

Leukaemia Section

Review

Classical Hodgkin lymphoma type PTLD

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Abstract

Post-transplant lymphoproliferative disorders (PTLDs) are serious, life-threatening complications of transplantation, which represent a heterogeneous group of lymphoproliferative diseases and show a spectrum of clinical, morphologic, and molecular genetic features ranging from reactive polyclonal lesions to frank lymphomas. Classical Hodgkin lymphoma (CHL) is the least common form of PTLT, which is almost always EBV-positive and should fulfill the criteria for CHL.

KEYWORDS

Post-transplant lymphoproliferative disorders; lymphoma

Clinics and pathology

Disease

The term "post-transplant lymphoproliferative disorder" or disease (PTLD) was first introduced in 1984 by Starzl (Starzl et al. 1984). PTLTs are serious, life-threatening complications of solid-organ transplantation (SOT) and bone marrow transplantation, and are associated with high mortality. PTLTs represent a heterogeneous group of lymphoproliferative diseases, which show a spectrum of clinical, morphologic, and molecular

genetic features ranging from reactive polyclonal lesions to frank lymphomas.

PTLTs are classified into early lesions, polymorphic, monomorphic, and classical Hodgkin's lymphoma-like PTLT.

P CHL type PTLT occurs in the post-transplant setting, most often in renal transplant patients, composed of variable numbers of HRS cells admixed with a rich inflammatory background. The composition of the reactive cellular infiltrate varies according to the histological subtype (Swerdlow, et al., 2008. Mucha, et al. 2010.).

Phenotype/cell stem origin

The majority (>90%) of PTLT in solid organ recipients are of host origin and only a minority of donor origin. Donor origin PTLT appear to be most common in liver and lung allograft recipients, and frequently involve the allograft. In contrast, the majority of PTLT in bone marrow (BM) allograft recipients are of donor origin, as would be expected, since successful engraftment results in an immune system that is nearly exclusively of donor origin (Chadburn, et al., 1995. Swerdlow, et al., 2008).

Phenotypically, CHL type PTLT cases show CD30+, CD15+, CD20- in HRS cells, but some cases are CD15-. Because RS like cells may be seen in early, polymorphic and some monomorphic PTLT, the diagnosis of CHL must be distinguished from

Hodgkin like lesions, in which the EBV+ RS like cells are CD45+, CD30+, CD15-, CD20+ and small to intermediate-sized EBV+ lymphoid cells can be seen as well (werdlow, et al ,2008. Pitman et al,2006. Ranfanathan, et al, 2004).

Epidemiology

The incidence of PTLD ranges from 1-3 % in renal to 5-20 % in lung and intestinal transplantation, related to the type of transplanted organ, intensity of IS, age, and viral infection, etc. (Opelz, 2003. Opelz,1993). In contrast, the incidence of PTLD after BMT is about 1.0 % for recipients from HLA-compatible related donors (lower than that of SOT), but in up to 25 % for high-risk patients (Curtis, 1999). However, the field has evolved during the last decade. Hoegh-Petersen et al. found a frequency of 8.1 % among 307 allo-HSCT recipients who had also received ATG-based conditioning. Kamani et al. found an overall incidence of 2.3 % for post-transplant malignancy (most of which were PTLD) in patients receiving such transplant for primary immunodeficiency disorders. The highest subgroup, those patients with Wiskott-Aldrich syndrome, had a 3.3 % frequency.

In our hospital, it is 1.5 % (9/585) from August 2002 to October 2006 and about 1 % (9/857) from November 2006 to November 2009 after allo-HSCT, respectively. The incidence of PTLD was higher in mismatched or unrelated HSCT group than that of conventional one, 3.4 % (7/208), 2.3 % (1/44) versus 0/323. It was also higher in patients with conditioning regimen including ATG than those without, 3.4 % (9/262) vs. 0/323. CHL type PTLD is the least common major form of PTLD (Swerdlow, et al ,2008. Chen, et al ,2013).

Clinics

The clinical features of PTLD differ from those of lymphomas observed in the general population.

Symptoms may be mild, such as fever, mononucleosis-like syndrome, lymphadenopathy, recurrent infections or severe organ dysfunction. The variable manifestation of PTLD depends on many factors, such as the type of transplanted organ or IS used, histopathology and time elapsed since transplantation. The first year after transplantation is important, in lung recipients, more than 50 % of all PTLDs develop during the first post-transplant year. Our data showed that 88.2 % of patients (15/17) were diagnosed within 7 months after transplantation (1.5-7 months), and the median interval after transplantation to the diagnosis was 2.5 months (mean 4.7 months, range 1.5-19 months), shorter than that of SOT. The frequent sites of PTLD include GI (jejunum more often than colon), lymph nodes, and central nervous system, different from type to type of transplantation (Opelz, et al, 2003. Swerdlow, et al ,2008).

