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# REVIEW

# **Post-transplant Lymphoproliferative Disorders**

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Post-transplant lymphoproliferative disorder (PTLD) is one of the most dreaded complications of orthotopic transplantation. It consists of a heterogeneous group of lymphoproliferative disorders of varying clonal composition, occurring in immunosuppressed organ allograft recipients and is frequently due to EBV infection. It is most common in heart/lung transplants followed by heart, liver, and kidney and rarely in bone marrow transplants. Clinically, PTLD can present in a number of ways ranging from features resembling infectious lymphoproliferative mononucleosis, masses involving both nodal and extranodal locations, to a fulminant form characterized by a combination of

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Post-transplant lymphoproliferative disorder (PTLD) consists of a heterogeneous group of lymphoproliferative disorders of varying clonal composition occurring in immunosuppressed organ allograft recipients frequently due to EBV infection.<sup>9,12,14,19,22,23,25,28</sup> PTLD is one of the most dreaded complications of orthotopic transplantation. The reported incidence varies according to the type of transplant, being about 1% in kidney transplants, about 3% in liver transplants, about 5% in heart transplants and 5 to 10% in heart/lung transplants. It is rare in bone marrow transplants.<sup>1,2,3,13,15,16,17,18,20,27</sup> Diagnosis is usually made from biopsy material obtained from patients suspected of having PTLD or other complications such as rejection. Recently it has been shown that fine needle aspiration material can be as sensitive in making the diagnosis when reviewed by experienced cytopathologists.5

peripheral lymphadenopathy, severe metabolic acidosis, organ failure or allograft dysfunction. Pathologically PTLD is characterized by a dense inflammatory infiltrate with a spectrum ranging from that found in infectious mononucleosis to a polymorphous B-cell hyperplasia to that of a monomorphous lymphoma. Analysis of EBV is especially useful for the diagnosis of early cases of PTLD. In addition, immunophenotyping to determine the lymphocyte type (B or T cell type) and monoclonality are most helpful in determining the prognosis. (Pathology Oncology Research Vol 3, No 3, 177–182, 1997)

Post-transplant lymphoproliferative disorders can occur as early as four to six weeks after transplantation but usually develop within six months of transplantation.<sup>17,18</sup> There seems to be a relationship between PTLD and increased immunosuppression given for rejection episodes.

The typical story is that of a transplant patient on cyclosporine A who suffers a rejection episode which either does not respond to steroids or rapidly relapses after tapering the steroids. Then treatment with one or two courses of OKT3 or antilymphocyte globulin is tried. Shortly after that the patient develops PTLD.<sup>11</sup> Some PTLDs regress following reduction of immuno-suppression whereas others progress despite treatment.

Clinically, PTLD can present in a number of ways:

- 1. As oropharyngeal hyperplasia or lymphadenopathy which resembles infectious mononucleosis.
- As a fulminant rapidly progressive polyclonal lymphoid hyperplasia.
- 3. Or most commonly as a single or metastatic polyclonal or clonal tumors. These lesions occur most often in extranodal locations, frequently involving the brain, gastrointestinal tract, or allograft organ.<sup>8,11</sup>

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**Figure 1.** PTLD of the stomach. Low-power view of the gastric mucosa showing a diffuse lymphoid infiltrate separating and distorting the gastric glands from one another.



**Figure 2.** PTLD of the liver. Low-power view of the liver showing marked widening of the portal tracts due to a dense lymphoid infiltrate.

The fulminant form of PTLD is characterized by a combination of peripheral lymphadenopathy, severe metabolic acidosis, organ failure or allograft dysfunction.<sup>15,17</sup> Evidence of a close association of active EBV infection, either primary or by reactivation, is found in approximately 90% of patients.19 EBV genomic DNA can be detected in up to 100% of patients depending on the sensitivity of the methods used.<sup>6,9,12,21</sup> Multiple forms of EBV are found in the polymorphous lymphoid infiltrate suggesting that the early changes of PTLD represent a spectrum of EBV driven lymphoid B-cell proliferations arising as polyclonal expansions of EBV infected cells. These then progress to a monoclonal monomorphous Bcell lymphoma.<sup>6,9,11,12,21,28</sup> The EBV-negative PTLDs have been reportedly primarily in kidney transplant patients and occur from 3.5 to 12 years following transplantation, a much later posttransplant time than the usual PTLDs.<sup>8</sup> Almost all cases of PTLD are of B-cell origin, although rare instances of T-cell proliferations have been reported.10 In some instances the proliferating B-lymphocytes were shown to be of donor origin apparently originating from "passenger" lymphocytes within the donor organ.<sup>17,25</sup> Epstein-Barr virus (EBV) has been implicated as a cofactor in most cases. In non-immunosuppressed individuals T lymphocytes play a central role in the coordinated host response to EBV-induced B cell proliferation and interference with this control in the allograft recipient is thought to be an important factor in producing an environment suitable for the development of PTLD.<sup>18</sup> PTLD can be either monoclonal or polyclonal. The polyclonal type is commonly polymorphous but many have been shown to have a monoclonal component by genotypic analysis. In some cases different monoclonal and polyclonal populations are present in the affected organs or sites.<sup>17,27</sup>

