VM106 INTERESTING OVARIAN TUMORS

Maria J. Merino, MD
National Institutes of Health
Bethesda, Maryland

September 20, 2004
LIPID, STEROID TUMOR

CASE HISTORY: A 35 year old female was found to have a lower abdominal mass but refused further diagnostic studies. Three months later, a questionable ovarian cyst was found on gynecological examination. At this time she mentioned that her menses had ceased four months earlier. She also started to note severe acne, facial hirsutism weight gain and peripheral edema. On physical examination there was increase in dorsal fat deposition, generalized hirsutism, hypertension and a right lower abdominal mass. Diagnosis of Cushing’s Syndrome was made. An abdominal CT scan demonstrated bilateral ovarian masses with normal adrenal glands. The Pituitary gland was unremarkable. The patient underwent an exploratory laparotomy. At the time of surgery, bilateral bulky ovarian masses and extensive abdominal disease were found. The liver and adrenals appeared normal. A TAH-BSO and omentectomy was performed.

Gross Features:
• Frequently unilateral masses between 4-7 cm
• Solid multinodular tumor replacing the ovarian stroma.
• Yellow, orange to brown in color
• Areas of hemorrhage and necrosis were present.
• Multiple nodules with same characteristics in omentum

Microscopic Features:
• Nodules, sheets and nests of polyhedral cells separated by delicate thin fibrovascular septae.
• Cells contained large often eccentric round to oval vesicular nuclei with prominent nucleoli.
• Abundant eosinophilic and granular cytoplasm
• Reinke crystalloids were not found.
• Mitoses, necrosis and hemorrhage were present.

Immunohistochemistry:
• Positive for α-Inhibin, ACTH and vimentin

Electron microscopy:
Ultrastructural examination revealed the tumor cells to be compatible with a cell capable of actively secreting steroids. Lipid droplets, abundant endoplasm reticulum, and the characteristic mitochondria with plate-like cristae were present.

Differential Diagnosis:
• Leydig cell tumor
• Oxyphilic Clear cell Carcinoma
• Malignant Melanoma

Follow-up:
Postoperatively the patient did well despite incomplete tumor removal. Eventually, the tumor recurred with exacerbation of the Cushing’s syndrome which was resistant to chemotherapy. She expired 17 months after initial diagnosis. At autopsy the patient was cushingoid with extensive abdominal tumor that extended from the dome of the bladder to the diaphragm. Bilateral pulmonary emboli were found in both lungs.
DISCUSSION:
Cushing’s syndrome resulting from an ovarian neoplasm producing ACTH is not a rare occurrence. The increased plasma and urinary cortisol and 17-hydroxysteroid excretion, which were not suppressed by dexamethasone, and the presence of a low plasma ACTH level provide evidence that ACTH from an ectopic site was the cause of the Cushing’s syndrome. Further data that the tumor produced excess cortisol was reflected by the undetectable ACTH value found on RIA of tumor tissue, plus cortisol levels from tumor that, when multiplied by the huge bulk of the tissue mass, could explain the plasma cortisol levels that were present. These factors together with the higher cortisol concentration in ovarian venous plasma compared to the simultaneously obtained plasma cortisol level are all strong evidence indicating the production of cortisol by the ovarian carcinoma. More definitively, the absence of a pituitary adenoma together with atrophy of the adrenal fasciculata-reticularis rule out all but a tumor sources for the cortisol production. The histological and ultrastructural features were compatible with a steroid-secreting ovarian stromal tumor.
Steroid cell tumors affect females at any age with a mean of 40 years. Very few cases have been documented in children who present with precocious pseudopuberty and virilization. In approximately 75-90% of the cases, the initial manifestations are those associated with signs of masculinization such as hirsutism and virilization. Evidence of estrogenic activity is seen in 15-20% of these tumors and patients present with irregular bleeding and endometrial hyperplasia. Cushing syndrome occurs in about 5-10% of the cases.

The distinction between SCT and Leydig cell tumors is based in the absence of crystalloids of Reinke in the former. Special stains for Inhibin and assist to confirm the diagnosis of lipoid tumors. EM is also helpful when the characteristic mitochondria are found.

