and lumina (inter- and intracellular) are usually absent.

Treatment and Prognosis
The treatment of choice for carcinoid tumors is surgery. Prognosis is excellent following removal. Metastatic disease rarely occurs. The treatment of choice for “atypical” carcinoid tumors is surgery. Adjuvant therapy (radiotherapy and chemotherapy) may be utilized but these modalities are of questionable benefit. Metastatic disease occurs often and involves regional lymph nodes, lung, bone, liver, digestive tract, and skin. Prognosis varies and is dependent on the extent of disease. SCUNC are highly malignant tumors commonly associated with metastatic disease. Due to high rate of metastatic disease, surgery is not considered appropriate therapy. The preferred treatment for SCUNC is systemic chemotherapy and therapeutic irradiation. Prognosis is poor. Metastatic disease is common involving lung, liver, bone, lymph nodes, and brain.

Mucosal Malignant Melanoma
Mucosal malignant melanoma (MMM) is a malignant neural crest-derived neoplasm originating from melanocytes, which have migrated to the mucosa of the upper respiratory tract.

Clinical
Primary (noncutaneous) upper respiratory tract malignant melanoma accounts for < 2% of all malignant melanomas. Affects men more than women; occurs over a wide age range but most frequently occurs in the 6th to 8th decades of life. MMM can be identified in all upper respiratory tract sites but is most commonly seen in the nasal cavity and paranasal sinuses; less common sites of involvement include: nasopharynx, pharynx, larynx and middle ear. Symptoms vary according to the site of occurrence and include: nasal obstruction, epistaxis, painful mass, hoarseness, and dysphagia. Nasal cavity malignant melanomas occur more frequently than those arising in the paranasal sinuses; however, concurrent nasal cavity and paranasal sinus melanomas frequently occur either as a result of direct extension or as multicentric tumors. Primary sites of involvement in the nasal cavity are: septum > lateral wall > middle and inferior turbinates; the left side is affected more often than the right. Primary sites of involvement in the paranasal sinuses are: maxillary (antrum) > ethmoid; other sinuses rarely involved as primary sites.

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Pathology

A variety of gross appearances can be seen including: polypoid or sessile with or without ulceration, brown, black, pink or white, friable to rubbery measuring from 1.0 cm to large tumors occluding the nasal cavity and/or paranasal sinus. In general, surface ulceration is a common finding.

In tumors with intact surface epithelium continuity of the tumor with the surface epithelium (junctional or pagetoid changes) can usually be identified. Cytomorphologic features include epithelioid or spindled cells; tumors with mixed epithelioid and spindle cells can be seen. Epithelioid cell features include a varied growth pattern varies including solid, organoid, nested, trabecular, alveolar and any combination of these patterns. The cells are round to oval, markedly pleomorphic with increased nuclear-cytoplasmic ratio, vesicular to hyperchromatic nuclei, prominent eosinophilic nucleoli, nuclear grooving, nuclear pseudo-inclusions, and eosinophilic to clear cytoplasm. Plasmacytoid features may be prominent but a paranuclear clear zone is not seen. Spindle cell features include a varied growth pattern including storiform or fascicular which may be associated with a myxoid stroma. The cells are oblong to cigar-shaped, markedly pleomorphic with large vesicular to hyperchromatic nuclei, absent to prominent nucleoli and scant eosinophilic cytoplasm. For both cytomorphicologic types, necrosis and increased mitoses with atypical mitotic figures are common findings. Neoplastic giant cells can be found rarely; glandular differentiation may be seen. Melanin may be heavily deposited with easy identification or may be limited or absent.

Histochemistry: tumor cells are argentaffin and argyrophilic positive; PAS-positivity may be seen.

Immunohistochemistry: diffuse S-100 protein and HMB-45 positive in both epithelioid and spindle cells.

Electron Microscopy: melanosomes and premelanosomes can be seen.

Treatment and Prognosis

Irrespective of the site of origin, aggressive radical surgical excision is indicated. Adjuvant radiotherapy may be used. In general, prognosis is poor with 5 year survival rates in the range of 6 to 17%. There is no correlation between size, location or histologic appearance of the tumor and survival. Up to 2/3 of patients with sinonasal melanoma will have recurrent disease in the first postoperative year; treatment for recurrent tumor include surgery, radio- and chemotherapy. In contrast to squamous carcinoma, sinonasal melanomas metastasize less frequently to regional lymph nodes (< 20%); metastatic disease occurs most frequently to the lungs, lymph nodes and brain. Nasal cavity melanomas have a better prognosis than paranasal sinus melanomas. Oral cavity melanomas tend to metastasize more frequently to regional lymph nodes than those melanomas originating in the sinonasal tract. Despite the overall poor prognosis, patients may experience long quiescent periods even with recurrent or metastatic disease. The possibility of metastasis to a mucosal site from a cutaneous melanoma should always be considered.
Nasal Type NK/Tcell Lymphoma.

Non-Hodgkin's lymphomas of the sinonasal tract (SNT-ML) are heterogeneous diseases, which can be clinically aggressive. Synonyms have included such terms as polymorphic reticulosis, lethal midline granuloma, and midline malignant reticulosis. Although the use of the terms polymorphic reticulosis, lethal midline granuloma, midline malignant reticulosis, and idiopathic midline destructive disease have been used over the years synonymously with SNT-ML, these designations are inaccurate. Nonneoplastic lesions, inflammatory and infectious diseases, as well as numerous benign and malignant neoplasms of the sinonasal tract may all result in a destructive process occurring in the midline aspect of this region. Therefore, idiopathic midline destructive disease is not a specific term and should never be used to indicate a diagnosis of a malignant lymphoproliferative neoplasm. The current designations for these lymphomas include angiocentric immunoproliferative lesions, peripheral T-cell lymphomas, and more recently, extranodal angiocentric T/NK cell (malignant) lymphomas.

Clinical

SNT-ML are uncommon accounting for only 1.5 percent of non-Hodgkin malignant lymphomas in the United States. The incidence has been reported to be higher, however, in Asian and South American countries where the incidence of primary non-Hodgkin's malignant lymphoma is approximately 6.7 to 8.0 percent of all malignant lymphomas. SNT-ML are slightly more common in men than women occurring over wide age range but is most common in the 6th to 8th decade of life. The median age is higher in women than in men.

The nasal NK/T cell lymphomas are most common in Asians and have been reported with significant frequency in South and Central America and Mexico. In these populations, the disease primarily is seen in individuals of Native American origin. These findings suggest a racial predisposition for the disease. Although uncommon, nasal angiocentric T/NK cell lymphomas occur in Western populations and can affect Caucasians.

The clinical presentations vary according to histologic type and/or immunophenotype. Low grade lymphomas may present with a nasal cavity or paranasal sinus mass associated with airway obstructive symptoms. High grade lymphomas are more likely present with aggressive signs and symptoms including nonhealing ulcer, cranial nerve manifestations, facial swelling, epistaxis, or pain. High grade B-cell lymphomas tend to present with soft tissue or osseous destruction particularly of the orbit with associated proptosis. Angiocentric NK/T cell lymphomas commonly present as a destructive process of the mid-facial region with nasal septal perforation or destruction, palatal destruction, orbital swelling or with obstructive symptoms related to a mass. Nasal-type NK/T cell lymphomas may involve the entire upper aerodigestive tract but may also involve non-upper aerodigestive tract, including skin and subcutaneous tissue (the most common site of secondary spread), gastrointestinal tract and testes. Lung involvement is rare.

SNT-ML is less common in Western countries than in Asian countries. Aside from the difference in occurrence, other dissimilarities have been reported between so-called Western and Eastern sinonasal tract lymphomas. These include primarily the finding of Epstein-Barr virus (EBV) positive T-cell phenotype in Asian countries and Peru, especially in the angiocentric immunoproliferative type, and EBV-negative lymphomas of B-cell origin in the United States and European countries. These distinctions are not definitive as, in a limited

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number of cases, EBV-positive T-cell lymphomas have been reported in the United States, 
EBV positive B-cell lymphomas have been reported in the United States, and both EBV-
positive B- and T-cell sinonasal tract lymphomas have been reported in the Orient. Some 
investigators have supported the predominance of a B-cell phenotype in Western SNT-ML 
even in the absence of EBV studies. An immunophenotypic difference exists between 
primary nasal cavity lymphomas versus primary paranasal sinus lymphomas, the nasal cavity 
lymphomas are predominantly of T-cell immunophenotype while the majority of B-cell 
lymphomas occur in the paranasal sinus.

**Pathology**

Virtually the entire spectrum of morphologic types of lymphomas (as classified by the 
Working Formulation) can be seen in the sinonasal tract.

**Nasal-type NK/T cell lymphoma**

A broad cytologic spectrum is usually present but usually includes the presence of 
cytologically atypical cells. The latter may vary from small and medium-sized cells to large, 
hyperchromatic cells. The atypical cells may have irregular and elongated nuclei, prominent 
nucleoli or clear cytoplasm. Increased mitotic activity is often seen. Epitheliotropism and 
pseudoepitheliomatous hyperplasia may be present. An associated prominent admixed 
inflammatory cell infiltrate may be present. The polymorphous cell population may obscure 
the atypical cells causing diagnostic difficulties. The benign inflammatory cell infiltrate may 
include plasma cells, histiocytes and eosinophils. Multinucleated giant cells or true 
granulomas are absent.

In adequately sampled material, the low-power appearance includes the presence of 
geographic necrosis characterized by bluish or so-called “gritty” necrosis. Necrosis is virtually 
constant (but not pathognomonic feature) in nasal and nasal-type NK/T lymphomas. The 
zonal pattern of distribution suggests a vascular pathogenesis. The atypical cells invade and 
destroy blood vessels. The vascular invasion and destruction is responsible for the 
designation of the term angiocentric lymphomas. Angiocentricity is defined as the presence 
of tumor cells around and within vascular spaces with infiltration and destruction of the vessel 
wall. Perivascular localization is not sufficient for the designation of angiocentricity.

Stains for microorganisms are negative. Immunohistochemical evaluation includes 
the presence of leucocyte common antigen (LCA; CD45), the T-cell markers UCHL-1 
[CD45RO] and CD3 (cytoplasmic), CD56 (neural cell adhesion molecule [NCAM]). Surface 
(membranous) CD3 is usually absent and B-cell associated antigens are absent. Clonal T-
cell receptor gene rearrangements and Ig gene rearrangement are usually negative.
Nasal NK/T cell lymphomas are positive for EBV by in-situ hybridization. Since EBV-positive cells are typically absent in the nasal cavity mucosa or in inflammatory diseases of the nasal cavity, the presence of EBV by ISH can be used in conjunction with light microscopy in the diagnosis of nasal cavity NK/T lymphomas. EBV virus may induce the expression of cytokines, which could lead to the presence of necrosis. This might then represent the pathogenesis for the observed necrosis in those cases without vascular invasion. A similar phenomenon can be seen in benign and malignant EBV-positive lymphoproliferative disorders, including infectious mononucleosis, post-transplant lymphoproliferative disorders and lymphomatoid granulomatosis.

**Treatment and Prognosis.**

Nasal NK/T cell malignant lymphomas are radiosensitive tumors but the prognosis is generally poor once dissemination occurs. The treatment in disseminated disease is aggressive chemotherapy. In some patients, surgical resection may be needed for symptomatic relief (e.g., airway obstruction). A complication seen in nasal NK/T cell malignant lymphomas is hemophagocytic syndrome, which adversely affects survival.

For B-cell lymphomas, prognosis is dependent on the clinical stage. The most important prognostic factor for patients with malignant lymphomas is the clinical stage based on the Ann Arbor classification, which was originally developed for Hodgkin’s disease. Treatment primarily includes radiotherapy and/or chemotherapy. Surgical resection may be needed for symptomatic relief. More recently, a multinational and multi-institutional cooperative study developed prognostic indices for non-Hodgkin’s malignant lymphomas. The authors of this study concluded that the indices they developed were significantly more accurate than the Ann Arbor classification in predicting long term survival, and that these indices should be used in patients with (aggressive) non-Hodgkin’s lymphoma and in the selection of appropriate therapeutic approaches.

**Rhabdomyosarcoma (RMS)**

**Definition:** Malignant neoplasm showing skeletal muscle differentiation

**Clinical**

- represents 8-19% of all soft tissue sarcomas:
  - head and neck is the most common site of origin with 35-45% of all cases
  - genitourinary tract second most common site with 35% of all cases
  - extremities represent from 15-20% of all cases
- in the head and neck, RMS is primarily but not exclusively a disease of the pediatric population:
  - 43% of patients are under 5 years of age;
  - 78% of patients are under 12 years of age
- in children and adolescents, RMS represents the most common aural-related malignant neoplasm
- no gender predilection although some reports show a slight male predominance
- most frequent sites in the head in neck include:
  - orbit > nasopharynx > middle ear and mastoid > sinonasal tract > other
• Symptoms vary according to site and include nasal obstruction, epistaxis, pain, refractory otitis media, otorrhea, temporofacial swelling or deformity and neurologic deficits.
• There are no known associated etiologic factors.

Pathology

Gross
The gross appearance may vary according to the site involved: nasopharyngeal RMS tend to be fairly well-circumscribed, polypoid or multinodular, tan-white, glistening or gelatinous and capable of attaining large sizes; aural RMS most commonly present as an otic (external or middle ear) polyp; sinonasal RMS tend to be small and appear as a nasal polyp. Approximately 25% of nasopharyngeal and sinonasal cavity RMS assume a sarcoma botryoides appearance with a "grape-like", multinodular or polypoid configuration. Sarcoma botryoides is a macroscopic identification and is not considered a separate histologic variant.

Histology
• the histologic classification of RMS has evolved over time; at present the International Classification of RMS, a modification of the conventional scheme, is advocated given its reproducibility and prognostic significance (Tables 2,3)
• the majority of RMS of the middle ear and mastoid are of the embryonal type that includes botryoid RMS
• the next most common histologic type is alveolar RMS; alveolar RMS tend to occur in older aged individuals as compared to embryonal RMS, including botryoid and spindle subtypes
• other histologic types may occur in the head and neck but are considered uncommon

Embryonal RMS:
• typically, there is a variation in the cellularity of these tumors with alternating hyper- and hypocellular areas; the latter often is associated with a myxoid stroma
• composed of primitive mesenchymal cells in various stages of myogenesis
• the cellular components consist of an admixture of cell types including:
  - small undifferentiated (primitive appearing) round or spindle-shaped cells with hyperchromatic nuclei and indistinct cytoplasm; mild nuclear pleomorphism, increased mitotic activity and necrosis are present
  - differentiated large round to oval cells with eosinophilic cytoplasm
  - cross striations are rare in round cells but are more apparent in spindle cell component and can be seen in 50-60% of cases; as compared to the cross striations of normal skeletal muscle, the cross striations in rhabdomyoblasts are more irregular in distribution and traverse only part of the cell
• uncommonly, embryonal RMS with foci of prominent cellular pleomorphism may occur; these tumors are still recognized as embryonal RMS given:
  - the presence of areas of more typical embryonal RMS;
  - frequent identification of cross striations;
  - prognosis is not altered except if the cellular pleomorphism is diffuse at which point differentiation from pleomorphic RMS is difficult

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• heterologous elements, including cartilage and bone may be identified; these findings are more often seen in RMS of the genitourinary tract and in retroperitoneal RMS

**Botryoid Variant of Embryonal RMS (Sarcoma Botryoides):**
• the Greek term *botryos* means bunch of grapes
• gross appearance in a hollow viscus or body cavity is as a polypoid mass
• histologically, contains a dense layer or aggregate of tumor cells localized beneath an epithelial surface (subepithelial condensation of tumor cells) referred to as a cambium layer; surface epithelium may show reactive hyperplasia or metaplasia (e.g., squamous metaplasia)
• polypoid nodules often with loose myxoid stroma
• immunohistochemistry: myogenic markers are positive (see below)
• favorable prognosis (see below)

**Spindle Cell RMS:**
• rare tumor type that tends to occur in young patients (less than 7 years of age) with a male predilection; most frequently found in the paratesticular region but second most common site of occurrence include mucosal sites of the head and neck
• grossly, appears well circumscribed but unencapsulated with a nodular, whorled appearance on cut section and measuring from 4-6 cm in greatest diameter
• histologically, comprised of densely arrayed fascicles or whorls of spindle shaped cells; may have storiform growth
• elongated fusiform or spindle cells have cigar-shaped or blunted central nuclei and tapered ends (similar to smooth muscle cells) and prominent nucleoli; the presence of eosinophilic fibrillar cytoplasm with distinct cell borders with or without identifiable cross striations point to skeletal muscle differentiation
• collagen rich (tumor cells separated by abundant collagenized stroma) and collagen poor forms are described
• immunohistochemistry: myogenic markers are positive (see below) that include markers of late stage myogenesis including titin and troponin T indicative of a greater degree of differentiation in this variant than other RMS variants
• favorable prognosis (see below)

**Alveolar RMS**
• comprised of ill-defined aggregates of poorly-differentiated small round to oval neoplastic cells; often there is central loss of cellular cohesion resulting in "alveolar" spaces; however, solid forms occur in which there is an absence of an alveolar pattern and the neoplasm is composed of densely packed clusters of tumor cells
• dense, hyalinized fibroconnective and/or fibrovascular septa surround and separate the neoplastic aggregates
• tumor cells in both alveolar and solid areas have round to oval hyperchromatic nuclei with a scant amount of indistinct cytoplasm; the cells at the center of the alveolar spaces are loosely arranged and often show degenerative changes as well as necrosis; the cells at the periphery of the alveolar spaces are better preserved and often adhere to the fibrous septa
• mitotic figures are readily identified
neoplastic rhabdomyoblasts with prominent granular eosinophilic cytoplasm are less
common in the alveolar type than in the embryonal type; cross striations are not commonly
identified and, if present, are found in spindle-shaped or strap cells
multinucleated giant cells are often found in alveolar RMS and represent a diagnostically
important finding; in contrast, multinucleated giant cells are not commonly found in
embryonal RMS; the giant cells typically have peripherally situated nuclei with weakly
eosinophilic cytoplasm and absence of cross striations
lymph node metastasis may precede identification of primary tumor; when alveolar RMS
metastasizes, the alveolar pattern may be retained in the metastatic site