Table 1. Post-transplant lymphoproliferative disorders. Histologic categories

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- a. Reactive plasmacytic hyperplasia b. Infectious mononucleosis pattern
- 2. Polymorphous B-cell hyperplasia and lymphoma

3. Monomorphous lymphomatous infiltrate

- 1. Multiple EBV infections.
- 2. Usually polyclonal
- 3. Lack oncogene and tumor suppressor genes
- 1.Commonly monoclonal but may be polyclonal
- 2. Usually single form of EBV
- 3. Lack oncogene and tumor suppressor genes.
- 1. Monoclonal. Usually B cell, rarely T cell
- 2. Usually single form of EBV
- 3. Contains oncogene (c-myc, ras) and tumor suppressor genes (p 53)

4. Miscellaneous PTLD patterns. a. Plasmacytoma-like b. Hodgkin's-like

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*Figure 3.* Polymorphous PTLD of the small intestine. The lymphoid infiltrate consists primarily of lymphocytes ranging from small mature cells to small and large cleaved lymphocytes.



**Figure 4.** Monomorphous PTLD of the colon. The infiltrate consists primarily of large atypical B cells with features of plasmacytoid and immunoblastic cell types.



**Figure 5.** Illustrates the monoclonality of monomorphous PTLD. This immunohistochemical stain of figure 4 shows kappa light-chain positivity in the monotypic lymphocytes.

# Pathology

*Grossly*, PTLD usually presents either as a tumorous mass or as an infiltrative lesion indistinguishable from the usual lymphomas. Gastrointestinal lesions are commonly superficially ulcerated and covered with a greenish-yellow fibrinous exudate. On cut surface the tumor has a grayish color, and a soft consistency. It may extend to the serosa sometimes resulting in perforation.<sup>15,17,18</sup> Lesions of the liver are diffuse and frequently cannot be identified grossly since the portal tracts are primarily involved. In advanced stages lymphomatous nodules may occur. <sup>15,17,18</sup>

*Histologically*, PTLD is characterized by a dense inflammatory infiltrate with a spectrum ranging from that found in infectious mononucleosis to that of lymphoma.<sup>8,11,27</sup> In the gastrointestinal tract the infiltrate is present in the mucosa and submucosa in the early stages (*Fig. 1*) and then progresses into the muscularis propria and beyond. In the liver the lesion is primarily located within the portal tracts although it often extends through the limiting plate into the adjacent lobule. (*Fig. 2*)

The infiltrate is either polymorphous or monomorphous, and may be associated with extensive necrosis. Morphologically there are three major categories (*Table 1*).

#### 1. Early reactive-like lesions

These involve mainly the oropharynx and lymph nodes with preservation of nodal architecture. Histologically, they can be difficult to differentiate from simple reactive hyperplasia. There are two major morphologic patterns namely, infectious mononucleosis pattern (infiltrate composed of lymphocytes, plasma cells and abnormal immunoblasts) and reactive plasmacytic hyperplasia. These lesions contain evidence of multiple EBV infections and lack evidence of oncogene and tumor suppressor gene alterations.<sup>11</sup>

### 2. Polymorphous B-cell hyperplasia and lymphoma (Fig. 3)

These lesions producing effacement of lymph node architecture and a dense lymphoproliferative infiltrate of many organs often with associated extranodal necrosis. The infiltrate shows a full range of B and T-cell infiltrates ranging from immature to mature lymphocytes including one or more of the following types, namely, small mature cells, small and large cleaved and/or non-cleaved cells, immunoblasts some of which may be atypical, as well as plasma and plasmacytoid cells Mitotic figures are commonly seen.