Pathology

CHL type PTLD is characterized by effacement of the architecture and composed of variable numbers of HRS cells admixed with a rich inflammatory background. The composition of the reactive cellular infiltrate varies according to the histological subtype. The diagnosis of CHL must be distinguished from Hodgkin like lesions, in which the EBV+ RS like cells are CD45+, CD30+, CD15-, CD20+ and small to intermediate-sized EBV+ lymphoid cells can be seen as well, especially from polymorphic PTLD, and the overall morphologic features should be depended on.

There are four histologic subtypes of classical Hodgkin lymphomas, i.e. nodular sclerosis cHL, mixed cellularity cHL, lymphocyte-rich cHL, and lymphocyte depleted cHL, according to their cellularity and background. MC subtype is most common.

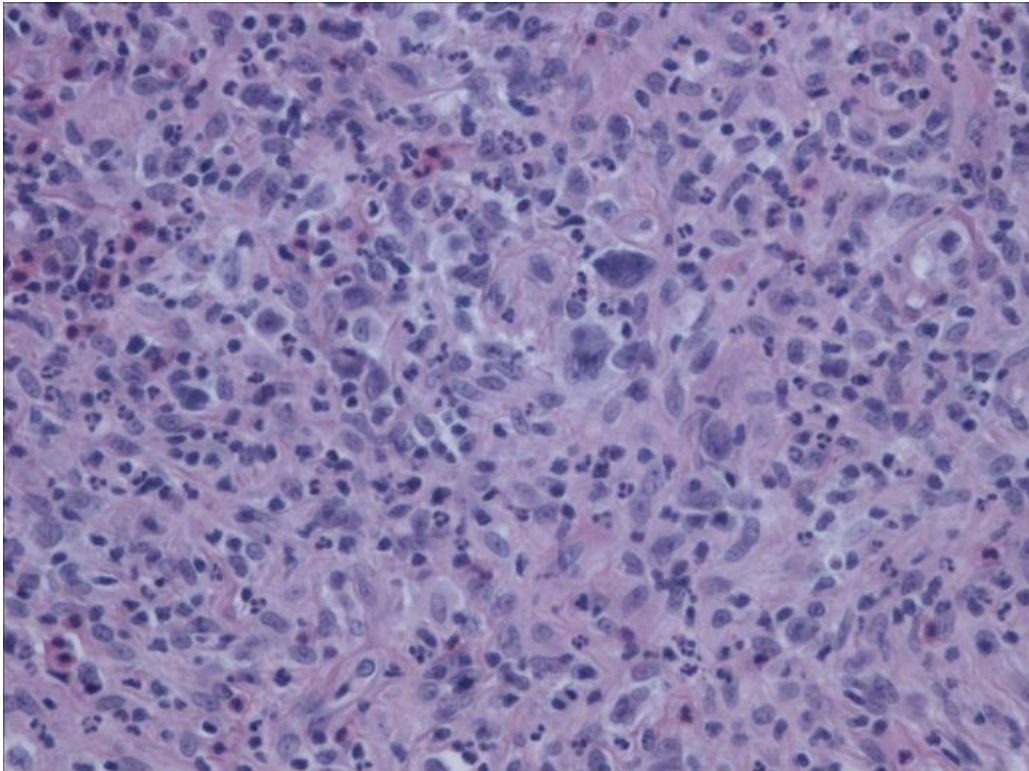


Figure 1. Hodgkin type PTLD. Effacement of the architecture and HRS cells surrounded by small lymphocytes, neutrophils and eosinophils (HE stain).