Pleomorphic RMS

rare high-grade variant of RMS occurring in almost exclusively in adults older than 45 years
(mean of 56 years) although may occur in younger aged patients (2nd and 3rd decades of life)
predilection to males
most common site of occurrence is the deep soft tissues of extremities, in particular the
thigh; less common sites of occurrence include the chest wall, retroperitoneum and, head
and neck
typically present as rapidly enlarging, painless mass growing over months; metastatic
disease (to lungs) may occur at presentation
tumors are usually large measuring over 10 cm in size
histology is characterized by the presence of loosely arranged, large, round or pleomorphic
tumor cells with hyperchromatic nuclei and deeply eosinophilic cytoplasm; the pleomorphic,
bizarre cells with deeply eosinophilic cytoplasm represents the best light microscopic
features in rendering this diagnosis
spindle-shaped, tadpole-shaped or racket-shaped cells rhabdomyoblasts with irregular
contours are present
cells with cross striations are rarely seen
the cellular proliferation usually is haphazardly arrayed but storiform and fascicular growth
patterns can be present

General considerations:
rhabdomyoblasts, the cell of origin for this sarcoma, take on numerous appearances
including small round cells to ribbon- or strap-shaped to large and pleomorphic;
rhabdomyoblasts with cross-striations are not always identified and their absence does not
exclude the diagnosis of rhabdomyosarcoma
an associated benign inflammatory infiltrate may predominate overrunning and masking the
presence of the neoplastic cells

Special Studies
in the presence of a poorly-differentiated neoplasm lacking evidence of cross striations
special stains are invaluable in confirming the diagnosis of rhabdomyosarcoma and include:
- histochemistry: cells contain glycogen as demonstrated by periodic acid-Schiff (PAS)
positivity cleared by diastase digestion; intracellular myofibrils can be seen by Masson
trichrome and phosphotungstic acid hematoxylin (PTAH) stains
- immunohistochemistry:
  - desmin, myoglobin, MyoD1 (Myf-4) and muscle specific actin positive
- keratin, S100 protein, leucocyte common antigen, chromogranin, synaptophysin, melanocytic markers negative

- ultrastructure:
  - bundles of thick (myosin) filaments with attached ribosomes (ribosome and myosin complex) and thin (actin) fibrils
  - admixture of alternating thin (actin) and thick (myosin) filaments in parallel (longitudinal) arrangement with hexagonally appearing (on cross section) Z banding
  - Golgi apparatus, mitochondria, glycogen droplets can be present
• cytogenetic findings (Table 4):
  1) Embryonal RMS:
     - consistent loss of heterozygosity at chromosome 11p15.5 which may result in activation of tumor suppressor gene including tyrosine hydroxylase gene
     - short arm of chromosome 11 abnormalities
  2) Botryoid Type:
     - deletion of short arm of chromosome 1
     - trisomies of chromosomes 13 and 18e
  3) Spindle cell RMS:
     - to date, no data regarding cytogenetic abnormalities
  4) Alveolar RMS:
     - t(2;13)(q36;q14) translocation occurs in the majority of cases
     - t(1;13)(p36;q14) translocation occurs in a minority of cases
     - the above translocations result in juxtaposition of PAX3 or PAX7 genes on chromosomes 2 and 1, respectively, with the FKHR gene on chromosome 13 producing chimeric genes encoding PAX3/FKHR and PAX7/FKHR fusion proteins. Approximately, 70-85% of histologically diagnosed alveolar RMS express either the PAX3/FKHR or PAX7/FKHR fusion transcript and of these fusion positive cases, 80-90% are PAX3/FKHR and 10-20% are PAX7/FKHR fusion
     - PAX3/FKHR and PAX7/FKHR fusion transcripts are uncommon in embryonal RMS
     - PAX7/FKHR fusion transcript positive cases tend to occur in young patients, more often arise in extremities and are associated with longer event-free survival

Treatment and Prognosis
• for all histologic types of RMS treatment includes a combination of surgery, radiation and/or chemotherapy
• following biopsy diagnosis, recommendations for treatment depend on several factors including site of the disease, clinical group of the disease and stage of the disease
• tumor staging is an important element in the overall approach to treating the disease; since there is a tendency to bone marrow metastasis, a bone marrow aspiration/biopsy is part of the staging process
• clinical staging of patients (Table 5)
• TNM classification (Table 6); this classification relies on pretreatment assessment of the extent of tumor
• favorable and unfavorable factors (Table 7)
• overall 5-year survival rates based on clinical staging include:
  - groups I, II: 85-88%
  - group III: 66%
  - group IV: 26%
• prognosis is best for orbital RMS followed by head and neck and genitourinary (nonbladder/prostate) RMS; 5-year survival rates include:
  - orbit: 92%
  - head and neck, nonprostate/bladder RMS: 80%
  - parameningeal, bladder, prostate, extremities: 70%
• adverse outcomes accounting for prognostic differences related to anatomic sites have been linked to:
  - late detection of tumor;
  - large tumor size;
  - difficulties during surgical excision;
  - meningeal involvement with or without spinal fluid spread
  - metastatic disease
• a problem specifically related to middle ear and mastoid RMS is the delay in diagnosis due to misinterpretation of the biopsy specimen as inflammatory polyps or as granulation tissue; this delay in diagnosis may result in more advanced stage disease placing patients at greater risk for treatment failure due to uncontrollable local disease
• metastatic disease occurs in up to 20% of cases; metastatic sites include:
  - regional lymph nodes – dependent on tumor location with greater incidence of nodal metastasis in patients with RMS of the prostate, paratesticular region and extremities as compared to RMS of the orbit, head and neck
  - distant hematogenous metastasis to the lungs, bone marrow > other viscera (brain, meninges, liver, kidney, pancreas and heart)

Table 2: Classification of RMS (1969 - modified Horn and Enterline Classification)

<table>
<thead>
<tr>
<th>Embryonal</th>
<th>Botryoid</th>
<th>Alveolar</th>
<th>Pleomorphic</th>
<th>Sarcoma not classified</th>
<th>Small round cell sarcoma, type indeterminate</th>
<th>Extraosseous Ewing’s sarcoma</th>
</tr>
</thead>
</table>
Table 3: International Classification of RMS (1995)

<table>
<thead>
<tr>
<th>Superior Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botryoid RMS</td>
</tr>
<tr>
<td>Spindle RMS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryonal RMS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Poor Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alveolar RMS</td>
</tr>
<tr>
<td>Undifferentiated RMS</td>
</tr>
</tbody>
</table>

Subtypes whose prognosis is not presently evaluable
RMS with rhabdoid features

Table 4: Cytogenetics of RMS

<table>
<thead>
<tr>
<th>Embryonal RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>loss of heterozygosity at chromosome 11p15.5</td>
</tr>
<tr>
<td>short arm of chromosome 11 abnormalities</td>
</tr>
<tr>
<td>PAX3/FKHR and PAX7/FKHR fusion transcripts uncommonly present</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Botryoid Variant of Embryonal RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>deletion of short arm of chromosome 1</td>
</tr>
<tr>
<td>trisomies of chromosomes 13 and 18e</td>
</tr>
</tbody>
</table>

Spindle Cell RMS no data regarding cytogenetic abnormalities

<table>
<thead>
<tr>
<th>Alveolar RMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(2;13)(q36;q14) translocation - majority of cases</td>
</tr>
<tr>
<td>t(1;13)(p36;q14) translocation - minority of cases</td>
</tr>
<tr>
<td>PAX3/FKHR fusion transcript (80-90% of cases)</td>
</tr>
<tr>
<td>PAX7/FKHR fusion transcript (10-20% of cases)</td>
</tr>
</tbody>
</table>
Table 5: Clinical Staging of RMS*

**Group I**
Localized disease, completely resected (regional nodes not involved)
Confined to muscle or site/organ of origin
Contiguous involvement with infiltration outside the muscle or organ of origin, as through fascial planes

**Group II**
Grossly resected tumor with microscopic residual disease
No evidence of gross residual tumor; no evidence of regional nodal involvement
Regional disease completely resected
Regional disease with involved nodes, grossly resected but with evidence of microscopic residual disease

**Group III**
Incomplete resection or biopsy with gross residual disease

**Group IV**
Distant metastatic disease at presentation

*Intergroup Rhabdomyosarcoma Studies Classification

---

Table 6: TNM Staging for RMS*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
<th>Tumor</th>
<th>Size</th>
<th>Node</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Orbit, head and neck, GU</td>
<td>T1 or T2</td>
<td>≤5 cm; &gt;5 cm</td>
<td>N0 or N1 or Nx</td>
<td>M0</td>
</tr>
<tr>
<td>2</td>
<td>Bladder, prostate, extremity, cranial parameningeal sites, other (trunk, retroperitoneum)</td>
<td>T1 or T2</td>
<td>≤5 cm</td>
<td>N0 or Nx</td>
<td>M0</td>
</tr>
<tr>
<td>3</td>
<td>Bladder, prostate, extremity, cranial parameningeal sites, other (trunk, retroperitoneum)</td>
<td>T1 or T2</td>
<td>≤5 cm; &gt;5 cm; N1 N0 or N1 or Nx</td>
<td>M0 M0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>All</td>
<td>T1 or T2</td>
<td>≤5 cm; &gt;5 cm</td>
<td>N0 or N1</td>
<td>M1</td>
</tr>
</tbody>
</table>

GU = genitourinary excluding bladder and prostate;
T1 = confined to anatomic site; T2 = extension and/or fixation to surrounding tissues;
N0 = regional lymph nodes not clinically involved; T1 = regional lymph nodes clinically involved; Nx – status of regional lymph nodes unknown
M0 = no distant metastasis; M1 = distant metastasis

*Intergroup Rhabdomyosarcoma Studies Classification

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Table 7: Favorable and Unfavorable Factors for RMS

<table>
<thead>
<tr>
<th>Prognostically Favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants and children</td>
</tr>
<tr>
<td>Orbital or genitourinary location (non-bladder or prostate)</td>
</tr>
<tr>
<td>Small size (less than 5 cm)</td>
</tr>
<tr>
<td>Botryoid or spindle cell type</td>
</tr>
<tr>
<td>Localized noninvasive tumor without regional lymph node</td>
</tr>
<tr>
<td>involvement or distant</td>
</tr>
<tr>
<td>Metastasis</td>
</tr>
<tr>
<td>Complete initial resection</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prognostically Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>Location in head and neck (nonorbital), paraspinal region,</td>
</tr>
<tr>
<td>abdomen, biliary tract, retroperitoneum, perineum or extremities</td>
</tr>
<tr>
<td>Large size (greater than 5 cm)</td>
</tr>
<tr>
<td>Alveolar (especially PAX3/FKHR fusion transcript positive) or</td>
</tr>
<tr>
<td>pleomorphic type</td>
</tr>
<tr>
<td>Local tumor invasion especially parameningeal or paraspinal</td>
</tr>
<tr>
<td>region, paranasal sinuses, or skeleton</td>
</tr>
<tr>
<td>Local recurrence whether during or not during therapy</td>
</tr>
<tr>
<td>Regional lymph node or distant metastasis</td>
</tr>
<tr>
<td>Incomplete initial resection or unresectability</td>
</tr>
</tbody>
</table>

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**Sinonasal Undifferentiated Carcinoma**


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Rhabdomyosarcoma


Case 3: Jugulotympanic Paraganglioma

Paragangliomas are benign neuroendocrine tumors arising from the neural crest-derived paraganglia of the autonomic nervous system. Paragangliomas can be divided into sympathetic and parasympathetic. Sympathetic paragangliomas arise from the adrenal medulla (pheochromocytomas), extra-adrenal sympathetic paraganglia and visceral autonomic paraganglia. Parasympathetic paraganglia are found throughout the body and give rise to almost all of the paragangliomas of the upper aerodigestive tract. Extra-adrenal paragangliomas are identified throughout the body are classified based on the anatomic site of occurrence. Paragangliomas in the head and neck region include carotid body, jugulotympanic, vagal, laryngeal, nasal and orbital paragangliomas. The most common site of occurrence in the head and neck is the carotid body followed by the jugulotympanic region.

Clinical

The jugulotympanic paragangliomas (JTP) are benign neoplasms arising from the paraganglia specifically located in the middle ear or temporal bone region. Synonyms include glomus jugulare tumor and glomus tympanicum tumor. JTP are considered the most common tumor of the middle ear. JTP are more common in women than in men and are most common in the 5th to 7th decades of life. JTP occur in one of three locations: 1) in the adventitia of the jugular vein where they are referred to as glomus jugulare tumor; 2) associated with the posterior auricular branch of the vagus nerve also known as Arnold's nerve; and 3) along the tympanic branch of the glossopharyngeal nerve also known as Jacobson's nerve. JTP located in association with either Arnold's or Jacobson's nerves are referred to as glomus tympanicum tumor. The majority of the JTP arise in the jugular bulb (85%) leading to a mass lesion in the middle ear or external auditory canal, approximately 12% take origin from Jacobson's nerve presenting as a middle ear tumor and approximately 3% arise from Arnold's nerve originating in the external auditory canal. The most common symptom associated with JTP is conductive hearing loss; other symptoms include tinnitus, fullness, otic discharge, pain, hemorrhage, facial nerve abnormalities and vertigo. Functioning JTP, as evidenced by endocrinopathic manifestations, occur but are extremely uncommon.

JTP are often locally invasive neoplasms with extension into and destruction of adjacent structures, including the temporal bone and mastoid. The histologic appearance does not necessarily correlate to the biologic behavior of the tumor; neurologic abnormalities including cranial nerve palsies, cerebellar dysfunction, dysphagia and hoarseness may be seen and correlate to the invasive capabilities of this neoplasm. The radiologic appearance includes a soft tissue mass often with evidence of extensive destruction of adjacent structures as seen by CT scan or MRI, and a vascularized lesion fed by branches of nearby large arteries as depicted by carotid angiography.
Functioning paragangliomas of the head and neck region with elevated catecholamine levels are rare. Paragangliomas, particularly the carotid body tumor may be familial inherited as an autosomal dominant pattern. In this setting they are often bilateral or multiple (30-33%) and associated with paragangliomas of other sites. Familial paragangliomas more frequently may be hormonally active as compared with sporadically occurring paragangliomas. On rare occasion, extra-adrenal paragangliomas may occur as a component of Carney’s syndrome (gastric epithelioid leiomyosarcoma, pulmonary chondroma and functioning extra-adrenal paraganglioma). The extra-adrenal paragangliomas in Carney’s syndrome may be carotid body tumors, jugulotympanic paragangliomas or thyroid paragangliomas.

Pathology

The clinical or gross appearance of JTP contrasts with that of other paragangliomas particularly carotid body tumors (CBT). CBT are encapsulated, ovoid, rubbery, red-pink to tan-gray tumor of varying size. JTP are red, friable mass identified behind an intact tympanic membrane or within the external auditory canal measuring from a few millimeters to a large mass completely filling the middle ear space. Typically, paragangliomas bleed profusely on manipulation.

Irrespective of the site of origin, the histologic appearance of all extra-adrenal paragangliomas is the same. The hallmark histologic feature is the presence of a cell nest or “zellballen” pattern. The stroma surrounding and separating the nests is composed of a prominent fibrovascular tissue. While this pattern is characteristic of paragangliomas it is not unique to paragangliomas and can be seen in other tumors, such as all types of other neuroendocrine tumors, including carcinoid and atypical carcinoid tumors, as well as in melanomas and carcinomas. Paragangliomas are predominantly composed of chief cells, which are round or oval cells with uniform nuclei, dispersed chromatin pattern and abundant eosinophilic, granular or vacuolated cytoplasm. The sustentacular cells, represent modified Schwann cells, are located at the periphery of the cell nests as spindle-shaped, basophilic appearing cells but are difficult to identify by light microscopy. Cellular and nuclear pleomorphism can be seen but these features are not indicative of malignancy. Mitoses and necrosis are infrequently identified. Paragangliomas lack glandular or alveolar differentiation.

Paragangliomas are often readily identified by light microscopic evaluation. However, in certain instances paragangliomas may be difficult to differentiate from other tumors that have similar histomorphologic features. Not infrequently, middle ear and temporal paragangliomas do not show the characteristic cell nest appearance as occurs in other sites. This Aloss@ of the organoid growth may be artifactually induced by surgical manipulation (Asqueezing@) of the tissue during removal. The absence of the typical growth pattern may result in diagnostic confusion with other middle ear tumors. Histochemical stains may be of assistance in the diagnosis paragangliomas. Reticulin staining may better delineate the cell nest growth pattern with staining of the fibrovascular cores surrounding the neoplastic nests. In addition, the tumor cells are argyrophilic (Churukian-Schenk). Argentaffin (Fontana), mucicarmine and periodic acid-Schiff stains are negative.

The diagnosis of paragangliomas is facilitated by immunohistochemical stains. The immunohistochemical antigenic profile of paragangliomas includes chromogranin,
synaptophysin, neuron specific enolase positivity in the chief cells and S-100 protein staining localized to the peripheral located sustentacular cells. In general, epithelial markers, including cytokeratin, as well as HMB-45 and mesenchymal markers (desmin and other markers of myogenic differentiation) are negative. Rare examples of cytokeratin reactive paragangliomas have been reported. Vimentin is variable reactive in both the chief cells and sustentacular cells. Ultrastructural evaluation shows the presence of neurosecretory granules.

