Post-transplant Lymphoproliferative Disorders
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Post-transplant lymphoproliferative disorder (PTLD) is an expansion of one or more clones of lymphoid cells that occur in the setting of induced immunosuppression for either solid organ or bone marrow transplant (BMT). While the etiology is not entirely understood, most cases are thought to arise as an exaggerated immune response to a primary Epstein-Barr virus (EBV) infection or reactivation. EBV infection is primarily controlled by T-cell immune surveillance and these cells are the primary target of immunosuppression typical of transplant regimens. As such, most cases of PTLD involve an expansion of B-cell clones. Still to be explained is the uncommon occurrence of T-cell forms of PTLD and EBV-negative PTLD which account for about 20% of cases.

The frequency, sites of involvement and onset of PTLD are all related to the type of graft and immunosuppressive regimen employed. PTLD affects 1-5% of patients with solid organ transplants with variation among the different types of allograft. BMT recipients are generally considered low risk for PTLD (~1%); however, HLA-mismatched transplants, T-cell depleted bone marrow grafts and immunosuppression for graft-versus-host disease (GVHD) can have rates as high as 20%. Patients may present with either nodal or extranodal involvement, while blood involvement is uncommon. Nodal and GI involvement are typical of cyclosporine or tacrolimus-based regimens, while azathioprine-based regimens typically have a clinical picture dominated by extranodal disease including CNS involvement.

In addition, PTLD affects the allograft in 25% of cases, thereby complicating evaluation of graft rejection. The majority of cases of PTLD in BMT patients occur in the first 5 months after transplant. The presentation in solid organ cases is more delayed, with a mean interval to PTLD of 15 months for those treated with cyclosporine A and 48 months in those treated with azathioprine. The median interval to EBV-negative PTLD is much greater (4-5 years) than that of EBV-positive PTLD (6-10 months).

The pathologic features of PTLD are quite variable, as expected with the proposed mechanism of an exaggerated immune response to EBV. In early lesions, one may see only plasmacytic hyperplasia or an infectious
mononucleosis-type reaction within lymph nodes. More advanced is the polymorphic form of PTLD, which is characterized by some degree of effacement in lymph node architecture. Finally, monomorphic PTLD and Hodgkin lymphoma-like PTLD shows lymphoid proliferations that mimic typical non-Hodgkin lymphoma or Hodgkin lymphoma respectively.

Studies to determine clonality, including immunophenotyping and molecular analysis of antigen receptors, demonstrate polyclonal proliferations in the early PTLD lesions, while monoclonal proliferations characterize the polymorphic and monomorphic variants. Interestingly, oncogene mutations are typically observed in the monomorphic but not the polymorphic forms. Of clinical relevance, decreasing immunosuppression leads to resolution in most cases of early PTLD (plasmacytic hyperplasia and infectious mononucleosis-like PTLD) and some cases of polymorphic PTLD, while the monomorphic variants generally require treatment with chemotherapy.

Bibliography