Leydig cell tumors can occur in two forms; as nodules or hyperplasia of the Hilus cells found in the hilum of the ovary near the nonmyelinated nerves and vascular spaces, or as tumors located in the ovarian stroma and that probably originate from ovarian stromal cells. Hilar cells probably increase in number after menopause. These cells are characterized by the presence of crystalloids of Reinke, which are absent in SCT.

Leydig cell tumors are as a rule, small, frequently solid although cystic areas may be present, and yellowish in color. Extensive hemorrhage and necrosis are rare. The tumors are composed of polygonal cells with marked eosinophilic some times granular cytoplasm and a vesicular nuclei with prominent nucleoli. Brown lipochrome pigment is common. Marked nuclear anaplasia and mitotic activity are rare except in tumors with aggressive behavior. Acidophilic, rod like structures, the crystalloids pathognomonic of these tumors can be easily identify by using PTAH or iron stains.

Differential diagnosis with oxyphilic clear cell carcinoma may be difficult, but areas of hobnailing and clear cells are frequently found. The clear cells are rich in glycogen and do not have lipid. They stain strongly with PAS stains. Also, clear cell tumors are negative for inhibin and will stain strongly for epithelial markers. Clear cell neoplasms are rarely associated with signs and symptoms of hormonal stimulation.

Amelanotic malignant melanoma should be included in the differential diagnosis. However, inhibin is rarely positive in melanomas, and when positive the pattern of staining is focal and not as intense as in SCT. Melanoma markers such as HMB45, Tirosanase and S-100 are strong positive.

Treatment and prognosis:
The behavior of these tumors is usually aggressive with pelvic dissemination and eventual metastases to lung. The treatment for this tumors is controversial but some patients receive therapy similar for adrenocortical carcinoma.
REFERENCES:

Adeyemi SD, Grange AO, Giwa-Osagie OF, et al. Adrenal rest tumour of the ovary associated with isosexual precocious pseudopuberty and cushingoid features.


Motlik K. Lipid cell tumors of the ovary. Int J Gynecol Pathol 6: (4) 389-389 DEC 1987


McCluggage WG. Value of inhibin staining in gynecological pathology
Int J Gynecol Pathol 20: (1) 79-85 JAN 2001

Yaziji H, Gown A. Immunohistochemical analysis of gynecologic tumors
Int J Gynecol Pathol 20: (1) 64-78 JAN 2001


MALIGNANT LYMPHOMA (PLASMA CELL TYPE)

CASE HISTORY: A 34 year old female was noted to have a pelvic mass on routine gynecologic examination. Ct scan revealed a large solid ovarian tumor and what appeared to be enlarged pelvic lymph nodes. She gave history of a associated symptoms such as fatigue, loss of appetite and occasional fever. Surgery was scheduled for an exploratory laparotomy with the intent to perform a unilateral oophorectomy.

Gross Features:
- Large, solid masses, ranging from 4 to 15 cm
- Smooth external surface
- Soft rubbery masses with the characteristic fleshy or white color.
- Areas of hemorrhage and necrosis may be present especially in large tumors.

Microscopic Features:
- Histology is similar to nodal lymphomas
- All types of lymphoma have been described

Immunohistochemistry:
Positive LCA and lymphoid markers
Negative epithelial and inhibin markers

Differential Diagnoses:
- Granulosa cell tumor
- Disgerminoma
- Small cell carcinoma
- Metastases from other sites such as breast cancer

DISCUSSION:
Malignant Lymphoma of the ovary is rare and can occur at any age. The most common clinical manifestation is that of unilateral or bilateral ovarian masses. Fewer than 1% of patients with disseminated malignant lymphoma initially present with ovarian enlargement.

The immunohistochemical findings indicate that malignant lymphomas involving the ovary are predominantly B-cell neoplasms. Thirty seven of 39 lymphomas (96%) analyzed by Monterroso et al, had a B-cell immunophenotype and of the 13 lymphomas, not studied immunophenotypically, nine were Burkitt’s lymphomas, three had a focally follicular pattern (two large cell, one small cleaved cell), and one case was a diffuse large-cell lymphoma. Only one tumor had a T-cell immunophenotype.