Treatment and Prognosis

For all paragangliomas, surgical excision is the treatment of choice. The prognosis is excellent following complete resection. While these tumors are overwhelmingly benign and behave in an indolent manner, recurrence may occur up to 20 percent of CBT and 29 percent of JTP. Recurrence may be more a function of inadequate excision rather than of malignancy. The prevalence of malignancy varies according to site. Up to approximately 13 percent of CBT are malignant, from < 1 to 25 percent of JTP are malignant and from 7 to 16 percent of vagal body paragangliomas are malignant. The histologic criteria for malignancy includes the presence of increased mitotic activity, necrosis usually seen within the center of the cell nests and vascular space invasion. However, these histologic features can also be identified in benign paragangliomas. Further, paragangliomas without histologic features of malignancy may be locally invasive, and in areas such as the skull base, these benign paragangliomas may invade vital structures resulting in the death of the patient. Malignancy in any paraganglioma should be determined by the presence of metastasis to regional lymph nodes and/or to distant sites. The more common sites for distant spread include to the lungs and bone.

JTP are slow-growing tumors but may be locally invasive with extension into and destruction of adjacent structures, including the temporal bone and mastoid. Intracranial extension may occur in up to 15% of cases. Neurologic abnormalities, including cranial nerve palsies, cerebellar dysfunction, dysphagia and hoarseness may be seen and correlate to the invasive capabilities of this neoplasm. Malignant JTP occur, are associated with histologic criteria of malignancy and may metastasize to cervical lymph nodes, lungs and liver. For JTP, the location and invasive nature of these lesions often preclude the capability of complete surgical eradication, and in such cases, radiotherapy is a useful adjunct to surgery. Radiotherapy results in a decrease or ablation of vascularity and promotes fibrosis. Preoperative embolization has been advocated as useful to decrease the vascularity of paragangliomas and allow for safer surgery. Although JTP are slow growing neoplasms, the prognosis is guarded as they often infiltrate and invade adjacent structures. While malignancy is rare, these neoplasms may result in increased morbidity and mortality as a result invasion of vital structures (cranial cavity).

Differential Diagnosis includes middle ear adenoma (with or without neuroendocrine differentiation), acoustic neuroma and meningioma.
Middle Ear Adenoma (MEA)

Clinical

MEA is a benign glandular neoplasms originating from the middle ear mucosa. MEA occurs equally in both genders and occur over a wide age range but are most common in the 3rd-5th decades of life. MEAs are found in any portion of the middle ear may be affected including the Eustachian tube, mastoid air spaces, ossicles and chorda tympani nerve. The most common symptom is unilateral conductive hearing loss but fullness, tinnitus and dizziness may also occur. Pain, otic discharge and facial nerve paralysis rarely occur and, if present, may be indicative of a malignant process. Otoscopic examination in the majority of cases will identify an intact tympanic membrane with tumor confined to the middle ear space with possible extension to the mastoid. Occasionally, the adenoma will perforate through the tympanic membrane with extension into and presentation as an external auditory canal mass. There are no known etiologic factors related to the development of MEA. MEAs are not associated with a prior history of chronic otitis media. Concurrent cholesteatomas may be seen with MEA but there is no known association between these two lesions.

Pathology

MEA are gray-white to red-brown, rubbery to firm mass free of significant bleeding on manipulation. Histologically, MEAs are unencapsulated lesions with glandular or tubule formation, as well as solid, sheetlike, trabecular, cystic and cribriform growth patterns. Rarely, MEAs may show a predominant papillary growth. The neoplastic glands occur individually or have back-to-back growth. The glands are composed of a single layer of cuboidal to columnar cells with a varying amount of eosinophilic cytoplasm and a round to oval hyperchromatic nucleus. Nucleoli may be seen and are generally eccentrically located. The cells may have a prominent plasmacytoid appearance, particularly evident in the more solid areas of growth but also in the cells forming the glandular structures. A paranuclear clear zone is not present. Often, adjacent to or intimately admixed with the glands is a more solid or sheetlike growth of similar appearing neoplastic cells. The cells may have a more dispersed or stippled nuclear chromatin with the “salt and pepper” pattern suggestive of neuroendocrine differentiation. Cellular pleomorphism may be prominent but mitoses are uncommon. The stromal component is sparse and may appear fibrous or myxoid.

Histochemical stains show the presence of intraluminal but not intracytoplasmic mucin-positive material. Periodic acid-Schiff (PAS) positive material is not present. By immunohistochemical evaluation, the neoplastic cells are cytokeratin positive but are not reactive with chromogranin, synaptophysin, S-100 protein, desmin, actin or vimentin. Some MEA may have immunoreactivity with one or more neuroendocrine markers, including chromogranin and synaptophysin. These MEA with neuroendocrine differentiation have been termed carcinoid tumors of the middle ear. However, these “carcinoid tumors” are better viewed as part of the histologic spectrum of MEA, albeit one with neuroendocrine differentiation, rather than representing a distinct middle ear neoplasm separate from MEA.
Treatment and Prognosis

The treatment for all MEA is complete surgical excision. Surgery may be conservative if the lesion is small and confined to the middle ear or more radical (mastoidectomy) for larger lesions associated with more extensive structural involvement. Recurrent tumor may occur and is a function of inadequate excision. Some MEA may be locally aggressive and rarely may invade vital structures causing death but metastatic disease does not occur. In general, the clinical, radiologic and pathologic findings are indicative of a benign tumor. Nevertheless, the histologic appearance is not always predictive of the clinical behavior.

Differential Diagnosis

MEA should be differentiated from glandular metaplasia that may occur in the setting of chronic otitis media (COM). These metaplastic glands may be misdiagnosed as neoplastic. In contrast to MEA, the glandular proliferation in COM is focal or haphazardly arrayed and occurs in the presence of histologic features of COM, including chronic inflammation with fibrosis and calcifications (tymanosclerosis). MEA may perforate the tympanic membrane and appear to represent a neoplasm of the external auditory canal, such as a ceruminal gland adenoma. The histologic features of these two tumor types are distinctly different and should allow for easy distinction. In contrast to the rare middle ear adenocarcinoma, MEA lack marked cellular pleomorphism, increased mitotic activity, necrosis or invasion of bone and other soft tissue structures.

Acoustic Neuroma (AN)

Clinical

AN is a benign neoplasm that originates from Schwann cells specifically from the VIIIth cranial nerve. Synonyms include neurilemmoma, acoustic Schwannoma and benign peripheral nerve sheath tumor. AN accounts for up to 10% of all intracranial neoplasms and represent up to 90% of all cerebellopontine angle tumors. AN are more common in women than in men and may affect any age but are most common in the 4th-7th decades of life. The majority of AN involve the superior or vestibular portion of the VIIIth nerve as compared with involvement of the cochlear portion of the VIIIth nerve. Symptoms include progressive (sensorineural) hearing loss, tinnitus and loss of equilibrium; with progression the tumor enlarges and may compress adjacent cranial nerves (V, VII, IX, X, XI), the cerebellum and the brainstem leading to facial paresthesia and numbness, headaches, nausea, vomiting, diplopia and ataxia. Up to 8% of ANs may be bilateral. Bilaterality of ANs may represent a potential indicator of neurofibromatosis type 2. Symptoms of neurofibromatosis may be seen in up to 16% of patients and those with neurofibromatosis who develop AN generally are symptomatic at an earlier age (2nd decade). The radiologic appearance of AN include flaring, asymmetric widening or erosion of the internal auditory canal by CT or MRI. Tumors as small as 1 cm or less are capable of being detected by CT or MRI analysis.

Pathology

The gross appearance of AN includes a circumscribed, tan-white, rubbery to firm mass which may appear yellow and have cystic change. Tumor sizes range from a few
millimeters up to 4-5 cm in greatest diameter. Histologically, the tumors are unencapsulated and similar in appearance to benign Schwannomas of all other locations. The cellular component includes elongated and twisted nuclei with indistinct cytoplasmic borders. The cells are arranged in short, interlacing fascicles and whirling or palisading of nuclei may be seen. Nuclear palisading with nuclear alignment in rows called Verocay bodies can be seen. The cellularity may vary and some benign Schwannomas can be very cellular (so-called cellular Schwannoma). Mitoses are usually sparse in number, and cellular pleomorphism with hyperchromasia can be identified but are not features of malignancy. Retregressive changes, including cystic degeneration, necrosis, hyalinization, calcification and hemorrhage may be seen. Schwannomas have prominent vascularity composed of large vessels with thickened (hyalinized) walls.

Immunohistochemical shows the presence of diffuse and intense S-100 protein reactivity. There is no immunoreactivity with cytokeratin or the neuroendocrine markers chromogranin and synaptophysin.

Treatment and Prognosis
Complete surgical excision is the treatment of choice. Complete removal usually is curative. AN may result in death secondary to herniation of the brainstem in untreated and/or large neoplasms. Malignant AN are exceedingly rare and, if present, neurofibromatosis should be suspected.

Meningioma

Clinical
Meningiomas are benign neoplasms arising from arachnoid cells forming the arachnoid villi seen in relation to the dural sinuses. Meningiomas represent from 13-18% of all intracranial tumors and are the second most common tumor to AN of the cerebellopontine angle. Meningiomas are more common in women than in men and are most commonly seen in the 5th decade of life. Meningiomas infrequently occur in children. The occurrence of a meningioma outside the central nervous system is considered ectopic and can divided into those meningiomas with no identifiable CNS connection (primary) and those with CNS connection (secondary). The development of primary meningiomas in the middle ear and temporal bone result either direct extension or from the presence of arachnoid cells ectopically located. The most common sites of occurrence of the ‘ectopically’ located meningiomas is the head and neck region, specifically the middle ear and temporal bone, including the internal auditory canal, jugular foramen, geniculate ganglion, roof of the Eustachian tube, sulcus of the greater petrosal nerve). The clinical presentation of middle ear meningiomas includes progressive hearing loss, loss of equilibrium, headaches, cerebellar dysfunction and cranial nerve abnormalities. Patients with neurofibromatosis have an increased incidence of developing a meningioma. In addition, patients with neurofibromatosis also experience increased incidence of multiple, separate occurring meningiomas in intra- and extracranial meningiomas. Radiologic findings include a soft tissue mass with variable vascularity. A pathognomonic feature for meningioma in this location is the presence of speckled calcification in a soft tissue mass.
Pathology

The histologic features of middle ear and temporal bone meningioma are similar to their intracranial counterparts. The immunohistochemical antigenic profile of meningiomas include reactivity with epithelial membrane antigen (EMA) and vimentin. In contrast with middle ear adenomas, meningiomas are generally non-reactive with cytokeratin and in contrast to jugulotympanic paragangliomas, meningiomas are nonreactive with neuroendocrine markers (e.g., chromogranin and synaptophysin).

Treatment and Prognosis

Complete surgical excision is the treatment of choice and is curative. Local recurrence relates to inadequate excision. Malignant change rarely, if ever, occurs. A diagnosis of middle ear meningioma should be made only after clinical evaluation is made to exclude secondary extension from an intracranial neoplasm.

Endolymphatic Sac Papillary Tumor

Clinical

The endolymphatic sac papillary tumor (ESPT) is an uncommon but distinct neoplasm possibly representing a manifestation of von Hippel-Lindau (VHL) syndrome. ESPT has been referred to by a variety of names, including adenoma of endolymphatic sac, adenoma/adeno carcinoma of temporal bone or mastoid, low-grade adenocarcinoma of probable endolymphatic sac origin, papillary adenoma of temporal bone, aggressive papillary tumor of temporal bone, aggressive papillary middle ear tumor, and more recently as the Heffner tumor. An endolymphatic sac origin for these tumors is supported by a combination of findings, including the early clinical manifestations of vestibular disease (e.g., sensorineural hearing loss, tinnitus and episodic vertigo), radiographic features showing the tumor to grow in the region site where the endolymphatic sac is located (i.e., posterior-medial petrous ridge), intraoperative identification of an in situ tumor originating from within the endolymphatic sac, and morphologic similarities and shared immunohistochemical and ultrastructural features of the tumor with the normal endolymphatic sac epithelium. The diagnosis of this tumor is based on clinical, radiographic and pathologic correlation. A diagnosis of ESPT should prompt the clinician to exclude the possibility that the patient has von Hippel-Lindau syndrome.

Pathology

The histopathologic appearance of ESPT is quite variable. ESPTs are papillary and focally cystic tumors. The papillary structures are generally not complex in their growth. The neoplastic cells vary in appearance from flattened or attenuated appearing cells to columnar appearing cells. Most often there is only a single row of cells. Occasionally, the surface epithelial cells may have the appearance suggesting a double layer of cells (epithelial and myoepithelial), however, the ‘outer’ row of cells, in all probability, represent a stromal element as they have not been shown to be immunoreactive with epithelial markers. The epithelial cells have uniform nuclei that are usually situated either in the center of the cells or toward the luminal aspect, and have a pale eosinophilic to clear appearing cytoplasm. The latter may predominate in any given tumor. Cell borders may be seen but, not infrequently, the
neoplastic cells lack a distinct cell membrane. In some cases, there are hypercellular areas
with crowded, variably-sized cystic glandular spaces that contain eosinophilic (colloid-like)
material. The latter appear remarkably similar to thyroid tissue. In all cases, pleomorphism is
minimal, and mitotic activity and necrosis are rarely present.

A granulation tissue reaction is seen in association with the neoplastic cells and
includes small vascular spaces lying in close proximity to the surface epithelium and/or within
the stroma of the papillary fronds. Due to the absence of a distinct cell membrane around the
neoplastic cells, a sharp demarcation separating the neoplastic cells from the subjacent
granulation tissue is not present. This appearance may create diagnostic confusion so that
the neoplastic proliferation is not appreciated, and the entire process is viewed as reactive.
This interpretation is further enhanced by the presence in the stroma of a mixed inflammatory
cell infiltrate, fibrosis, vascular proliferation, fresh hemorrhage and/or hemosiderin (within the
neoplastic cells or within macrophages), cholesterol granulomas and dystrophic calcification.
The latter does not include laminated calcific concretions (psammomatoid bodies).

Intracytoplasmic diastase-sensitive, periodic acid-Schiff (PAS) positive material can
be seen. The colloid-like luminal material stains strongly with periodic acid Schiff (PAS) with
and without diastase digestion. Intra-cytoplasmic and intraluminal mucin staining is rarely
positive. Iron stains are positive. ELSTs are diffusely cytokeratin positive and also show
variable reactivity with epithelial membrane antigen (EMA), S-100 protein, vimentin, neuron
specific enolase (NSE), glial fibrillary acidic protein (GFAP), Ber-EP4, synaptophysin and
Leu-7. Thyroglobulin immunoreactivity is not seen. Ultrastructurally, ELST shows the
presence of intercellular junctional complexes, microvilli, basement membrane material,
rough endoplasmic reticulum and intracytoplasmic glycogen and secretory granules.

Treatment and Prognosis

Radical surgery, including mastoidectomy and temporal bone resection that may
necessitate sacrifice of cranial nerves is the treatment of choice, and is potentially curative.
Local recurrence will result following inadequate surgical removal; operative morbidity may
be high. Despite its relatively slow-growth, these neoplasms are capable of widespread
infiltration and destruction, and may be lethal. The prognosis is dependent on the extent of
disease and the adequacy of resection. Earlier detection when the tumors are relatively
small and confined may decrease the operative-associated morbidity and be curative.

Differential Diagnosis

The differential diagnosis includes middle ear adenoma. However, the clinical,
radiographic and pathologic features that are unique to ESPT should allow for its distinction
from middle ear adenoma. The same would apply for the other common neoplasms of the
middle ear and temporal bone. The differential diagnosis also includes choroid plexus
papilloma and metastatic carcinoma of thyroid gland or renal origin. Choroid plexus
papillomas are intracranial (i.e., intraventricular) tumors with histologic features different
from that of ESPT. The absence of thyroglobulin reactivity would differentiate ESPT from
metastatic thyroid papillary carcinoma. Metastatic renal cell carcinoma would not have the
immunohistochemical antigenic features seen in ESPT.
Immunohistochemical Reactivity of Middle Ear Neoplasms**

<table>
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<th></th>
<th>CK</th>
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<th>SYN</th>
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<td>RMS</td>
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</tbody>
</table>

MEA – middle ear adenoma; NE – neuroendocrine features; JTP – jugulotympanic paraganglioma; MEN – meningioma; AN – acoustic neuroma; ELSPT – endolymphatic sac papillary tumor; RMS – rhabdomyosarcoma; CK - cytokeratin; EMA - epithelial membrane antigen; CG - chromogranin; SYN - synaptophysin; NSE - neuron specific enolase; GFAP - glial fibrillary acidic protein; VIM - vimentin; DES - desmin; + = positive; - = negative; +/- = variably positive

* - positive in the peripherally situated sustentacular cells

References

General References

Jugulotympanic Paragangliomas


Middle Ear Adenomas


Acoustic Neuromas


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**Meningioma**


**Endolymphatic Sac Papillary Tumor**


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**Case 4: Infectious Mononucleosis (IM)**

**Definition:** Infectious mononucleosis (IM) is a systemic, benign, self-limiting infectious lymphoproliferative disease primarily caused by but not limited to the Epstein-Barr virus (EBV) infection.

**Clinical**

EBV is a DNA virus that is a member of the Herpesviridae family. The virus penetrates the nasopharyngeal epithelium and infects B lymphocytes. The EBV infected B-cells proliferate and elicit humoral and cellular immune responses.