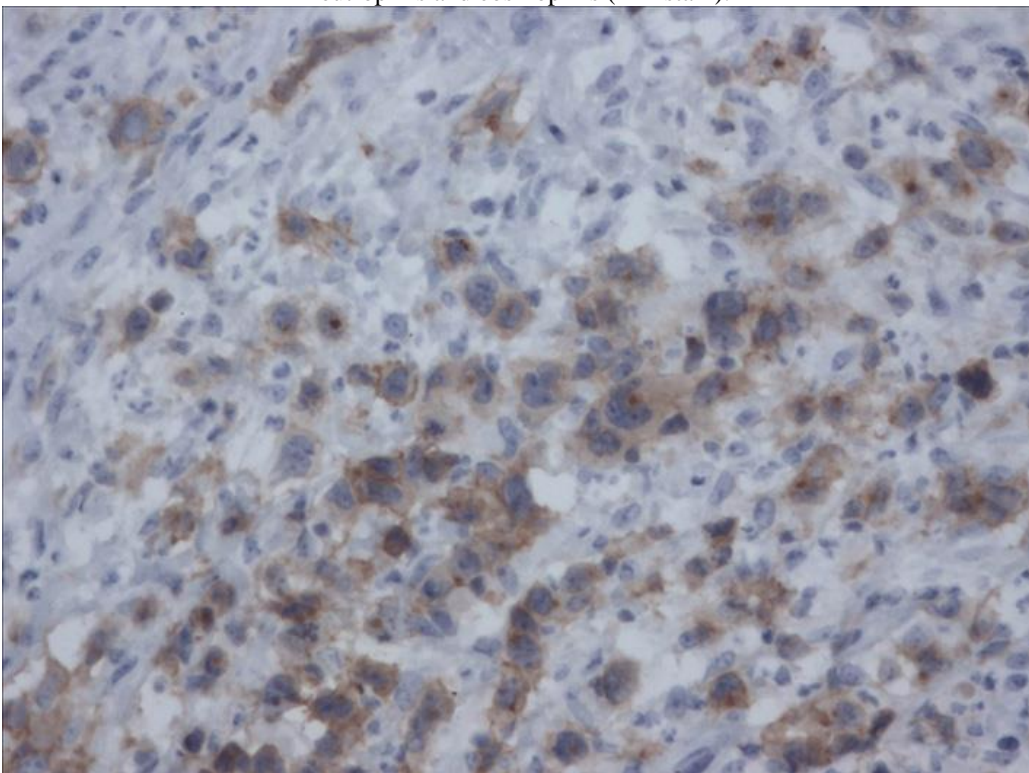


Figure 2. HRS cells are positive for CD30.

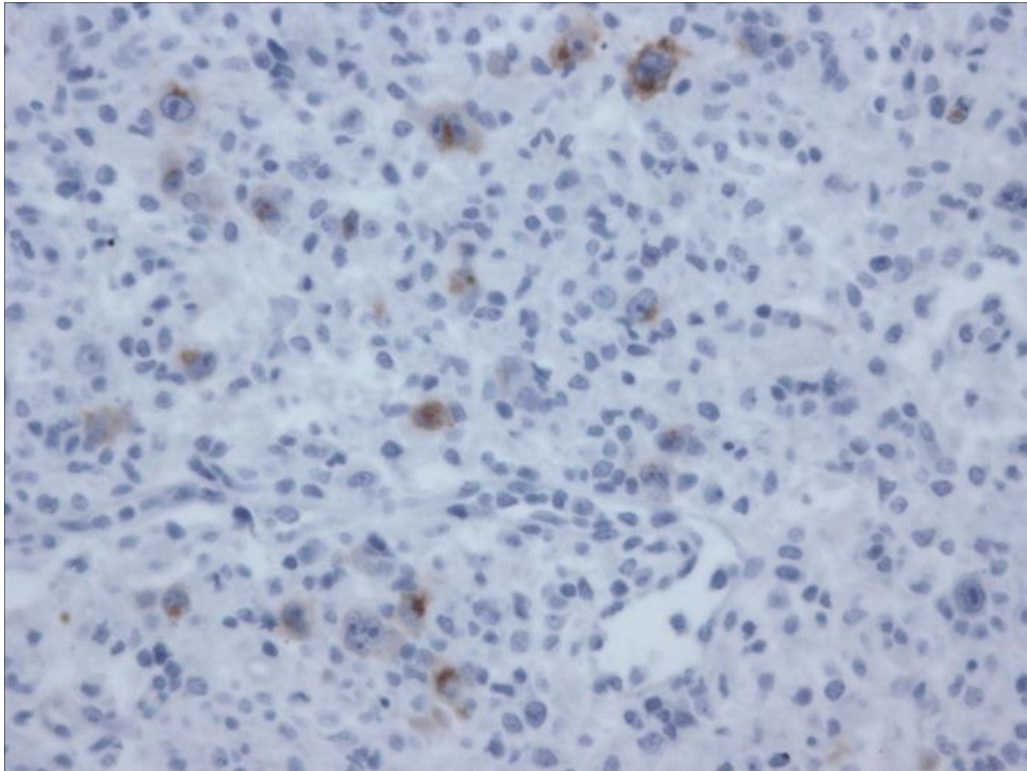


Figure 3. Some HRS cells are positive for CD15.