Lymphomas arising within the ovaries are rare. Guided by criteria previously used by others, these neoplasms can be divided into two groups: primary and secondary. The primary group of lymphomas is usually confined to the ovary. Patients with secondary ovarian lymphomas had extensive disease at other sites or a history of lymphoma. Another group of tumors could be designated as uncertain. These neoplasms have extensive involvement of the ovary with a lesser degree of tumor in regional lymph nodes or pelvic structures in a pattern consistent with a primary ovarian tumor.

The presence of normal lymphoid tissue in the ovaries is controversial. Woodruff et al. have stated lymphoid aggregates may be found in the hilus and medulla of normal ovaries. In contrast, Nelson et al. had stated earlier that normal lymphoid tissue is not present in the ovaries. To address this point, we studied the ovaries of 24 women, 16 under
the age of 45 years, selected consecutively from patients who had undergone autopsy at our hospital.

We identified small numbers of lymphocytes in the ovaries, surrounding blood vessels in the hilus, and within or surrounding corpora lutea in 13 patients (54%). In two patients, well-defined aggregates of lymphocytes were found.

Prior studies suggest, that the vast majority of lymphoid neoplasms involving the ovaries are non-Hodgkin’s lymphomas, and only eight cases of Hodgkin’s disease involving the ovary have been reported. Furthermore, some of these eight cases have been poorly documented and were reported before the widespread availability of immunophenotypic analysis. Thus, Hodgkin’s disease involving the ovary is a truly rare occurrence.

For several reasons, lymphomas involving the ovary are difficult to stage. First, the Ann Arbor staging system was designed for Hodgkin’s disease and has inherent deficiencies in the staging of non-Hodgkin’s lymphomas, particularly those neoplasms arising at extranodal sites. Second, the Ann Arbor system is inadequate for the staging of children with non-Hodgkin’s lymphomas, in whom measures of tumor bulk correlate best with prognosis. The Ann Arbor system does not effectively address the issue of tumor bulk. Third, the Ann Arbor system does not address the issue of bilateral ovarian involvement. Are patients with bilateral ovarian involvement with no other sites of disease best considered as stage IV? Bilateral involvement by lymphomas in other extranodal sites such as the orbit and the breast does not appear to affect prognosis adversely.

The results of this study also suggest that bilateral ovarian involvement is a sign of systemic lymphomas, justifying the designation of patients with bilateral disease as being stage IV in the Ann Arbor system. All four patients with primary ovarian lymphomas had unilateral involvement. In contrast, the patients with bilateral ovarian involvement had clinical and histologic findings akin to systemic lymphomas secondarily involving the ovaries.

**Prognosis and Treatment:**

Patients with Ovarian lymphoma usually have a poor outcome, although long time survivals have been reported for patients with localized disease and treated with chemotherapy. The prognosis also depends of the stage of the disease.

**HISTOLOGIC AND IMMUNOPHENOTYPIC FINDINGS:**

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REFERENCES:


Boyle FM, Taylor KM, Bell JR: Ovarian Follicular Non-HODGKINS-Lymphoma, Pathology 23: (2) 164-166 1991


Gerstner GJ: BURKITTS-Lymphoma of the ovary- Geburtsh Frauenheilk 47: (10) 745-746 1987


**BRENNER TUMORS**

These neoplasms are characterized by the presence of epithelial cells similar to the transitional epithelium of the urinary bladder. They comprise about 2% of all ovarian tumors and can occur at any age. Brenner tumors can be associated with mucinous cystoadenomas and teratomas in up to 10% of the cases and can occasionally be hormonally active.

**Benign Brenner:**

The majority of Brenner tumors are an incidental finding. Grossly, they appear as white-grey solid homogeneous masses, of variable size (up to 10 cm). The ovarian surface is smooth and without papillae. Histologically, the tumors have nests of cells with grooved nuclei embedded in a dense proliferative stroma. The clusters of cells can undergo mucinous metaplasia.

**Proliferative Brenner:**

Borderline tumors of Brenner type have not been described, since there are no reported cases with potential for metastases or death of the patient. Only two cases of PB with aggressive behavior have been reported; one that developed local recurrences and another patient that developed distant metastases. The true nature of these two cases however remains controversial. PB tumors occur predominantly in postmenopausal women that clinically present with abdominal masses.