IM may occur in all age groups but primarily affects adolescents and young adults. There is no gender predilection. EBV is estimated to cause from 80 to 95% of the cases of infectious mononucleosis. The clinical presentation of EBV-associated IM includes acute pharyngotonsillitis with patients experiencing sore throat, fever, malaise, and cervical or generalized lymphadenopathy. In addition, hepatosplenomegaly with chemical evidence of hepatitis may represent the systemic manifestations of the disease. Pharyngotonsillitis is often severe and may be exudative; markedly enlarged tonsils may result in upper airway obstruction. The lymphadenopathy commonly affects posterior cervical lymph nodes but both anterior and posterior nodes may be involved. A prodromal period of from 2 to 5 days consists of malaise and fatigue and frequently occurs prior to the onset of the full syndrome.

The diagnosis of infectious mononucleosis is established in a patient with typical clinical presentations and appropriate laboratory findings; tissue confirmation of the diagnosis is usually not required. It is in the atypical case where the patient presents with adenotonsillar and/or lymph node enlargement without fever, sore throat or splenomegaly that a biopsy may be needed in order to establish a diagnosis and rule out a malignant process.

Laboratory findings in IM include:

- absolute lymphocytosis with >50% lymphocytes in a total leukocyte population of >5000/mm3;
- prominent atypical lymphocytes (Downey cells) which are often >10% of the total leukocyte count; the atypical lymphocytes in the peripheral blood include both activated B- and T-cells but are thought to represent mostly activated T-lymphocyte populations in response to B cell infection;
- mild to moderate elevations of liver enzymes, including aspartate and alanine aminotransferase;
- diagnosis can be confirmed by the demonstration of serum antibodies to horse red cells (positive Mono-Spot test) or sheep erythrocytes (positive Paul-Bunnell heterophile antibody test).

Other microorganisms associated with mononucleosis-like syndromes include: cytomegalovirus (CMV), Toxoplasma gondii, rubella, hepatitis A virus and adenoviruses. Human herpes virus 6 (HHV-6) is among the most widespread of the human herpes viruses. In immunocompetent children, it causes exanthem subitum, febrile episodes without skin rash, and non-Epstein-Barr and non-cytomegalovirus infectious mononucleosis. In patients with IM exhibiting the typical clinical presentation and hematologic findings but who are heterophile antibody negative, the most likely agents are EBV and CMV; the non-EBV infectious agents causing infectious mononucleosis are not associated with a positive heterophile antibody test and Mono-Spot test. Patients who consistently prove to be heterophile antibody or Mono-Spot negative, serodiagnosis is invaluable and includes:
- an appreciable serum response to EBV viral capsid antigen (VCA) with both IgM and IgG antibodies at the time of clinical presentation;
- at presentation or shortly thereafter, many infected patients will develop antibodies to early antigen complex (EA);
- during the early phase of primary infection, antibodies to EBV nuclear antigens (EBNA) are usually not demonstrable;
- IgM antibodies to VCA disappear within 2-3 months following infection; antibodies to EA disappear within 2-6 months following infection; IgG antibodies to VCA and anti-EBNA antibodies persist for life and are indicative of a chronic carrier state.

The heterophile antibody test and EBV-specific antibody tests remain the principal means of diagnosis of initial infection in otherwise healthy patients. Enzyme-linked immunosorbotent assays have replaced the traditional immunofluorescence assays for EBV-specific antibodies. Several newer molecular diagnostic tests have become available that facilitate accurate monitoring of infection. The role of these tests for patients with uncomplicated infectious mononucleosis is limited, although these tests are being increasingly used to monitor the state and level of EBV replication for severe infections and among immunocompromised patients.

In immune deficient patients (e.g., post-transplantation, AIDS, congenital X-lined lymphoproliferative disorders) EBV infection may result in life-threatening diseases rather than the self-limited form of IM seen in the immuno competent person. Such diseases include fatal IM, post-transplant lymphoproliferative disorders and hematolymphoid malignancies.

Pathology

Gross

Moderate to severe pharyngitis may be seen characterized by marked swollen and enlarged tonsils covered by dirty gray exudates. Tender lymphadenopathy particularly of the posterior cervical lymph nodes occurs.
Microscopic

At low magnification there is distortion and/or partial effacement of the nodal/tonsillar architecture with reactive follicular hyperplasia characterized by enlarged and irregularly-shaped germinal centers. There is expansion of the interfollicular areas with polymorphous proliferation of small lymphocytes, transformed lymphocytes, immunoblasts, plasma cells, and Reed-Sternberg-like cells imparting a mixed pattern of lymphoid hyperplasia. The lymphocytic and immunoblastic proliferation often displays marked cytologic atypia with one or more prominent nucleoli, increased mitotic activity and phagocytosis. The immunoblasts may cluster or occasionally form sheets effacing portions of the tissue simulating a malignant lymphoma; immunoblasts may occasionally be binucleate simulating the appearance of the Reed-Sternberg (RS) cells of Hodgkin lymphoma. In contrast to RS cells of Hodgkin lymphoma, those seen in IM lack the eosinophilia and inclusion-like appearance. Further, the cells that surround the RS-like cells of IM are activated T-cells or immunoblasts, which contrast to the small lymphocytes and eosinophils seen surrounding the RS cells of Hodgkin disease. The marked immunoblastic proliferation in the paracortical area results in a “moth eaten” or mottled appearance similar to other viral infections. Necrosis may be seen and is usually focal characterized by individual cell necrosis although larger confluent zones of necrosis may be present. IM-associated lymph node infarction may simulate the appearance of lymph node infarction associated with malignant lymphoma. A vascular proliferation with prominent endothelial cells is always present. In nodal involvement at least some subcapsular sinuses are patent and contain a polymorphous lymphoid infiltrate similar to the interfollicular infiltrate.

Immunohistochemical (IHC) studies show the immunoblasts of IM to be reactive for both B-cell (CD20, CD74, CDw75, CD79a) and T-cell markers (CD3, CD43, CD45RO1 [UCHL-1]). The RS-like cells of IM are CD15 (Leu M1) and CD30 (Ki-1) negative and positive for B-cell markers. RS cells of Hodgkin disease are CD15 and CD30 positive, and negative for B-cell markers. Immunoblasts may stain with CD30 but are CD15 negative. By IHC and in situ hybridization, immunoblasts and RS-like cells in IM express EBV antigens.

Molecular diagnostic evaluation shows an absence of gene rearrangements. PCR analysis shows detection of virus (generation of proteins containing EBV-encoded polypeptide sequences and represent a more reliable and sensitive means for detecting the presence of virus than serodiagnosis). Molecular testing is increasingly important in the diagnosis and monitoring of patients affected EBV infection. In biopsy tissues, molecular detection of EBV-encoded RNA transcripts by in situ hybridization remains the gold standard for proving that a histopathological lesion is EBV-related. EBV-encoded RNA hybridization and EBV LMP1 immunostains are used routinely to detect latent EBV in tissues affected by post transplant lymphoproliferative disorder (PTLD) or in enlarged nodes from patients with infectious mononucleosis. Traditional serology is the best test for evaluating acute versus remote infection in healthy individuals. High serological titers serve as a tumor marker for some EBV-related malignancies, but titers are not a dependable tumor marker in immunocompromised hosts.

Differential Diagnosis

The differential diagnosis of infectious mononucleosis includes non-Hodgkin malignant lymphomas especially of large cell or immunoblastic lymphoma (B-cell lineage)
and Anaplastic CD30+ large cell lymphoma; 2) Hodgkin disease; 3) HIV-associated changes (see later in chapter).

The markedly atypical interfollicular cellular proliferation can easily be misinterpreted as a non-Hodgkin lymphoma. Attention to the clinical history especially the relatively typical demographics associated with IM should at least alert the pathologist to the possibility of this diagnosis. Confirmatory laboratory analysis and absence of immunohistochemical and/or molecular biologic confirmation of a neoplastic process assist in avoiding the potential trap of misdiagnosing IM for a lymphoma. Anaplastic CD30+ large cell lymphoma is characterized by the presence of large cells with highly pleomorphic (RS-like) nuclei forming solid/cohesive sheets in the paracortical area and sinuses; these cells are strongly reactive for CD30 and are positive for anaplastic lymphoma kinase (ALK) protein and epithelial membrane antigen. Such findings are not identified in IM. Primary Hodgkin lymphoma of the tonsils and/or mucosal sites of the upper aerodigestive tract is exceedingly rare; when Hodgkin disease involves these sites it usually does so secondarily following primary nodal disease.

**Treatment and Prognosis**

Infectious mononucleosis is associated with a favorable clinical course often with resolution of symptoms over a period of several months. Therapy is supportive, including rest and fluid intake. Antiviral therapy has a limited, short-term effect on oropharyngeal shedding but has proven ineffective for the clinical manifestations of infectious mononucleosis. Corticosteroids may have a role in hastening resolution of some complications, especially upper airway obstruction and possibly immune-mediated anemia and thrombocytopenia, but should be used judiciously. Tonsillectomy may be required in patients with severe airway obstruction.

Unusual complications associated with IM include hemophagocytic syndrome, hemolytic uremic syndrome, life threatening thrombocytopenia, severe gastritis, CNS infections, interstitial nephritis. Rarely, serious and potentially fatal complications may develop and include airway obstruction and splenic rupture, the latter secondary to splenic involvement with massive splenomegaly, fatal fulminate hepatitis with hepatic failure, diffuse pneumonia with acute respiratory failure progression to fatal malignancies; Epstein-Barr virus is a tumorigenic herpes virus. EBV-associated malignancies occur in immunocompetent and immunocompromised patients and may include hematologic malignancies such as non-Hodgkins lymphomas (B-cell and T-cell), Hodgkin disease, nasopharyngeal carcinoma and other epithelial malignancies (breast, gastric, lung, prostate), smooth muscle tumors and gastric carcinoma.

**References**

**Infectious Mononucleosis**


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Walter RB, Hong TC, Bachli EB. Life-threatening thrombocytopenia associated with acute Epstein-Barr virus infection in an older adult. Ann Hematol 2002;81:672-5.


Case 5: Spindle cell squamous carcinoma.

Spindle Cell Squamous Carcinoma

Spindle cell squamous carcinoma (SCSC) is defined as a tumor composed of conventional squamous cell carcinoma (in-situ or invasive carcinoma) associated with a malignant spindle cell stromal component. Synonyms: "Sarcomatoid" carcinoma,

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carcinosarcoma, pleomorphic carcinoma, metaplastic carcinoma, collision tumor, pseudosarcoma, Lane tumor.

Clinical

The overwhelming majority of SCSC occur in men (85%) most frequently in 6th-8th decades of life. SCSC can occur anywhere in the upper aerodigestive tract. The most common sites include: larynx (true vocal cords > false vocal cords and supraglottis) > oral cavity (lips, tongue, gingiva, floor of mouth, buccal mucosa) > skin > tonsil, pharynx and nasopharynx. Symptoms vary according to site: larynx - hoarseness, voice changes, airway obstruction, dysphagia; oral cavity or skin - mass or nonhealing sore with or without pain; sinonasal tract and nasopharynx - airway obstruction, pain, epistaxis, discharge, facial deformity, unilateral otitis media, orbital symptoms. There is no specific correlation with known risk factors (alcohol, tobacco or environment/occupation). SCSC has been reported in areas of prior irradiation. The histogenesis of the spindle cells is controversial as evidenced by the array of names given to this tumor. Epithelial derivation is supported by: intimate association with conventional squamous cell carcinoma; presence of cytokeratin immunoreactivity in the majority of cases and lack of immunoreactivity with other antibodies; despite the presence of heterologous elements, including malignant bone or cartilage, neither of these components have been reported to metastasize and in all probability represent a metaplastic phenomenon.

Pathology

SCSC often is a grossly polypoid or fungating mass commonly found in the larynx, hypopharynx, oral cavity and sinonasal tract. Variations in the gross appearance may correlate with the primary site of occurrence: larynx - polypoid or exophytic; sinonasal/nasopharynx - fungating and/or ulcerative. SCSC are firm, tan-white, gray or pink mass varying in size from 1 to 6 cm.

The histologic features define SCSC and include the identification of a malignant undifferentiated spindle cell proliferation and the presence of a conventional squamous cell component. The latter includes either in-situ squamous carcinoma or frankly invasive squamous carcinoma (typically keratinizing and of varying differentiation. The spindle cell component generally is the dominant cell type and varies from a bland to an overtly pleomorphic-appearing infiltrate. Its growth pattern varies including: fascicular, storiform or palisading and may include an associated myxomatous stroma. Generally, the spindle cell proliferation is hypercellular and pleomorphic with large, hyperchromatic nuclei, prominent nucleoli, many mitoses (typical and atypical), and multinucleated giant cells. Necrosis is not uncommon. The spindle cell proliferation may be sparsely cellular (hypocellular) with marked stromal collagenization (so-called collagenized SCSC), but nuclear pleomorphism and mitotic figures are still present. The growth pattern varies and includes fascicular, storiform or palisading; an associated myxomatous stroma may be present. Heterologous elements can be seen including bone and cartilage, which may in and of itself be malignant (chondroosarcomatous or osteosarcomatous foci).

The spindle cells are cytokeratin immunoreactive in the majority of cases but in up to 40% of cases may be cytokeratin negative. Cytokeratin staining may vary from focal to diffuse. Expression of vimentin and various myogenic markers (desmin, actins) have been
reported. S100 protein and HMB-45 are negative. Ultrastructurally in the majority of cases SCSC show evidence of epithelial derivation, including desmosomes, tonofilaments, macula adeherens. The histogenesis of the spindle cells is controversial as evidenced by the array of names given to this tumor.

Epithelial derivation is supported by the intimate association with conventional squamous cell carcinoma, and the presence of cytokeratin immunoreactivity in the majority of cases and lack of immunoreactivity with other antibodies. Despite the presence of heterologous elements, including malignant bone or cartilage, neither of these components have been reported to metastasize and in all probability represent a metaplastic phenomenon. Identical immunohistochemical p53 expression patterns in the epithelial and spindle cell components of SCSC supports the concept that these phenotypically divergent cell populations share similar developmental pathways and divests the concept that SCSC represents a reactive process or a collision tumor between epithelial and mesenchymal components.

Treatment and Prognosis
Surgery is the preferred therapy. Radiotherapy may be utilized as an adjunct to surgery but neither radiotherapy nor chemotherapy has merit as the sole therapeutic modality. The prognosis is dependent on the clinical stage but, in general, is considered poor. Polypoid lesions may behave less aggressively than flat, ulcerative tumors perhaps correlating with limited (superficial) invasion. Vocal cord lesions which manifest symptoms early in the disease course may have a better prognosis than SCSC arising in other sites (supraglottis, hypo- and nasopharynx) where symptoms occur only after the tumor has become large and extensively infiltrative. Metastatic disease primarily occurs to cervical lymph nodes and lung, and may include: 1) conventional squamous cell carcinoma alone, 2) spindle cell carcinoma alone or 3) both conventional and spindle cell squamous carcinoma.

Differential Diagnosis
The squamous cell component of SCSC may be limited requiring multiple sectioning for identification or it may be absent. The differential diagnosis includes: reactive myo- or fibroblastic proliferations, mucosal malignant melanoma and sarcomas including malignant fibrous histiocytoma, fibrosarcoma, malignant peripheral nerve sheath neoplasm, osteosarcoma, and chondrosarcoma. These sarcomas, while uncommon in relation to a mucosal surface of the head and neck region, do occur. In general, these tumors are deeply-seated in any given location and do not usually result in a polypoid mass protruding from a mucosal surface. As a rule, in the absence of any other confirmatory studies (i.e. immuno-histochemistry, electron microscopy), a malignant spindle cell neoplasm of a mucosal surface of the upper aerodigestive tract presenting as a polypoid lesion or identified in more superficial locations of the submucosa, should be considered as a SCSC. This is true even in the absence of a squamous carcinomatous component, the presence of heterologous matrix-producing elements, or in the absence of cytokeratin immunoreactivity.

Reactive and neoplastic lesions composed of myofibroblastic cells include nodular fasciitis-like lesions and inflammatory myofibroblastic tumors (IMT). These lesions are moderately cellular with a proliferation of spindle-shaped cells, but do not display a striking degree of nuclear pleomorphism. Mitotic figures may be encountered but atypical mitoses
are not seen. The findings of atypical mitoses should prompt consideration of a true malignancy. While the lesions are not encapsulated, they do not exhibit the insidious pattern of infiltration of adjacent tissues, which is characteristic of more aggressive lesions. The lesions may fill the submucosal region, abutting the basement membrane on which the mucosal epithelial cells are resting; however, the spindle cell proliferation does not infiltrate into the mucosal epithelial cells. Nevertheless, the overlying mucosa may appear atrophic in areas. These lesions are cytokeratin negative. In addition, the myofibroblastic cell component may be muscle specific actin (HHF35), smooth muscle actin, and vimentin positive. Recent evidence has shown the presence of anaplastic lymphoma kinase (ALK) gene rearrangements and expression in IMT indicating oncogenic ALK expression as an important mechanism in the pathogenesis of IMT and supports the concept that IMTs are neoplastic.

References

**Spindle Cell Squamous Carcinoma**


Sarcomas


Inflammatory Myofibroblastic Tumors


Case 6: Necrotizing Sialometaplasia (NS)

**Definition:** NS represents a benign, self-healing (reactive) inflammatory process of salivary gland tissue, which clinically and histologically may be mistaken for a malignant neoplasm.