There may be extensive necrosis and then numerous neutrophils and histiocytes are seen. Most cases are monoclonal although rarely polyclonal lesions are seen. The lesions usually contain a single form of EBV but lack oncogene (c-myc, ras) and tumor suppressor gene (p53) alterations.<sup>8,11</sup>

# 3. Monomorphous monoclonal lymphomatous infiltrate (Fig. 4,5)

These lesions have the features of high-grade lymphomas. The monomorphous infiltrate consists primarily of large atypical B-cell lymphocytes, frequently with features of immunoblastic lymphoma and may also show extensive necrosis.<sup>17</sup> The monomorphous infiltrate contains a single form of EBV (*Fig. 6*) but unlike the polymorphous PTLD it contains oncogene (c-myc, ras) and tumor suppressor gene (p53) alterations.<sup>8,10</sup> on rare occasions T-cell lymphomas have been found.<sup>7</sup>

# 4. Miscellaneous PTLD patterns.

These include cases with a plasmacytomalike pattern and Hodgkin's-like appearance. <sup>4,8,27</sup>

Unfortunately, analysis of clonality cannot be used to reliably predict the behavior in individual patients. For example Nalesnik et al<sup>17</sup> have shown that polymorphous polyclonal proliferations developing shortly after transplantation, often have a fulminant and fatal course.

### Diagnostic workup

Analysis for EBV is especially useful for the diagnosis of early cases of PTLD. There are a number of diagnostic methods now available to detect EBV. These include EBV by polymerase chain reaction (PCR) for EBV DNA, insitu hybridization for EBV RNA (EBER) and EBV latent membrane protein (LMP). EBER and PCR are the most sensitive but EBER and LMP can be done on formalin fixed tissues.<sup>14</sup> In addition, immunophenotyping to determine the lymphocyte type (B or T cell type), monoclonality or not (on frozen tissue) and flow cytometry on fresh tissue, can also be very helpful. Finally, oncogene (c-myc, ras) and tumor suppressor gene (p53) markers, and preservation of fresh tissue for molecular genetic analysis, is quite helpful for the advanced lesions but not critically important currently with regards to treatment.

## Differential diagnosis<sup>8</sup>

Once a monomorphous monoclonal lymphoproliferative lesion has developed in the clinical setting of posttransplantation, there is usually no diagnostic problem. Problem areas occur in the early stages trying to differentiate other inflammatory causes such as rejection, infections other than EBV, and rare disorders such as HIVassociated hyperplastic lymphadenopathy and systemic



*Figure 6.* EBV positivity in case of PTLD of the colon. Note the numerous positively staining nuclei within the atypical lymphocytic infiltrate.



**Figure 7.** Atypical lymphoid infiltrate mimicking PTLD. Note the dense infiltrate within the portal tracts of the liver. This atypical infiltrate occurred within the recipient liver two days following liver transplantation. The infiltrate disappeared about ten days later.



*Figure 8.* Atypical lymphoid infiltrate mimicking PTLD. High power view of the lymphoid infiltrate which resembles polymorphous PTLD. Note the presence of a mixture of mature lymphocytes, plasma cells and large atypical immunoblastic cells.

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Castleman's disease, which may resemble PTLD.<sup>11</sup> PTLD in liver transplants can be a problem since the early lesions may resemble other common inflammatory disorders in these patients, namely rejection and recurrent chronic hepatitis. Recently, we detected a lesion in a liver transplant that showed features typical of PTLD within one week postransplant. (*Fig. 7,8*) Since PTLD does not occur so rapidly in a first post-transplantation patient we were unsure of the cause. The lesion resolved without treatment in about a week and most likely represented a viral infection. Once PTLD is suspected, as mentioned above, clinical setting and the presence of immunohistochemical markers for EBV and monoclonality are helpful in arriving at a diagnosis.

# Treatment

Reduction of immunosuppression is the primary treatment of choice. Although some reported cases of monoclonal PTLD have regressed completely simply by discontinuing all immunosuppressive therapy, there is evidence that monoclonal PTLD, especially involving multiple sites, has a worse prognosis and usually does not regress with discontinuance of immunosuppression alone.<sup>16,23,24</sup> This reduction of immunosuppression is usually coupled with the administration of Acyclovir and surgical treatment of symptomatic and resectable lesions, such as intestinal perforation. Antilymphoma chemotherapy is given at most centers only in cases in which there is tumor progression in spite of a reduction of immunosuppression.<sup>18</sup>

Tumor regression can often occur remarkably rapidly. Disappearance of tumors within 1–2 weeks is not unusual and in some instances tumor regression appears to be accompanied by maturation of the clonal PTLD cells into mature plasma cells together with a decrease in numbers. In other instances, tumor regression results in progressively more malignant clones and ultimately death.<sup>17,18</sup>

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