Grossly the tumors have a smooth surface, can be solid and cystic and have a size that varies between 5 and 30 cm. The solid areas, look similar to benign Brenners tumors. The cysts can contain papillary structures. Microscopically, the papillae are lined by transitional epithelium identical to low grade TCC. There is no evidence of stromal invasion. These tumors have excellent prognosis and the recommended modality of treatment is unilateral oophorectomy.

**REFERENCES:**


SMALL CELL CARCINOMA, HYPERCALCEMIC TYPE

Ovarian small cell carcinoma, which is associated with paraneoplastic hypercalcemia in two-thirds of cases, is a rare and distinctive type of undifferentiated carcinoma. First described by Dickersin et al. in 1982, the largest series of cases was published by Young and coworkers in 1994. Numerous case reports can be found in the literature. The histogenesis of these tumors remains uncertain. The nature of the substance secreted by the ovarian small cell carcinoma that results in hypercalcemia is also unclear. Some publications have reported reactivity to parathyroid hormone and/or parathyroid-hormone related protein. Nevertheless, in most instances, attempts to recover these substances have been unsuccessful. Presently, the neuroendocrine differentiation of these tumors has not been proven.

These are rare and often lethal neoplasms, which occur in young women. The age of the patients has ranged from 9 to 45 years of age (average, 24). These tumors are the most frequently encountered forms of undifferentiated ovarian carcinoma in women under 40 years old. The familial occurrence of small cell carcinoma of the hypercalcemic type, appears to be a rare phenomenon; few such cases have been reported. Most patients have presented with nonspecific symptoms including abdominal pain or swelling, nausea, vomiting, anorexia, and weight loss; symptoms have rarely been related to hypercalcemia. These tumors are unilateral in 99% of cases. By the time of discovery at laparotomy, extraovarian spread is already present in about 50% of patients.

The tumors range in size from 6 to 26 cm (average, 15.3). On gross examination, these neoplasms are usually large and solid, often with cystic degeneration. The cut surface of the ovary reveals a lobulated, white-cream to gray, fleshy, or friable surface with large or focal areas of necrosis and hemorrhage. Cystic degeneration can be seen and one tumor was described in the literature as a unilocular cyst.

On light microscopy, different histologic patterns have been described. The most common appearance is a diffuse, solid sheet of generally small and rounded, closely packed epithelial cells. These cells can also grow in nests, cords, trabeculae, and irregular groups. Individual cells have little cytoplasm and small round-ovoid, hyperchromatic nuclei with single small nucleoli. Focal areas with a spindle-cell pattern have also been noted. Follicle-like structures of varying sizes lined with neoplastic cells are present in 80% of the tumors. These spaces can be either empty or can contain an eosinophilic or basophilic material. Mitotic figures are numerous and often atypical. Mucin-rich cells ranging from benign-appearing and atypical to scattered signet-ring cells are seen in about 12% of cases. The scant stromal matrix can be dense, myxoid, or edematous.

In approximately 50% of the tumors, there are focal areas composed of large cells with copious, pale to slightly eosinophilic cytoplasm, central, and often vesicular nuclei, and prominent nucleoli. Large, pale intracytoplasmic hyaline globules have been described within these large cells. However, these cells rarely predominate. Young et al. designated small cell carcinomas of the hypercalcemic type with a predominance of large cells as the large cell variant of small cell carcinoma, hypercalcemic type. A case report of this variant has been recently published. The clinicopathology, immunohistochemistry, and the range of histologic patterns are similar to conventional small cell carcinomas of the hypercalcemic type. The presence of large cells does not appear to predict a worse outcome.

Special staining and ultrastructural examination have not revealed any features that identify the cell of origin of this tumor. Tumor cells have been reported variably positive for vimentin, cytokeratin, neuron-specific enolase, chromogranin, parathyroid hormone-related protein, and epithelial membrane antigen reported that 80% of tumors exhibit p53 protein accumulation in immunohistochemistry studies. By electron microscopy, large amounts of dilated and filled cisternae of rough endoplasmic reticulum have been their most constant
feature; in addition, the epithelial nature of the tumor cells has been. A prominent ultrastructural finding in cases of large cell variant is the presence of numerous paranuclear whorls of microfilaments, which corresponds with the dense globular appearance of the cytoplasm under light microscopy. The presence of convincing neurosecretory granules has not yet been confirmed in ovarian small cell carcinomas. although there is one report of scattered structures that were interpreted as dense core granules of the neuroendocrine type. Flow cytometry analysis reveals that the tumor cells show a diploid DNA pattern, a surprising characteristic in view of the high degree of malignancy of this tumor. However, one case of the large cell variant of small cell carcinoma with hypercalcemia was reported as aneuploid. Overall, DNA ploidy and proliferative activity of this neoplasm do not correlate with stage and outcome.