**Synonym:** Adenometaplasia

**Clinical**

NS tends to affect men more than women and it occurs over a wide age range with the average age of occurrence in the 5th and 6th decades of life. NS most commonly involves the intraoral minor salivary glands particularly involving the palate. However, major salivary glands, as well as the minor salivary glands of virtually every site in the upper aerodigestive tract can be affected. The larynx may be affected but is a rare site of occurrence. The most common presenting problem is that of a painless ulcerated lesion or a nodular swelling, which is usually unilateral but may be bilateral. The lesions are usually asymptomatic but may be associated with pain, numbness or a burning sensation, and dysphagia. Uncommonly, NS may present with anaesthesia of the greater palatine nerves. The pathogenesis for NS is felt to be secondary to trauma and/or an ischemic event with compromise of the vascular supply to salivary glands leading to ischemic necrosis. The ischemia may be iatrogenically-induced following an operative procedures (surgery, post-
intubation, post-bronchoscopy), anesthesia or radiotherapy. There is a mean duration of 18 days from the time of the insult to the development of the lesion. In experimental studies on rat submandibular and sublingual glands, the induction of sialometaplasia occurred 6-8 days following arterial ligation. The inciting event is primarily but not exclusively thought to be due to ischemia. NS may occur de novo unassociated with a traumatic event or it may occur in association with other nonneoplastic lesions or in association with a neoplasm (benign or malignant).

Pathology

Gross

NS typical appears as a deep, crater-like ulcerative lesion measuring from 1-3 cm. However, the lesion may appear as a submucosal nodular swelling that may slough leaving a crater-like ulcer.

Histology

The histologic appearance is that of lobular necrosis of the salivary glands with preservation of the lobular architecture of the minor salivary glands. The histologic hallmark is squamous metaplasia of residual acinar and ductal elements. The necrotic lobules consist of acinus-sized pools of mucin, which may extend into adjacent tissue eliciting a granulation tissue reaction with associated acute and chronic inflammation. The lobular architecture is maintained and the metaplastic lobules vary slightly to moderately in size and shape, and have smooth edges surrounded by granulation tissue and an intense mixed acute and chronic inflammatory reaction. The squamous cells are bland in appearance with uniform nuclei and abundant eosinophilic cytoplasm with occasional preservation of ductal lumina or scattered mucocytes.

Mucicarminophilic material is seen within lumina and within the cytoplasm of residual mucocytes. With regeneration, mitoses, individual cell necrosis, enlarged nuclei and prominent nucleoli can be seen. Associated findings include ulcerated mucosa and pseudo-epitheliomatous hyperplasia (PEH). PEH results when the metaplastic lobules present in excretory ducts and merge with surface epithelium. This reaction may be so striking presenting a diagnostic nightmare in separation from an infiltrating squamous cell carcinoma.

Differential Diagnosis

The differential diagnosis for NS includes mucoepidermoid carcinoma, adenosquamous carcinoma and squamous cell carcinoma (Table). Retention of the overall lobular architecture, bland appearance of the squamous nests with rounded or smooth edges, and retention of residual ductal lumina and mucocytes help in differentiating NS from these malignant neoplasms.

Treatment and Prognosis

NS are self-limiting lesions, which heal by secondary intention. Depending on the size of the lesion, the healing process in most cases occurs from 3-12 weeks. Debridement and saline rinses may aid in the healing process. Recurrences do not usually occur.
Subacute necrotizing sialadenitis (SANS) is a nonspecific inflammatory condition of unknown etiology affecting oral minor salivary glands. While some authors believe that SANS should not be included within the spectrum of necrotizing sialometaplasia and most likely represents an infectious process or perhaps an immune response to an unknown allergen, other authors believe that SANS may represent the early or minimal form of NS. In either case, SANS most often is characterized by a localized palatal swelling, accompanied by an abrupt onset of pain. SANS most often affect intraoral sites, including the hard palate, soft palate, buccal mucosa and tonsils. The lesions typically are nonulcerated swellings, develop over a short period of time (7-10 days) and range in size from 0.3 to 2.5 cm in diameter. Patients range in age from 15 to 45 years, with a mean age of 21.9 years. Histopathologic features include diffuse involvement of minor salivary glands by lymphocytes, histiocytes, neutrophils, and variably by eosinophils. In addition, there is loss of acinar cells, early acinar cell necrosis surrounded by a dense polymorphous inflammatory infiltrate, and atrophy of ductal cells. Squamous metaplasia is not usually seen. SANS appears to be a self-limiting process with most cases resolving 2 to 3 weeks after biopsy without recurrences. The main differences from NS are smaller size of lesion, scarcity of ulceration, and absence of squamous metaplasia.

<table>
<thead>
<tr>
<th>NECROTIZING SIALOMETAPLASIA - DIFFERENTIAL DIAGNOSIS</th>
<th>NS</th>
<th>MEC, LOW-GRADE</th>
<th>SCC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Architecture/Growth</strong></td>
<td>Retention of lobular architecture</td>
<td>Haphazard, infiltrative growth</td>
<td>Haphazard, infiltrative growth</td>
</tr>
<tr>
<td><strong>Cellular Components</strong></td>
<td>Smooth round to oval nests of metaplastic squamous epithelium with bland cytology; may show residual ductal lumina with mucous cells</td>
<td>Admixture of mucous, intermediate (“basaloid”) and epidermoid (squamous) cells; bland cytology; irregular cell nests</td>
<td>Nests and cords of squamous cells with irregular outlines and variable amount of cytologic atypia; may entrap residual glands but the tumor itself contains no mucin</td>
</tr>
<tr>
<td><strong>Cyst Formation</strong></td>
<td>Absent</td>
<td>Present (prominent component)</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Surface Epithelium</strong></td>
<td>May show PEH; usually not connected with NS</td>
<td>Uninvolved; not connected with tumor</td>
<td>Often dysplastic and/or in direct continuity with the carcinoma; may be ulcerated</td>
</tr>
<tr>
<td><strong>Extravasated Mucin</strong></td>
<td>May be present</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td><strong>Necrosis</strong></td>
<td>Lobular infarction of salivary gland acini</td>
<td>Absent</td>
<td>May show tumor necrosis</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>May be prominent</td>
<td>May be prominent with mucin extravasation</td>
<td>May be present; associated desmoplasia</td>
</tr>
</tbody>
</table>
NS – Necrotizing sialometaplasia; MEC – Mucoepidermoid carcinoma; SCC – Squamous cell carcinoma; PEH – Pseudoepitheliomatous hyperplasia

References

Necrotizing Sialometaplasia


Granich MS, Pilch BZ. Necrotizing sialometaplasia in the setting of acute and chronic sinusitis. Laryngoscope 1981;91:1532-5.


Case 7: Human Immunodeficiency Virus (HIV) Infection of Waldeyer’s tonsillar tissues

Definition: Human immunodeficiency virus infection of the extranodal lymphoid tissues of the tonsils and adenoids that clinical result in enlargement of the these tissues.[Wenig]

Clinical
The clinical enlargement of tonsillar and particularly nasopharyngeal lymphoid tissue (adenoids) may represent the earliest clinical manifestations of HIV infection. Patients are usually adults with a male predilection. The clinical presentation includes enlargement of the tonsils or adenoids resulting in airway obstruction, and general symptomatology associated with non-descript tonsillitis. Clinically the enlargement may be unilateral raising the clinical concern for a possible diagnosis of lymphoma.

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These tissues of the tonsils and adenoids are a major site of viral replication.[Frankel] Mechanisms for the possible routes of transmission/infection are discussed elsewhere.[Wenig] The infected cells may include macrophages and/or dendritic cells [Dargent; Frankel; Orenstein]

Pathology

Primary HIV infection results in a spectrum of histopathologic changes that may represent the initial manifestation of HIV infection in otherwise asymptomatic patients.[Wenig] The presence of the HIV in these tissues causes a unique constellation of diagnostic histopathological features in lymph nodes as well as the extranodal lymphoid tissues of the tonsils and adenoids, including florid follicular hyperplasia, follicle lysis and productively HIV infected multinucleated giant cells of probable dendritic cell origin.[Wenig] Serologic evaluation is confirmatory of HIV infection. The histomorphologic changes in HIV-induced tonsillar and adenoidal enlargement vary with the progression of disease. In the early stages of infection, the histomorphology may include florid follicular hyperplasia with and without follicular fragmentation, and follicle lysis with areas of follicular involution. Additional findings included the presence of monocytoid B-cell hyperplasia, paracortical and interfollicular zone expansion with immunoblasts and plasma cells, interfollicular clusters of high endothelial venules, intra-follicular hemorrhage and the presence of multinucleated giant cells (MGC). The MGCs characteristically cluster adjacent to or within the adenoidal surface epithelium or the tonsillar crypt epithelium.

The histologic features in patients with more advanced stages of disease contrast with those described above and correlate with the lymphoid obliteration seen in the terminal stages of HIV infection or AIDS. In these cases, there is effacement of nodal architecture, loss of the normal lymphoid cell population with replacement by a benign plasma cell infiltrate, and the presence of increased vascularity. The multinucleated giant cells characteristically seen in the early and chronic stages of disease are not identified in the more advanced stages of HIV infection. erythrophagocytosis can be identified in all phases of disease but is most frequently identified in the advanced (profoundly immunodeficient) state.

Special stains for microorganisms (other than HIV) are negative. Reactivity for HIV p24 (gag protein), an indicator of active HIV infection is consistently identified in the early and chronic stages of disease.[Wenig] Anti-HIV p24 reactivity is seen within the follicular dendritic cell (FDC) network of the germinal centers, in scattered interfollicular lymphocytes, in the multinucleated giant cells and within intraepithelial cells of crypt epithelium. The HIV p24 positive intraepithelial cells are S-100 protein (a dendritic cell marker) positive and their morphologic appearance correlates with the appearance of dendritic cells (DC). Reactivity with both B-cell (CD20) and T-cell markers or subsets (CD45RO, CD3, OPD4) is seen within the germinal centers and in the interfollicular regions, as well as in scattered intraepithelial cells. The MGCs are immunoreactive for CD68, 3A5, major histocompatibility complex Class II, variable S-100 protein reactivity and no reactivity for CD1a, CD21, CD35, and CD83.[Dargent]

Although HIV-associated p24 protein is consistently present in MGCs, no immunoreactivity is present for Epstein-Barr virus (EBV) or human herpes virus 8 (HHV8) infection.[Dargent]
The patients in more advanced stages of disease, characterized by loss of germinal centers and the presence of a predominant plasma cell infiltrate, show a relative absence of lymphoid cell markers (CD45RB, CD3 or OPD4). In these cases, the plasma cell infiltrate show reactivity with kappa and lambda light chains indicative of a benign proliferation. Surface and crypt epithelia are cytokeratin reactive. Immunoreactivity with Epstein-Barr virus-latent membrane protein (EBV-LMP), herpes simplex virus (HSV) or cytomegalovirus (CMV) is not present.

Evidence of HIV RNA by in situ hybridization is seen in the follicular dendritic cell network, in the multinucleated giant cells, and in mature lymphocytes localized to the germinal centers, interfollicular zones and within the surface and/or crypt epithelia. The strongest signal is present in the multinucleated giant cells.[Wenig]

Differential Diagnosis
The differential diagnosis includes other infectious diseases, infectious-related proliferative processes (e.g., infectious mononucleosis) and malignant lymphoma. Special stains for microorganisms (other than HIV) are consistently negative excluding other infectious diseases. The clinical and laboratory findings are not those associated with infectious mononucleosis. Similarly, the light microscopic and immunohistochemical findings would not support a diagnosis of a lymphoma.

Treatment and Prognosis
Once the diagnosis of HIV infection is established, therapy includes highly active antiretroviral therapy (HAART).

References

HIV Tonsils and Adenoids


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Case 8: Diagnosis: Thyroid papillary carcinoma, follicular variant

Thyroid Neoplasms - General Considerations

Thyroid carcinoma is the most common endocrine malignancy but only represents approximately 1% of all cancers diagnosed in the United States. The annual incidence is 10,000, and the annual death rate is 1000. Approximately 4% of people between 30-60 years have 1 or more palpable thyroid nodules. The differential diagnosis of a thyroid nodule must include thyroid carcinoma. Epithelial neoplasms of the thyroid take origin from either the follicular cells (follicular adenoma/carcinoma; papillary carcinoma) or from the thyroid C cells (medullary carcinoma).

Thyroid Papillary Carcinoma

Thyroid papillary carcinoma (TPC) is a malignant epithelial tumor with evidence of follicular cell differentiation, typically with papillary and follicular structures and characteristic nuclear features.

Clinical

TPC represents the most common malignant thyroid neoplasm in countries with iodine-sufficient or iodine-excess diets comprising up to 80% of all thyroid tumors. TPC tends to occur more frequently in women than in men and is most common in the 3rd-5th decades but can affect any age group. Clinically apparent TPC present as an asymptomatic, palpable thyroid mass or as enlargement of regional lymph nodes. Any part of the gland can be affected. The etiology remains speculative and includes: 1) iodine excess; 2) radiation; 3) genetic; 4) pre-existing thyroid lesions; 5) others. The clinical work-up includes: thyroid imaging (1-123 or technetium-99m) - poorly functional or "cold" nodule; Fine Needle Aspiration (FNA).

Pathology

The diagnosis of TPC is based on a constellation of features that include architectural pattern and cytomorphology (Table 1). Numerous variations in the architectural patterns of papillary carcinoma can occur but the nuclear changes usually remain constant and represent the single most important criteria for the diagnosis of TPC. These features include nuclear enlargement, clearing or dispersion of the nuclear chromatin, alterations in the orientation of the nuclei within the cell, nuclear grooves and intranuclear inclusions.
Table 1: Thyroid Papillary Carcinoma - Diagnostic Features

<table>
<thead>
<tr>
<th>Architectural Features</th>
<th>Cytomorphologic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Growth patterns:</td>
<td>1. Nuclear enlargement;</td>
</tr>
<tr>
<td>- papillary, follicular, solid, trabecular, organoid; multiple growth patterns can occur;</td>
<td>2. Nuclear irregularities in size and shape;</td>
</tr>
<tr>
<td>2. Elongated or twisted follicles with little colloid;</td>
<td>3. Dispersed to optically clear appearing (Orphan Annie) nuclear chromatin;</td>
</tr>
<tr>
<td>3. Psammoma bodies;</td>
<td>4. Margination of the chromatin along the nuclear membrane;</td>
</tr>
<tr>
<td>4. Intratumoral irregular fibrosis;</td>
<td>5. Loss of nuclear basal polarity with haphazardly arrayed nuclei within the cell;</td>
</tr>
<tr>
<td>5. Insipissated colloid (darker appearing colloid as compared to the surrounding thyroid).</td>
<td>6. Crowding and overlapping nuclei;</td>
</tr>
<tr>
<td>6. Papillary protrusions into follicles;</td>
<td>7. Eosinophilic nuclear (pseudo)inclusions;</td>
</tr>
<tr>
<td>7. Squamous metaplasia</td>
<td>8. Nuclear grooves;</td>
</tr>
<tr>
<td></td>
<td>9. When present, nucleoli tend to localize along the nuclear membrane;</td>
</tr>
<tr>
<td></td>
<td>10. Nondescript cytoplasmic changes.</td>
</tr>
</tbody>
</table>

Nuclear Enlargement

As a general rule, the nuclei in papillary carcinoma are always larger than those of the normal (nonneoplastic) thyroid follicle and larger than the nuclei of adenomatoid nodules and follicular tumors (adenomas, carcinomas). Characteristically, there are irregularities in size and shape of the nuclei, and the nuclei may take on many appearances including semi-lunar, crenated or convoluted shapes. It should be noted that the presence of cytoplasmic oxyphilia seen in numerous thyroid lesions may induce nuclear enlargement of a size similar to that seen in TPC and may be suggestive of a diagnosis of TPC. However, these enlarged nuclei tend to remain round and regular lacking the other cytomorphologic features required for the diagnosis of TPC (see below). Therefore, one should be hesitant in diagnosing TPC on the basis of nuclear enlargement alone without the full constellation of cytomorphologic characteristics of TPC.

Nuclear Chromatin

The classic nuclear chromatin changes in TPC include an optically clear appearance that is likened to the eyes of the cartoon character Orphan Annie (so-called “Orphan Annie eyes”). This change is an artifact of fixation that is not seen in frozen section material. Further, not all examples of TPC include the so-called Orphan Annie nuclei. Rather, the nuclear chromatin may be very fine and evenly dispersed with a powdery or dusty chromatin pattern. There may be margination of the chromatin along the nuclear membrane that may result in fine but distinct appearing nuclear membrane.
Nuclear Orientation

The nuclei in TPC often show crowding or overlapping with loss of basal polarity of the nuclei. Instead of a linear orientation along the basal aspect of the cells, the nuclei in TPC appear randomly dispersed in all portions of the cell.

Nuclear Grooving

Nuclear grooves represent linear creases or lines in the nuclei and is often utilized as an essential and diagnostic feature of TPC. While nuclear grooves are a helpful diagnostic feature of TPC, nuclear grooves are not unique to TPC and may be seen in nonneoplastic thyroid lesions, as well as in other thyroid neoplasms (benign and malignant). A diagnosis of TPC should not be predicated only on finding nuclear grooves.

Intranuclear Inclusions

Intranuclear inclusions appear as large, round eosinophilic inclusions and represent cytoplasmic invaginations into the nucleus. Care should be taken not to mistake pseudoinclusions as real inclusions. Distortional changes in processing may result in intranuclear "bubbles" that simulate the appearance of the true intranuclear inclusions of TPC.

Additional Findings

Other less diagnostic features that can be seen in TPC include changes in the nucleoli and cytoplasm. Nucleoli may be inconspicuous to readily apparent in TPC. There may be a tendency of the nucleoli in TPC to be located along the nuclear membrane but this is not always true and the nucleoli may be centrally located. The nucleoli in follicular adenomas or carcinomas tend to be centrally situated within the nucleus. There are no specific cytoplasmic changes that assist in diagnosing TPC. The cytoplasm in TPC may be amphophilic, basophilic, eosinophilic or clear. There are certain variants of papillary carcinoma that are named according to their cytoplasmic appearance, including oxyphilic cell TPC and clear cell TPC. Additional features that can be seen in association with TPC include a lymphocytic infiltration, squamous metaplasia, multicentricity, intraglandular spread, capsular or vascular invasion. Cellular pleomorphism, mitotic activity and necrosis are generally not seen.