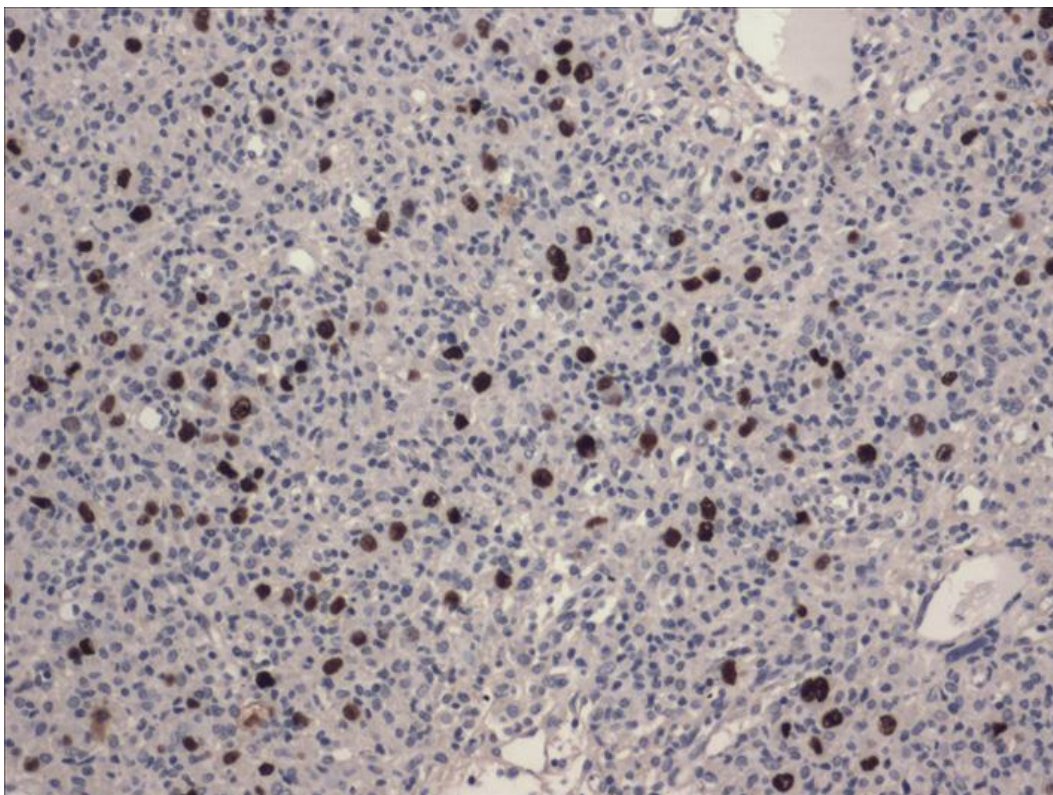


Figure 4. HRS cells are positive for EBV (in situ hybridization).

Treatment

There is no consensus on the optimal treatment of PTLD. It is generally agreed that three major
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strategies should be applied: restoration of the recipient's immunity (to limit the EBV infection), elimination EBV and removal of neoplastic B cells.

Reduction of IS or even withdrawal remains the first-line treatment. With reduction of immunosuppression, virtually all early lesions regress and generally show good prognosis, whereas half of P-PTLD regress and some will progress, the majority of M-PTLDs do not regress. DLI was effectively used in EBV-associated PTLD after mismatched/haploidentical haematopoietic stem cell transplantation (HSCT). Patients with lymph node localization have a relatively good outcome, and disseminated disease in contrast has a poor prognosis (Mucha, et al, 2010. Xu, et al, 2010).

Staging of CHL type PTLD determines the mode of therapy.

Prognosis

The prognosis of PTLD is poor. The treatment of rejection episodes with OKT3 or ATG enhances the PTLD risk in patients who did not receive antibody induction, rejection therapy with OKT3 or ATG adds to the already increased lymphoma risk HLA matching is also a risk factor in the pathogenesis of PTLD, and HLA-B or HLA-DR mismatches especially seem to be critical. The number of HLA

mismatches parallels with an increased risk of PTLD (Opelz, et al, 2003. Opelz, et al, 2010).

Both clinical and laboratory parameters of CHL type PTLD are relevant to prognosis. histologic subtype is less important as a predictive factor (Allemani, et al, 2006).

Genetics

Note

HRS cells contain clonal immunoglobulin (IG) gene rearrangements in more than 98% of cases, and clonal T cell receptor gene rearrangements in rare cases. Some studies indicate that HRS cells of B-cell lineage are derived from a germinal centre B cell (Swerdlow, et al ,2008. Melzner ,et al,2006).

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