Small cell carcinomas of the hypercalcemic type can be confused with ovarian small cell carcinomas of the pulmonary type, granulosa cell tumors (adult or juvenile), malignant lymphomas, primitive neuroectodermal tumors, primary or metastatic malignant melanoma, metastatic alveolar rhabdomyosarcoma, and desmoplastic small round cell tumors.

The cells of small cell carcinoma do not have the characteristic pale and often grooved nuclei of adult granulosa cell tumors. The much higher mitotic rate in small cell carcinomas and the formation of Call-Exner bodies in adult granulosa cell tumors also aid in the distinction between these two entities. The morphologic appearance of the tumor with the follicle-like spaces and the young age of most patients result in misinterpretation of some cases as juvenile granulosa cell tumors (JGCT). Typical small cell carcinomas are composed of small cells with little cytoplasm in contrast to JGCT cells with abundant amounts of cytoplasm. More difficulty exists with the large cell variant of small cell carcinoma, however these tumors tend to have at least focal areas of typical small cell carcinoma with scant cytoplasm, which are not features of JGCTs. JGCTs have mitotic figures, but usually much less than small cell carcinomas. A thecal cell component, which is usually present in JGCTs, is not observed in small cell carcinomas. In addition, clinical evidence of estrogen production, which is associated with most granulosa cell tumors, has not been found in cases of small cell carcinoma, nor has hypercalcemia been seen in cases of granulosa cell tumors. Finally, small cell carcinomas are negative for alpha-inhibin and can be positive for epithelial membrane antigen, in contrast to JGCTs.

Small cell carcinomas can be differentiated from diffuse malignant lymphomas by determining the epithelial nature of the tumors with immunohistochemistry stains, which show reactivity to various cytokeratins, vimentin, and epithelial membrane antigen. However, in most cases the clinical and cytologic features of the two tumors permit their distinction. Confusion with metastatic malignant melanoma has occurred in cases of melanoma with small cells and follicle-like structures. The clinical history and special studies are important in making the correct diagnosis in these cases. The differential diagnosis of small cell carcinoma also includes other small cell malignant tumors of the ovary, such as primitive neuroectodermal tumors and various small cell sarcomas. All of these tumors have distinctive clinical, light microscopic, immunohistochemical, and electron microscopic features that differ from those of the small cell carcinoma of hypercalcemic type. As in any case, thorough sampling of the tumor is very important.

Small cell carcinoma of the hypercalcemic type is a very aggressive tumor with poor prognosis. In the largest series of these cases in the literature by Young and coworkers, almost all the patients with stages higher than IA died of disease. Of 42 patients with stage IA tumors, (with follow-up information), 14 had disease-free follow-up, which ranged from 1 to 13 years (average, 5.7) post-surgery; 23 died of the disease within 2 years, and five were alive with recurrences. Apparently, there is no significant difference in prognosis between the large cell variant and the classical small cell carcinoma of hypercalcemic type. Tumors that occur in women older than 30 years of age, lack hypercalcemia, and are less than 10 cm are
associated with a more favorable prognosis. There appears to be no place for conservative surgery regardless of an early stage of disease, or the young age of the patient. The role of adjuvant therapy is unclear. Combination chemotherapy and radiation therapy for high-stage tumors have been generally unsuccessful. Serum calcium levels can be used as a marker in monitoring treatment response and recurrence, since levels usually fall to normal for those cases in which the tumor has been completely removed.

REFERENCES:
Daubenton JD, Sinclair-Smith C. Severe hypercalcemia in association with a juvenile granulosa cell tumor of the ovary. Med Pediatric Oncol 34: (4) 301-303 APR 2000