Architectural Features

The architectural features of TPC are additive but not a requirement for its diagnosis. The classic example of TPC includes the presence of papillary growth. The papillae tend to be narrow with thin fibrovascular cores and show complexity in growth with arborization. Other growth patterns in TPC may include solid, trabecular, microfollicular, macrofollicular, cystic. These patterns may be the only one seen in any given tumor or multiple patterns can be seen in any one tumor. A diagnosis of TPC should be considered in the presence of a single tumor that demonstrates multiple growth patterns. Predominantly solid tumors are those in which solid elements make up nearly all of the neoplasm. TPC may lack papillary growth and be entirely composed of a tumor with a follicular growth (so-called follicular type of TPC). An extremely valuable feature in TPC without a papillary architecture is the presence of elongated or twisted follicles. Elongated
and/or twisted follicles are features that are usually not seen in follicular adenomas or carcinomas. Intraoperative consultation cases in which the cytomorphologic features are equivocal for the diagnosis of TPC, elongated or twisted follicles may represent the diagnostic clue for this diagnosis. Another helpful clue and common feature of TPC is the presence of dense intratumoral fibrosis arranged in an irregular pattern.

Psammoma bodies are round, calcified concretions with concentric lamination that are felt to represent necrotic tumor cell(s) that form the nidus for deposition of calcium salts. The name is derived from Greek and means “salt-like.” Psammoma bodies are identified in up to 50% of TPC and are often seen in those tumors with a predominantly papillary growth pattern. Psammoma bodies are located in the tip of papillary stalk but can be found in solid neoplastic component or in the stroma between neoplastic follicles. Psammoma bodies found within follicle lumens are not diagnostic and should be disregarded. Naked psammoma bodies represent the presence of TPC. This is true whether found in normal thyroid or in cervical lymph nodes. Psammoma bodies are not specific for TPC but considered rare in benign thyroid diseases.

Fine Needle Aspiration (FNAB)
Due to the fact that the diagnosis of TPC is predicated on the nuclear changes, the cytologic features of papillary carcinoma are diagnostic by FNAB making needle aspiration an excellent diagnostic tool for TPC. This contrasts with follicular adenoma and follicular carcinoma which are differentiated on the basis of invasive growth (i.e., capsular or vascular space). The presence or absence of invasion cannot be assessed by FNAB.

The FNAB features of TPC include the presence of cellular smears with scant to absent colloid. The cells may be arranged in papillary formations, monolayers, follicles, small or large cell clusters (syncytium-like formations) or are individually dispersed. The papillary formations may be sharply outlined with complex branching and a central vascular core. Similar to the histologic diagnosis of TPC, the cytologic diagnosis of papillary carcinoma based on the nuclear features which include all of the features enumerated previously in this manuscript. The cytoplasmic features are not of much assistance in the diagnosis. Psammoma bodies can be seen and are very helpful in the diagnosis of papillary carcinoma. Multinucleated cells can be seen and sometimes are abundant.

Differential Diagnosis
The differential diagnosis of TPC includes lesions that may have a papillary architecture such as adenomatoid nodules, Graves' disease, and dyshormonogenetic goiter. Not all lesions with a papillary architecture are papillary carcinomas. Conversely, the absence of a papillary architecture does not exclude a diagnosis of thyroid papillary carcinoma (e.g., follicular type of TPC). Other thyroid lesions that may present difficulties in differentiating from TPC include follicular adenoma, follicular carcinoma and medullary carcinoma.

The differentiation of follicular adenoma or carcinoma from TPC rests on the absence of the typical morphologic features associated with TPC. Differentiating TPC from thyroid medullary carcinoma is readily accomplished by immunohistochemical analysis. Thyroid
medullary carcinomas are immunoreactive with cytokeratin, calcitonin and neuroendocrine markers (e.g., chromogranin and synaptophysin). TPC lacks calcitonin and neuroendocrine marker reactivity but will be reactive with thyroglobulin and cytokeratin. More recently, thyroid transcription factor-1 (TTF-1) has been shown to demonstrate dedicated reactivity to lesions of follicular epithelial origin and would be expected to be reactive in TPC and absent in TMC.

Diagnostic problems in TPC may occur in the presence of a lymphocytic cell infiltrate. Lymphocytic thyroiditis may induce changes in the cells of TPC that simulate the appearance of TPC. These changes include cytoplasmic oxyphilia that in turn may result in nuclear enlargement. However, in contrast with the nuclei in TPC, the nuclear enlargement seen in these oxyphilic cells remain round and regular and lack the spectrum of nuclear alterations associated with TPC.

**Histologic Subtypes of Thyroid Papillary Carcinoma**

There are several histologic subtypes of TPC (Table 3). The patient demographics, including gender predilection, age range, the clinical presentation (except for occult TPC), risk factors, treatment, prognosis, and prognostic factors of these histologic subtypes are the same as those of the conventional or usual type of TPC. For completion, Table 2 also includes a list of the purported aggressive types of TPC. These entities and the validity of whether to consider these tumor types aggressive on the basis of morphology have been discussed elsewhere and will not be addressed in this article.

### Table 2: Histologic Types of Thyroid Papillary Carcinoma

<table>
<thead>
<tr>
<th>I. “Conventional” Thyroid Papillary Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Occult, small or microscopic</td>
</tr>
<tr>
<td>- Encapsulated variant</td>
</tr>
<tr>
<td>- Follicular variant</td>
</tr>
<tr>
<td>- Macrofollicular variant</td>
</tr>
<tr>
<td>- Oncocytic or oxyphilic variant</td>
</tr>
<tr>
<td>- Clear cell variant</td>
</tr>
<tr>
<td>II. Purported Biologically Aggressive Types of Thyroid Papillary Carcinoma</td>
</tr>
<tr>
<td>- Diffuse sclerosing type</td>
</tr>
<tr>
<td>- Tall cell type</td>
</tr>
<tr>
<td>- Columnar cell type</td>
</tr>
</tbody>
</table>

The **occult, small or microscopic TPC** is defined as a papillary carcinoma measuring < 1.0 cm in size. It is usually an incidental finding in thyroid glands removed for other reasons but may present as an occult primary tumor with cervical lymph node metastasis. This tumor may be encapsulated or unencapsulated. Increased sclerosis may be present which is readily apparent at low magnification. At higher magnification, this tumor has the typical features of TPC. Microscopic TPC have an excellent prognosis. Finding a microscopic focus of TPC is generally of limited, if any, biologic import, and a
diagnosis of microscopic TPC is not, in and of itself, an indication for additional surgical intervention.

The **encapsulated type of TPC** comprises approximately 10% of all TPC. It has a well-defined capsule separating the neoplastic follicles from the adjacent thyroid parenchyma. Architecturally, this variant may be papillary or follicular. Cytomorphologic features are usually the typical ones associated with TPC. Capsular invasion can be seen and in cases showing equivocal cytomorphologic features of TPC, the presence of invasion is definitive for a diagnosis of carcinoma. In such cases where there is capsular invasion but features suggestive of but not diagnostic for TPC, a way of handling the diagnostic designation of these tumors may include “thyroid carcinoma favor thyroid papillary carcinoma” with a comment explaining why the neoplasm is malignant (i.e., invasive growth) but less than definitive cytomorphologic features for TPC. It should be noted that in spite of the capsular invasion, these tumors are still considered relatively indolent and do not merit more aggressive treatment.

Encapsulated tumors and invasive growth does not alter the treatment or prognosis.

The **follicular type of TPC** is exclusively composed of a follicular pattern of growth without the papillary structures. Despite the absence of papillary growth, other architectural features of TPC can be seen including elongated and/or twisted follicles and intratumoral irregular fibrosis. Psammoma bodies may be seen in the interfollicular stroma. If enough sections are taken, foci of papillary growth may be found. The diagnosis of the follicular type of TPC is primarily based on the tumor’s cytomorphologic (nuclear) features showing the characteristic changes associated with TPC.

The **macrofollicular type of TPC** is essentially the same as the follicular variant except that the neoplastic follicles are large (macrofollicles). This type of TPC resembles adenomatoid or hyperplastic nodules and without evaluating the cellular content may be misdiagnosed as such. A feature that may suggest this diagnosis is the presence of cellular foci seen throughout the neoplasm both in central and peripheral locations. The cellular foci show characteristic nuclear features of TPC. The presence of papillae are not required for a diagnosis but abortive papillary structures can usually be found.

The **oxyphilic or oncocytic type of TPC** is rare. This tumor type tends to be circumscribed or encapsulated. The characteristic cytomorphologic feature is the presence of cells with an abundant eosinophilic, finely to coarsely granular cytoplasm representing increased cellular mitochondria. The nuclei are typical for TPC. Prominent eosinophilic nucleoli (one or two) may be seen. Although not seen in all cases, the nuclei have a tendency to localize to the apical (“tips”) portion of the cell. Architecturally, this tumor shows a prominent papillary growth with complex configurations and fibrovascular cores; other patterns of growth may include follicular, trabecular and solid; psammoma bodies may be present.

The **clear cell type of TPC** is characterized by the presence of clear cytoplasm. Clear cell features may be associated with a number of thyroid tumors and is not limited to any one type. Clear cell features can be seen in limited areas of TPC or comprise most or all of the neoplasm. Other than the distinct clear cell features, both architecture and nuclear morphology are those of the conventional TPC.
This type of TPC may require immunohistochemistry to prove these tumors are of follicular cell origin (thyroglobulin positive) and that these are not of thyroid C cell origin (medullary carcinoma) or represent metastatic disease to the thyroid particularly a renal cell carcinoma.

**Warthin Tumor-like Variant**
- Rare variant that shows histologic similarity to salivary gland Warthin tumor, including papillary architecture with fibrovascular cores and associated lymphoplasmacytic cell infiltrate.
- Papillae are lined by cells with eosinophilic granular (oncocytic) cytoplasm and characteristic nuclear alterations associated with TPC; the lymphoplasmacytic cells infiltrate the core of the papillae.
- Treatment and prognosis is the same as that of conventional TPC.

**TPC with Nodular Fasciitis-like Stroma**
- Unusual histologic variant of TPC characterized by the presence of a fasciitis-like or fibromatosis-like stromal component; the latter is confined to the thyroid gland and likely represents an exaggerated stromal response to the presence of invasive carcinoma.
- The stromal component may be so exuberant that it obscures the neoplastic nature of the lesion.
- This tumor type shows histologic similarities to fibroadenoma or phyllodes tumor of the breast.
- The neoplastic cells are arranged in anastomosing cords, tubules and papillae; nuclear features characteristic for TPC are present; associated squamous metaplasia may be identified.
- The stroma is composed of spindle-shaped cells with an irregular fascicular growth, a vascularized fibromyxoid matrix and extravasated red blood cells;
- Similar to the myofibroblastic nature of nodular fasciitis, the spindle cells in this TPC variant show an immunohistochemical antigenic profile of myofibroblasts, including vimentin, smooth muscle actin and/or desmin reactivity; the spindle cells are cytokeratin and thyroglobulin negative.
- Treatment and prognosis are similar to those of conventional TPC.
- Nodal metastasis typically includes only the carcinomatous component and not the nodular fasciitis-like component.

**Intraoperative Diagnosis of Thyroid Papillary Carcinoma**
- The intraoperative diagnosis of TPC may be extremely challenging. In the face of a single encapsulated thyroid lesion with a follicular growth pattern, it is not infrequent to defer the frozen section diagnosis. This may be due to artifactual changes seen with frozen sections that result in equivocal features. It is recognized that the characteristic nuclear changes of TPC are poorly seen or absent on frozen sections only to become apparent on permanent sections of the lesion. In the setting of equivocal frozen section findings, an invaluable aid in the frozen section diagnosis of TPC is touch.
preparations and/or needle aspiration of the mass. The nuclear characteristics seen on touch preparation or needle aspiration may allow for the intraoperative diagnosis of TPC. Additional features that may be of assistance in the intraoperative diagnosis of TPC include the presence of elongated or twisted follicles, the presence of intratumoral fibrosis and psammoma bodies.

**Biologically Aggressive Variants of TPC**

**Diffuse Sclerosing Variant**
- occurs more commonly in women than in men; tends to occur in younger age groups (childhood to mid-thirties)
- present with bilateral goiter rather than as a single mass simulating a clinical appearance of thyroiditis by thyroid scan; however, may present as a "dominant" nodule
- histomorphologic features, which characterize this variant, include:
  - nuclear features of conventional TPC
  - diffuse involvement of the thyroid gland (one or both lobes) with extrathyroidal extension
  - prominent papillary growth often located within intrathyroidal spaces (lymphatic invasion)
  - numerous psammoma bodies
  - marked lymphocytic infiltrate
  - extensive squamous metaplasia
  - pronounced fibrosis
- high incidence of cervical lymph node metastasis
- greater incidence of distant metastasis (lung)
- shorter periods of disease-free survival
- despite greater incidence of pulmonary metastases, the tumor death rate is low

**Tall Cell Variant**
- tall cell is defined as a cell that is twice as tall as it is wide with an intensely eosinophilic cytoplasm
- more common in women than men; occurs in older age groups (> 6th decade of life)
- tumors are large measuring > 5 cm and have extrathyroidal extension
- histomorphologic features, which characterize this variant, include:
  - prominent papillary growth
  - cells lining papillae are twice as tall as they are wide with an abundant eosinophilic cytoplasm
  - nuclei are situated in the center or apical portion of the cell and are normochromic or hyperchromatic with nuclear grooves and intranuclear cytoplasmic invaginations
  - associated lymphocytic infiltrate in and around the tumor as well as within the papillary cores
  - readily identifiable mitotic figures
  - extrathyroidal extension and vascular space invasion
- high incidence of cervical lymph node metastasis and distant metastasis (lung and bone)
- tendency toward local recurrence in the neck often with invasion into the trachea
- high mortality rates
Columnar Cell Variant
- rare with only a limited number of published cases in the literature
- considered more common in men than women; occurs over a wide age range
- tumors are usually large measuring > 5 cm
- histomorphologic features, which characterize this variant, include:
  ▪ prominent papillary growth
  ▪ tall columnar appearing cells with nuclear stratification
  ▪ cytoplasm may vary from a nondescript eosinophilic appearance to a clear or vacuolated with subnuclear vacuolization similar to that seen in secretory-type endometrium
- extrathyroidal extension
- high incidence of cervical lymph node metastasis and distant metastasis (lung and bone)
- high mortality rates with death occurring within 4 years from diagnosis

Treatment and Prognosis
The standard treatment for TPC is surgery, but the extent of surgery remains a controversial area varying from lobectomy to subtotal thyroidectomy to total thyroidectomy. The standard approach in the past has been toward aggressive management by performing a total thyroidectomy and neck dissection. Presently, there is still no standard method in the surgical treatment of thyroid papillary carcinoma that may include aggressive management such as total thyroidectomy with postoperative radioactive iodine therapy versus more conservative approaches such as or subtotal thyroidectomy (lobectomy with or isthmusectomy) followed by suppression of thyroid-stimulating hormone secretion. A conservative approach would seem the most reasonable in a low-risk patient population (see below) with tumor localized to a single lobe without extrathyroidal extension that does not belong to a histologic unfavorable category (e.g., anaplastic carcinoma). Otherwise, more radical surgical intervention may be justified. Complications of thyroidectomy may include hypoparathyroidism and vocal cord paralysis. In the absence of cervical lymph node enlargement, a (modified) neck dissection need not be performed. However, in the face of apparent nodal involvement by tumor, a modified lymph node dissection with preservation of the sternocleidomastoid muscle is performed.

TPC tend to be biologically indolent with an excellent prognosis (> 90% at 20 years). Relapse after initial therapy is highest in the 1st decade and may be associated with increased mortality. Metastatic spread is preferentially via lymphatic drainage manifesting as intrathyroidal and/or regional lymph node metastasis. Distant (visceral) metastatic disease is unusual; the lung is the most common visceral metastatic site (bone, liver and brain metastasis may also occur). The overall mortality rates for thyroid papillary carcinoma are low.

Factors associated with an adverse prognosis include patient age and gender, tumor size, extrathyroidal extension, histology and distant spread.

Age and Gender
Mortality increases with patient age; in general, TPC in patients less than 40 years generally do not cause patient death as compared to patients greater than 40 years of age. Further, overall TPC tends to

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be more indolent in women than men. Low-Risk group includes men less than 41 years of age and women less than 51 years of age. High-Risk group includes men greater than 41 years of age and women greater than 51 years of age.

**Tumor Size**

Tumor recurrence and spread increases when the tumors are greater than 5 cm; the best prognosis is seen with tumors that measure less than or equal to 1.5 cm in diameter.

**Staging:**

- **Extrathyroidal Extension:**
  - The presence of extrathyroidal extension of tumor (i.e., extension beyond the confines of the thyroid gland into adjacent soft tissues) represents one of the worst prognostic indicators in TPC;
  - Microscopic foci of extrathyroidal extension have outcomes that are better than those TPCs with extensive invasion outside the gland;
  - Invasion into adjacent anatomic structures (e.g., trachea, esophagus, other) is an unfavorable prognostic finding associated with decreased survival;
  - Encapsulated tumors and/or tumors showing limited invasion are associated with a favorable prognosis.

- **Distant Metastasis:** the presence of distant metastasis is associated with a worse prognosis; the site of the distant metastasis impacts on prognosis:
  - Osseous and visceral (other than pulmonary) metastasis represents an ominous prognostic finding;
  - Pulmonary metastasis is not associated with as dire a prognosis as with osseous (or other distant) metastatic disease, but is associated with a moderate adverse outcome.

- **Nodal Metastasis:**
  - in general the presence of nodal metastasis has limited impact on survival; however, the presence of extranodal extension of tumor into soft tissues adversely impacts on survival with increased risk of distant metastasis and worse prognosis.

**Histology** (type & differentiation): adverse prognosis has been related to the cell type and/or growth pattern (e.g. columnar cell, tall cell, insular and diffuse sclerosing variants) with some variants of TPC associated with more aggressive clinical course and higher mortality rates. However, this has not been definitively proven but these histologic types of TPC may have an associated adverse prognostic feature (e.g. older age, male predilection, extrathyroidal extension) that better correlates with a more aggressive behavior. The same cannot be said of poorly differentiated tumors (undifferentiated or anaplastic carcinoma) that by virtue of their histology are associated with a poor prognosis.

5) Factors associated adverse prognosis but still of questionable prognostic significance include:
- Angioinvasion, especially into large caliber sized vascular spaces;
- Tumor ploidy: aneuploid tumors, particularly occurring in older aged patients (greater than 60 years), are associated with a worse prognosis;
- Histologic growth patterns: solid or trabecular areas;
- Immunoreactivity for LeuM1, epithelial membrane protein, and p53, and absence-to-diminished reactivity for E-cadherin and retinoblastoma protein;
- Oncogene abnormalities: the presence of point mutations such as in N-ras gene may be associated with a more aggressive behaving TPCs;

Factors associated with better prognosis but still of questionable prognostic significance include:
- prominent papillary architecture and presence of psammoma bodies;
- presence of lymphocytic thyroiditis in the adjacent thyroid parenchyma;
- diploid tumors.

The effect of treatment (surgery, external radiation, radioactive iodine or chemotherapy) does not appear to be a significant predictor of survival in thyroid papillary carcinoma.

References

**Thyroid Neoplasms - General Considerations**


**Thyroid Papillary Carcinoma**


Occult, Small Or Microscopic


Encapsulated Variant


Follicular Variant


Macrofollicular Variant

Oncocytic Papillary Carcinoma


**Clear Cell Variant**


**Diffuse Sclerosing Variant**


**Tall Cell Variant**


Columnar Cell Variant


Treatment And Prognosis


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Immunohistochemical/Molecular Biologic Studies


**Case 9: Parathyroid carcinoma.**

Parathyroid carcinoma is a malignant neoplasm of parathyroid parenchymal cells.

**Clinical**

Parathyroid carcinoma is a rare neoplasm responsible for less than 3% of cases of hyperparathyroidism. There is no gender predilection. Parathyroid carcinoma is most common in fifth and sixth decades, but rare cases have been reported in children. As a general rule, patients with parathyroid carcinoma have severe hypercalcemia with mean serum calcium levels of 14.0 mg/100 ml, in contrast to mean serum calcium of 12.0 mg/100 ml in benign hyperparathyroidism. Occasionally, normocalcemic patients have been described. Symptoms are similar to those in patients with hyperparathyroidism of benign etiology, but tend to be more severe due to the higher serum calcium levels in carcinoma. Presenting symptoms include fatigue and weakness, depression, bone disease (high incidence in earlier series), nephrolithiasis (up to two thirds of patients in earlier studies, but
probably decreasing with routine biochemical screening and earlier detection), and peptic ulcer disease. A palpable neck mass is uncommon but is more common in patients with carcinoma than in hyperplasia or adenoma. Some cases have reported in familial parathyroid proliferative diseases.

Several imaging methods have been utilized for localization of hyperfunctioning parathyroid tissue, including retrograde phlebotomy for determination of serum parathormone levels, CT scanning, ultrasonography, magnetic resonance imaging (MRI), thallium subtraction scanning, and the more recent technetium-99m sestamibi imaging. The latter appears to be the most useful.

Pathology

The average size is larger than parathyroid adenomas with mean weight of 6.7 g (range 1.5- 27 g) though smaller tumors are being identified more often in recent years. Parathyroid carcinomas may be encapsulated or infiltrative. Carcinomas may have a smooth, firm cut surface indistinguishable from an adenoma or they may be distinctly indurated. An important intraoperative observation that is often correlated with parathyroid carcinoma is that they are difficult to dissect and/or adhere to the thyroid gland due to their infiltrative growth. Parathyroid carcinomas may be very difficult to distinguish from a parathyroid adenoma or they may be obviously malignant. The growth patterns vary and include solid sheets, glandular or acinar formations, cords, rosettes, and, of particular differential diagnostic significance, trabeculae. Nuclear palisading may be prominent in trabecular areas. Spindling of cells is also a feature more often seen in carcinomas than in benign proliferations. Acellular fibrous bands extending from a thickened capsule frequently divide the tumors into irregular compartments. The presence of these fibrous bands is an important feature associated with parathyroid carcinoma but it is not invariably present. The glandular formations may contain eosinophilic “colloid-like” material.

The tumor cells may present with variable morphology, with some very similar to benign chief cells, with slightly eosinophilic to clear cytoplasm. Other areas may contain enlarged cells with more distinctly eosinophilic cytoplasm, large nuclei with prominent nucleoli. Monotony of nuclear size and shape is frequently present in carcinomas; pleomorphism, when present, is usually more diffuse than in adenomas. Nuclear pleomorphism is less common than in adenomas. Mitotic activity is identified in most but not all parathyroid carcinomas. Although a high mitotic rate is a helpful feature, the presence of mitotic activity exceeding 1 per 10 HPF in a minority of parathyroid adenomas and in parathyroid hyperplasia has been reported. This overlap makes mitotic activity a useful finding only when coupled with other features of malignancy. Atypical mitoses are virtually diagnostic of malignancy. Many parathyroid carcinomas are encapsulated. Usually the capsule of a carcinoma is thicker than that seen in most adenomas. Some adenomas in which hemorrhage and degenerative changes have occurred have thick and uneven capsules; the presence of hemosiderin and other evidence of long-standing degenerative changes such as chronic inflammation and areas of cystic change are helpful in differentiating these adenomas from carcinomas.

Capsular invasion may be obvious in some cases, or may be represented only by irregular tongues or islands of parathyroid tissue protruding into the capsule. Invasion beyond the capsule is indicative of malignancy. Entrapped islands of parathyroid parenchymal cells in
benign disease should be distinguished from these invasive foci by their rounded contours and lack of desmoplastic reaction. Vascular invasion is diagnostic of carcinoma, but is present in a minority of cases. It is usually found within vessels in the thick tumor capsule. Artifically displaced clumps of tumor cells in vascular spaces should be distinguished from true invasion by their frequently degenerated appearance and by their lack of attachment to the vessel wall. Perineural invasion, though rarely seen, is also virtually diagnostic of malignancy.

The colloid-like material in the glandular structures is PAS-positive. This appearance may suggest a tumor of thyroid origin. Immunohistochemical stains are negative for thyroglobulin. Parathyroid carcinomas (and adenomas) are also positive for cytokeratin, neuroendocrine markers (chromogranin and synaptophysin), as well as for parathormone. Immunohistochemistry for parathormone has been less than satisfactory in many labs; in-situ hybridization for messenger RNA for parathyroid hormone has been much more sensitive. Recent evidence suggests that loss of the retinoblastoma tumor-suppressor gene may play an important role in the development of parathyroid carcinoma, and that its absence may be helpful in distinguishing parathyroid adenomas from carcinomas. Immunoreactivity for Ki-67, a cell cycle-associated antigen, may also prove helpful in distinguishing between adenomas and carcinomas, with recently reported increases in labeling indices for Ki-67 in parathyroid carcinomas. Although flow cytometric features of adenomas and carcinomas show significant overlap, with aneuploidy in some adenomas and diploidy in some carcinomas, there is some evidence that aneuploidy may be associated with a more aggressive course in parathyroid carcinomas.

**Treatment and Prognosis**

En bloc resection, to include the ipsilateral thyroid lobe and adjacent soft tissues and lymph nodes, at the time of initial surgery is the preferred therapy. Lymph node metastases are uncommon at the time of diagnosis; however, the presence of nodal disease is considered an indication for neck dissection. The prognosis of parathyroid carcinoma appears to be changing as a result of earlier detection. The proportion of well-differentiated encapsulated lesions is increasing; a correlation of risk of recurrence with extraglandular invasiveness has been found. Up to 50% of patients are cured by en bloc resection. Recurrences generally manifest within 3 years of the first surgery with locally recurrent disease. Metastatic disease occurs rather late in the course of disease and is found in 35% of patients, usually several years after primary diagnosis. Metastases most commonly involve lung, cervical lymph nodes, and liver, in decreasing order. Monitoring for recurrent disease is most effectively accomplished with serum calcium levels. Surgical resection of metastatic or locally recurrent disease is frequently helpful due to the rather indolent nature of parathyroid carcinoma. Patients usually survive for several years after recognition of tumor recurrence. The major difficulty in management of recurrent disease is severe hypercalcemia and its complications. Death is related to excessive hormonal product with subsequent hypercalcemia rather than directly to tumor burden.

**Differential Diagnosis** primarily includes the other parathyroid proliferative diseases (parathyroid adenoma and parathyroid hyperplasia) - see TABLES 1-3.
Table 1: Clinical features associated with malignancy in parathyroid neoplasms

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium level &gt; 14 mg/100ml</td>
</tr>
<tr>
<td>Serum parathormone levels 2-3 times normal</td>
</tr>
<tr>
<td>Severe metabolic manifestations: nephrolithiasis, bone disease, etc.</td>
</tr>
<tr>
<td>Palpable neck mass</td>
</tr>
<tr>
<td>Difficulty in surgical dissection</td>
</tr>
</tbody>
</table>

Table 2: Pathologic features associated with malignancy in parathyroid neoplasms

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large size (mean weight 6.7 g)</td>
</tr>
<tr>
<td>Adherence thyroid tissue</td>
</tr>
<tr>
<td>Irregular contour; lack of distinct encapsulation</td>
</tr>
<tr>
<td>Thick capsule</td>
</tr>
<tr>
<td>Fibrous bands within tumor</td>
</tr>
<tr>
<td>Mitotic activity (especially &gt; 5 per 10 HPF)</td>
</tr>
<tr>
<td>Atypical mitoses</td>
</tr>
<tr>
<td>Capsular invasion, especially with extraglandular extension</td>
</tr>
<tr>
<td>Vascular invasion</td>
</tr>
<tr>
<td>Trabecular growth</td>
</tr>
<tr>
<td>Spindling of tumor cells</td>
</tr>
<tr>
<td>Macronucleoli</td>
</tr>
</tbody>
</table>

Table 3: Comparative features of parathyroid proliferative diseases

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hyperplasia</th>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Calcium</td>
<td>11.7 mg/10 ml (average)</td>
<td>12.5 - 13.5 mg/10 ml</td>
<td>Often &gt; 14 mg/10 ml</td>
</tr>
<tr>
<td>Intraoperative findings</td>
<td>2 or more glands enlarged, easily dissected. Enlargement may be asymmetrical</td>
<td>1 gland enlarged; easily dissected</td>
<td>1 gland enlarged; often adherent to surrounding tissues</td>
</tr>
<tr>
<td>Weight of gland (s)</td>
<td>Total gland weight usually &lt; 1 g, but may be up to 5 g</td>
<td>0.3 - 1.0 g commonly</td>
<td>&gt; 1.5 g (often much larger)</td>
</tr>
<tr>
<td>Capsule</td>
<td>Circumscribed by capsule of parathyroid gland,</td>
<td>Thin tumor capsule, often surrounded by rim of uninvolved parathyroid</td>
<td>Thickened capsule; rim of normal parathyroid rarely</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Adenoma</td>
<td>Carcinoma</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>may be incomplete. No compressed rim of atrophic or normal parathyroid tissue</td>
<td>which may appear atrophic</td>
<td>seen</td>
<td></td>
</tr>
<tr>
<td>Gross appearance</td>
<td>Gray-brown, soft. Cut surface may be homogeneous or nodular. Lacks fibrous bands</td>
<td>Red-brown, firm. Usually homogeneous, lacks fibrous bands</td>
<td>Gray-white, firm, often lobulated or irregular. Fibrous bands produce coarse nodularity</td>
</tr>
<tr>
<td>Histologic pattern</td>
<td>Diffuse, trabecular, or nodular, sometimes pseudofollicular or acinar</td>
<td>Diffuse, trabecular, or nodular, frequently pseudofollicular or acinar</td>
<td>Diffuse, nodular, pseudofollicular, or acinar. Often trabecular with nuclear pallisading</td>
</tr>
<tr>
<td>Cytologic features</td>
<td>Chief cells predominate; transitional and oxyphilic cells often present</td>
<td>Chief cells predominate, but mixture of chief, transitional and oxyphilic cells may be seen. Rarely, purely oxyphilic</td>
<td>Cells usually resemble chief cells, but variable cytoplasmic oxyphilia may be seen. Cells borders often indistinct</td>
</tr>
<tr>
<td>Intracytoplasmic lipid</td>
<td>Decreased</td>
<td>Decreased in tumor; abundant in atrophic gland</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Stromal fat cells</td>
<td>Scanty to absent</td>
<td>Usually absent in tumor; present in atrophic gland</td>
<td>Absent</td>
</tr>
<tr>
<td>Nuclear morphology</td>
<td>Normal to slightly increased N-to-C ratio; usually without nuclear pleomorphism</td>
<td>Nuclei enlarged and variable in size; scattered large pleomorphic, hyperchromatic nuclei, or multinucleated cells</td>
<td>Increased N-to-C ratio; enlarged atypical nuclei, often with a very monotonous pattern</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
<th>Hyperplasia</th>
<th>Adenoma</th>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoli</td>
<td>Inconspicuous to</td>
<td>Inconspicuous to small</td>
<td>Frequently prominent and enlarged</td>
</tr>
<tr>
<td></td>
<td>small</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoses</td>
<td>Usually rare</td>
<td>Usually rare</td>
<td>Usually present (80% of cases), may include atypical mitoses; may be numerous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(occasionally &gt; 1 per 10 high power fields)</td>
<td></td>
</tr>
<tr>
<td>Capsular and</td>
<td>Absent</td>
<td>Absent. Beware of entrapment of tumor cells in capsule if degenerative changes present</td>
<td>Capsular invasion present in two thirds of cases. Vascular invasion present in 10-15% (usually in capsular vessels)</td>
</tr>
<tr>
<td>vascular invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degenerative</td>
<td>May be seen in very large glands; includes hemorrhage, areas of fibrosis, and cystic change</td>
<td>Common, especially in larger adenomas; includes hemorrhage, fibrosis, and cystic change, sometimes calcification</td>
<td>Tumor cell necrosis; calcification and cystic changes may be present</td>
</tr>
<tr>
<td>changes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgical removal of 3 glands leaving a remnant of the 4th or total parathyroidectomy with autotransplantation of parathyroid tissue in the forearm</td>
<td>Surgical removal of the enlarged gland</td>
<td>En bloc resection, including ipsilateral thyroid lobe and adjacent soft tissues and lymph nodes</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Very good</td>
<td>Surgery is curative</td>
<td>Up to 50% of patients are cured by en bloc resection; indolent malignancy even in presence of recurrence or metastasis with long</td>
</tr>
</tbody>
</table>
### Hyperplasia | Adenoma | Carcinoma
--- | --- | ---

| Recurrence and Metastasis | Recurrence in approximately 16% of cases due to inadequate neck exploration and may not be evident for years | Absent | Recurrence in two thirds of patients usually within 3 years of the first surgery; metastasis in 35% - late event usually preceded by local recurrence; most commonly to lung, lymph nodes and liver |
| Famial and/or MEN association | Yes, in approximately 20% of cases | None | None |

### References

**Parathyroid Carcinoma**


Case 10: Metastatic Neoplasms To The Neck Region From An Occult Primary Neoplasm

Overt neck mass harboring a histologically proven metastatic neoplasm in the absence of signs and symptoms of a primary neoplasm or of a clinically detectable mass.

Clinical

The most common clinical manifestation of a metastatic tumor to the neck from an occult primary neoplasm is that of a unilateral, fixed mass. Affects men more than women and is most frequently seen in the 5th-7th decades of life. The majority of metastatic tumors to the cervical lymph nodes take origin from a head and neck primary tumor and, therefore, the most common histologic appearance is that of a squamous cell carcinoma. Etiologic factors relate to the development of squamous carcinoma of the head and neck and, as
such, are linked to tobacco and alcohol use. Metastatic tumors to the neck are not limited to origin from a head and neck neoplasm but may represent primary occult neoplasms from organ systems in the thorax, abdomen and pelvis. The most common primary site for a metastatic tumor originating from below the clavicle are the lungs; virtually every other organ may be the primary focus of a metastasis to the head and neck. In the head and neck, difficulty in histologically classifying a given tumor or the presence of an unusual histologic appearance should alert the pathologist to the possibility that the neoplasm may represent a metastasis from a distant site. The lymphatic drainage to the cervical lymph nodes is predictable and the anatomic location of the metastatic focus assists in the search for the primary focus (Table 1). The diagnostic work-up for a patient with a metastatic tumor in the neck of occult primary origin includes: 1) panendoscopic evaluation of the upper respiratory tract including direct laryngoscopy, bronchoscopy and esophagoscopy; 2) any mucosal abnormality should be biopsied and if no abnormalities are grossly seen random biopsies especially of Waldeyer's tonsillar ring (nasopharynx, tonsil and base of tongue) are indicated; 3) radiographs. By far, the nasopharynx, tonsils and base of tongue, collectively referred to as Waldeyer's tonsillar ring, are the areas harboring the occult primary tumor in the majority of squamous carcinomas metastatic to the neck. Other common but less frequent sites of the occult tumor include: thyroid, hypopharynx and larynx (supraglottic region). The frequency and cystic appearance of tumors originating in Waldeyer's tonsillar ring merit special consideration. Metastatic Cystic Squamous Cell Carcinoma represents metastatic deposits from Waldeyer's tonsillar ring. The histologic appearance of these metastases strongly suggests origin from Waldeyer's tonsillar ring. Along with the metastatic cystic squamous cell carcinoma, the other metastatic tumor with a histologic appearance virtually identifying its site of origin is the undifferentiated carcinoma of the nasopharynx. Confusion and controversy exists between the diagnosis of metastatic cystic squamous cell carcinoma vs. carcinoma arising in a branchial cleft cyst (branchiogenic carcinoma). Criteria for the diagnosis of a branchiogenic carcinoma include: 1) the metastatic tumor occurs along the line extending from a point anterior to the tragus along the anterior border of the sternocleidomastoid muscle to the clavicle; 2) histology supports origin from a branchial cleft-derived structure; 3) histology supports carcinoma arising in the wall of an epithelial-lined cyst; 4) a minimum of 5 year follow-up demonstrates no evidence of a primary source for this neoplasm. Despite the fulfillment of these criteria it is highly unlikely that carcinoma arises in a branchial cleft cyst, rather, all these cystic squamous cell carcinomas take origin from a primary tumor in Waldeyer's tonsillar ring. The neoplasm may be so small as to defy clinical detection but nevertheless is capable of metastasizing. The histology demonstrates partial or complete replacement of the lymph node by an epithelial-lined structure with central cystic change. The epithelium varies from areas which are bland composed of uniform cells lacking pleomorphism, crowding or loss of polarity to overtly malignant appearing epithelium composed of pleomorphic cells with increased cellularity, mitoses and a loss of polarity.
Table 1. Cervical Node Region and Possible Origin of an Occult Primary Neoplasm

<table>
<thead>
<tr>
<th>Lymph Node(s) Region</th>
<th>Drainage and Potential Source of the Metastatic Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preauricular</td>
<td>Skin of upper face and temple</td>
</tr>
<tr>
<td>Submental</td>
<td>Lip, anterior floor of mouth</td>
</tr>
<tr>
<td>Submaxillary</td>
<td>Skin of lateral face, floor of mouth and tongue (anterior)</td>
</tr>
<tr>
<td>Upper jugular</td>
<td>Tongue (lateral and posterior), palate and tonsil</td>
</tr>
<tr>
<td>Middle jugular</td>
<td>Pharynx, larynx</td>
</tr>
<tr>
<td>Low jugular</td>
<td>Thyroid, esophagus (cervical segment)</td>
</tr>
<tr>
<td>Posterior Cervical</td>
<td>Nasopharynx, thyroid</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>Below the clavicle</td>
</tr>
</tbody>
</table>

**Treatment and Prognosis**

Treatment modalities are not fixed and are dependent on the clinical stage, location of the lymph node involved and histologic appearance of the tumor:
- single mobile lymph node in submaxillary, subdigastic or midjugular regions - neck dissection preferred over radiotherapy due to exposure and complications of radiation to the oral cavity, pharyngeal and laryngeal mucosae
- single mobile lymph node in the posterior cervical region - radiotherapy with fields including the nasopharynx, tonsillar fossa and base of tongue
- multiple mobile ipsilateral or bilateral lymph nodes - radiotherapy
- large fixed lymph nodes - neck dissection or radiotherapy to the entire neck

The single most important factor in prognosis is the clinical stage. Other factors that correlate with prognosis include:
- location of the lymph node: supraclavicular nodal involvement has a poor prognosis
- histologic appearance: metastatic adenocarcinomas have worse survival rates.

**Nasopharyngeal Undifferentiated Carcinoma**

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma arising from the surface epithelium and subtyped according to the World Health Organization (WHO) into two histologic variants: keratinizing, and non-keratinizing. The nonkeratinizing type is further subdivided into nonkeratinizing differentiated and nonkeratinizing undifferentiated. Nasopharyngeal carcinoma, by definition, takes origin from the surface epithelium, therefore, the use of this term is to the exclusion of all other malignant tumors, which may arise in this...
region (minor salivary gland tumors, sarcomas, lymphomas). Synonyms for nasopharyngeal carcinoma include: Lymphoepithelioma; Rigaud and Schmincke types of lymphoepithelioma; transitional carcinoma.

Clinical (Table 2)

Overall, NPC is an uncommon neoplasm in the United States accounting for approximately 0.25% of all cancers. In China, it accounts for 18% of all cancers. NPC affects men more than women and occurs over a wide age range but is most common in the 6th decade of life. Irrespective of the histologic type the clinical presentation is similar and includes: neck mass, hearing loss, nasal obstruction, nasal discharge, epistaxis, pain, otalgia and headache. The signs and symptoms are often subtle and nonspecific leading to delay in diagnosis and eventual presentation with advanced disease. The lateral wall of the nasopharynx (fossa of Rosenmüller) is the most common site of occurrence.

Suggested etiologic factors include:
- genetic and geographic: increased incidence in China especially in southern (Kwantung province) and northern provinces and Taiwan; although the incidence among Chinese people decreases after emigration to low-incidence areas, it still remains higher than in non-Chinese populations; HLA-A2 histocompatibility locus has been suggested as the marker for genetic susceptibility to nasopharyngeal carcinoma;
- Epstein-Barr virus (EBV): elevated titers of anti-EBV antibodies are associated with nasopharyngeal carcinoma (undifferentiated and nonkeratinizing types); however, no clear cause and effect has been established between the presence of EBV and the development of nasopharyngeal carcinoma;
- other suggested implicating factors are diet, poor hygiene, and environmental.

Radiologic findings include:
- plain film radiographs findings are variable and non-specific including a soft tissue mass, bone destruction and sinus opacity;
- CT may demonstrate bone invasion including invasion of the base of skull and expansion of sinuses with progression of disease.

Pathology (Table 2)

The gross appearance of NPC varies from a mucosal bulge with an overlying intact epithelium to a clearly demonstrable mass with extensive involvement of the surface epithelium to a totally unidentifiable lesion fortuitously sampled and identified by microscopic evaluation. Three histologic types are identified based on the predominant appearance and include: 1. Keratinizing; 2. Nonkeratinizing; 3. Undifferentiated.

Treatment and Prognosis (Table 2)

As a result of the anatomic constraints imposed by the nasopharynx and the tendency of these neoplasms to present in an advanced stage, supervoltage radiotherapy (6500 - >7000 rads) is considered the treatment of choice. Responsiveness to radiation varies per histologic type and thereby impacts on prognosis. The Keratinizing subtype is not radioresponsive. These tumors have a tendency to remain localized without (nodal)
dissemination. However, based on the radioresistance, the 5 year survival rate is in the range of 10-20%. The Nonkeratinizing subtype is variably radioresponsive. These tumors have a tendency to metastasize to regional lymph nodes. Based on their relative radioresponsiveness, the 5 year survival rate is in the range of 35-50%. The Undifferentiated subtype is radiosensitive. These tumors have a tendency to metastasize to regional lymph nodes. Nevertheless, despite the tendency to disseminate and to be the least differentiated of all the subtypes, based on their radiosensitivity the 5 year survival rate is approximately 60%. Factors which may affect prognosis include: 1) clinical stage; 2) patient age (the younger the age the better the prognosis) which probably correlates to the fact that nasopharyngeal carcinoma occurring in younger patients is predominantly of the undifferentiated type; 3) lymph node metastasis (positive nodes decreases survival by approximately 10-20%). The sole utility for chemotherapy is for widespread disease. The Regaud and Schmincke types of nasopharyngeal carcinoma refer to those neoplasms with syncytial vs. individual cell invasive growth patterns, respectively; these designations and their correlated growth have no bearing on the biology of the disease.

Table 2. Nasopharyngeal Carcinoma

<table>
<thead>
<tr>
<th>Percent of Cases</th>
<th>Keratinizing</th>
<th>Nonkeratinizing</th>
<th>Undifferentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F; &gt; 6th decade</td>
<td>Approximately 25%</td>
<td>Least common - &lt; 15%</td>
<td>Most common &gt; 60%</td>
</tr>
<tr>
<td>Histology</td>
<td>Keratinization, intercellular bridges; conventional squamous carcinoma graded as well, moderately or poorly differentiated; desmoplastic response to invasion</td>
<td>Little to absent keratinization, growth pattern similar to transitional carcinoma of the bladder; typically, absence of desmoplastic response to invasion</td>
<td>Absence of keratinization, syncytial growth, cohesive or noncohesive cells with round nuclei, prominent eosinophilic nucleoli, scant cytoplasm and mitoses; prominent non-neoplastic lymphoid component; typically, absence of desmoplastic response to invasion</td>
</tr>
<tr>
<td>IHC</td>
<td>CK positive</td>
<td>CK positive</td>
<td>CK positive; LCA and DES negative</td>
</tr>
<tr>
<td>Presence of EBV</td>
<td>Weak association</td>
<td>Strong association</td>
<td>Strong association</td>
</tr>
<tr>
<td>Treatment</td>
<td>Radioresponsiveness is not good</td>
<td>Variably Radioresponsive</td>
<td>Radiosensitive</td>
</tr>
<tr>
<td>Prognosis</td>
<td>10-20% 5 year survival</td>
<td>35-50% 5 year survival</td>
<td>60% 5 year survival</td>
</tr>
</tbody>
</table>

IHC = Immunohistochemistry: CK = cytokeratin; LCA = leukocyte common antigen; DES = desmin

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Differential Diagnosis of Nasopharyngeal Undifferentiated Carcinoma

The differential diagnosis of NUC includes non-Hodgkin's malignant lymphoma (large cell or immunoblastic), mucosal malignant melanoma and rhabdomyosarcoma (Table 3). This section will be limited to the malignant lymphoma.

Primarily when it occurs as a diffuse cellular infiltrate composed of dyscohesive cells, the nasopharyngeal undifferentiated carcinoma is difficult to differentiate from a malignant lymphoma by light microscopy. Waldeyer's tonsillar ring includes the lymphoid tissues of the nasopharynx, tonsils and base of tongue. Waldeyer's tonsillar ring represents an extranodal but not an extralymphatic site. Waldeyer's ring lymphomas accounts for approximately 50 percent of all extranodal non-Hodgkin's malignant lymphoma in the head and neck and is second only to the gastrointestinal tract in the incidence of extranodal non-Hodgkin's lymphomas. Waldeyer's ring lymphomas affect men more than women and occur in all age ranges but are most common in the 5th to 7th decades of life. The most common sites of occurrence (in order of frequency) are the tonsils, nasopharynx and base of tongue. The most common symptoms include: airway obstruction, otalgia, decreased hearing, pain and sore throat.

Grossly, a large submucosal mass with or without surface ulceration may be seen. In the majority of cases involvement is unilateral. Although any pattern and cell type can be seen, the most common histologic pattern is a diffuse growth, and the most common histologic cell type is large cell or immunoblastic of B-cell phenotype. Typically, the cellular infiltrate is dyscohesive but occasionally may demonstrate a syncytial or cohesive growth simulating an epithelial malignancy. For large cell lymphoma, the cells are medium to large with a large round to oval vesicular (noncleaved) nucleus with several nucleoli often located at the periphery of the nucleus. Numerous macrophages (starry sky) or epithelioid cells may be present. Mitotic activity, necrosis and apoptotic figures can be seen. In the immunoblastic lymphoma, the cells are large with round to oval nuclei and a large prominent and usually centrally located nucleolus. Necrosis (individual cell or confluent areas) and increased mitotic activity with atypical forms are common features. Numerous macrophages (starry sky) or epithelioid cells may be present. These tumors may show plasmacytic differentiation.

Immunohistochemistry is essential in confirming the diagnosis and in differentiating a malignant lymphoma from carcinoma. Leucocyte common antigen (LCA or CD45), will be reactive in malignant lymphomas. The overwhelming majority of Waldeyer's ring lymphomas are of follicular center cell origin reflected in their expression of B-cell lineage markers (L-26 or CD20) and absence of T-cell lineage markers. The B-cell predominance of Waldeyer's ring malignant lymphomas is also true in Asian populations, where T cell lymphomas are more common, representing over 85 percent of Waldeyer's ring lymphomas. The large cell and immunoblastic lymphomas can be difficult to differentiate from the undifferentiated carcinoma of Waldeyer's ring and the differentiation often depends on immunohistochemical findings. Lymphomas will be leukocyte common antigen (LCA or CD45) positive and cytokeratin negative, while the undifferentiated carcinoma will be leukocyte common antigen (LCA or CD45) negative and cytokeratin positive. In addition to the immunohistochemical features, other findings associated with large cell lymphoma or immunoblastic (B-cell) lymphoma include the presence of immunoglobulin or T cell receptor (TCR) gene rearrangement, Epstein-Barr virus (EBV) and HTLV-1 have been found in a proportion of cases and the chromosomal translocation t(14;18). The t(14;18) chromosomal
translocation is seen in most patients with follicular lymphomas and is associated with the deregulation of the bcl-2 proto-oncogene resulting in overexpression of the bcl-2 protein, which is known to inhibit cell death.

The most important prognostic factor for patients with Waldeyer’s ring lymphomas is the clinical stage based on the Ann Arbor classification, which was originally developed for Hodgkin’s disease. Treatment primarily includes radiotherapy and/or chemotherapy. Surgical resection may be needed for symptomatic relief. Patients with diffuse large cell lymphoma and stage IIE disease have reported 5-year survival rates ranging from 58 to 86 percent. Patients with stage IIIE or higher have a much worse prognosis. More recently, a multinational and multi-institutional cooperative study developed prognostic indices for non-Hodgkin’s malignant lymphomas. In this study, two indices designated as the international index (for all ages) and the age-adjusted international index (for patients #60 years) were identified. Both models identified four risk groups of patients based on rate of complete response and the rate of relapse from complete response. The international index incorporated clinical features reflecting the growth and invasive potential of the tumor (tumor stage, serum lactate dehydrogenase level, and number of extranodal disease sites), the patient’s response to the tumor (performance status), and the patient’s ability to tolerate intensive therapy (age and performance status). The age-adjusted international index used tumor stage, serum lactate dehydrogenase level, and performance status. For the international risk group (total of 2031), patients with low or low to intermediate risk (0 to 2 risk factors) had 5-year survival rates of 73 and 51 percent, respectively. Patients at high intermediate to high risk (3 to 5 risk factors) had 5-year survival rates of 43 and 26 percent, respectively. For the age-adjusted index (>60 years) (total of 1274), patients with low or low to intermediate risk (0 to 1 risk factors) had 5-year survival rates of 83 and 69 percent, respectively. Patients at high intermediate to high risk (2 to 3 risk factors) had 5-year survival rates of 46 and 32 percent, respectively. For the age-adjusted index (> 60 years) (total of 761), patients with low or low to intermediate risk (0 to 1 risk factors) had 5-year survival rates of 56 and 44 percent, respectively. Patients at high intermediate to high risk (2 to 3 risk factors) had 5-year survival rates of 37 and 21 percent, respectively. The authors of this study concluded that the indices they developed were significantly more accurate than the Ann Arbor classification in predicting long term survival, and that these indices should be used in patients with (aggressive) non-Hodgkin’s lymphoma and in the selection of appropriate therapeutic approaches.
## Table 3. Nasopharyngeal Undifferentiated Carcinoma – Differential Diagnosis

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Gender/Age</th>
<th>Clinical</th>
<th>Histology</th>
<th>IHC</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPC, UND</td>
<td>M&gt;F; &gt; 6th decade</td>
<td>Airway obstruction; aural symptoms;</td>
<td>Cohesive v dyscohesive; large cells with</td>
<td>Epithelial markers +</td>
<td>Radiotherapy</td>
<td>60% 5 year survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>neck mass</td>
<td>round nuclei, prominent eosinophilic nucleoli; 8 mitotic activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ML</td>
<td>M&gt;F; 5th-6th decade</td>
<td>Airway obstruction; aural symptoms;</td>
<td>Dyscohesive; diffuse growth; pleomorphic</td>
<td>Lymphoid markers +; B-cell</td>
<td>Radiotherapy</td>
<td>Dependent on clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>neck mass</td>
<td>large cells and immunoblasts; large cells</td>
<td>phenotyp e more common</td>
<td></td>
<td>stage: I: 50% II: 25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>with round nuclei, prominent eosinophilic</td>
<td>than T-cell phenotyp e</td>
<td></td>
<td>III: 17% IV: Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nucleoli; 8 mitotic activity; necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMM</td>
<td>M&gt;F; 5th-6th decade</td>
<td>Airway obstruction; aural symptoms;</td>
<td>Varied growth including solid, organoid,</td>
<td>S-100 protein and HMB-45 +</td>
<td>Surgery plus radiotherapy</td>
<td>Poor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pain; epistaxis</td>
<td>alveolar and storiform; pleomorphic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>epithelioid and spindle cells; numerous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>mitoses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RMS</td>
<td>M=F; 1st-2nd decades but can</td>
<td>Airway obstruction; aural symptoms;</td>
<td>Various histologic types: embryonal, alveolar,</td>
<td>Desmin, myoglobin and</td>
<td>Surgery, radiotherapy and</td>
<td>Dependent on clinical</td>
</tr>
<tr>
<td></td>
<td>be seen in adults</td>
<td>pain</td>
<td>pleomorphic; small round cells to large</td>
<td>muscle specific actin +</td>
<td>chemotherapy</td>
<td>stage: I: &gt;80% II: 70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pleomorphic cells</td>
<td></td>
<td></td>
<td>III: 50% IV: 20%</td>
</tr>
</tbody>
</table>

NPC - Nasopharyngeal undifferentiated carcinoma; ML - Malignant lymphoma; MMM - Mucosal malignant melanoma; RMS - Rhabdomyosarcoma

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References

**Metastatic Neoplasms To The Neck**


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