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Leukaemia Section

Review

Florid follicular hyperplasia 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. Florid follicular hyperplasia (FFH) PTLD is a kind of early lesions, which shows characteristic clinicopathological features and molecular involvement.

Clinics and pathology

Disease

The term "post-transplant lymphoproliferative disorder" or disease (PTLD) was first introduced in 1984 by Starzl (Starzl et al., 1984) .PTLDs are serious, life-threatening complications of solid-organ transplantation (SOT) and bone marrow transplantation, and are associated with high mortality. PTLDs 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.

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

FFH PTLD is a kind of early lesions, which shows characteristic clinicopathological features and molecular involvement. The early lesions are defined as lymphoid proliferations in an allograft recipient, characterized by architectural preservation of the involved tissue, with preservation of the nodal sinuses or tonsillar crypts, and residual or sometimes floridly reactive follicles in some cases. FFH PTLD is defined as a distinct entity in 2016 WHO classification of lymphoid neoplasms. Such lesions, although reactive, may have clonal chromosomal abnormalities and may lead to uncontrolled lymphoid proliferation in solid organ transplant recipients. (Swerdlow, et al ,2008. Mucha, et al. 2010. Swerdlow, et al, 2016. Vakiani, et al, 2007).

Phenotype/cell stem origin

The majority (>90%) of PTLD in solid organ recipients are of host origin and only a minority of donor origin. Donor origin PTLD appear to be most common in liver and lung allograft recipients, and frequently involve the allograft. In contrast, the majority of PTLD 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 (Chadbum, et al ,1995. Swerdlow, et al, 2008).

Phenotypically, FFH PTLD cases show follicular hyperplasia and the size of the follicles varied, but they all contained large, polarized, germinal centers with many mitoses and mantle zones that were often attenuated. Some cases of FFH may lack increased numbers of plasma cells. Some cells of which may express CD20, PAX5, CD3, CD5 , with markedly enlarged germinal centers (CD10+, BCL6+, BCL2-)

containing numerous tingible-body macrophages and expanded follicular dendritic cell meshworks (CD21+). EBV detected by in situ hybridization is usually positive, and the number of EBV-positive cells are usually fewer, but some cases of FFH may be EBV negative (Swerdlow, et al, 2008. Vakiani, et al, 2007).

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. FFH PTLD accouted for 4 of 15 cases in a study of eraly lesions of PTLD. (Swerdlow et al, 2008. Chen, 2013. Nelson et al, 2012).

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.
Early lesions mostly develop within 1 year after transplantation, and most patients with early lesions affected tonsils, Waldeyer ring, adenoids or lymph nodes, of which FFH PTLD often affects adenotonsillar, nodal, and extranodal lymphoid tissue.They often show spontaneous regression or regress following reduction in IS, and express EBER or EBV-LMP-1 (Opelz, 2003. Swerdlow, et al, 2008. Johnson, 2006. Vakiani et al, 2007).

Pathology

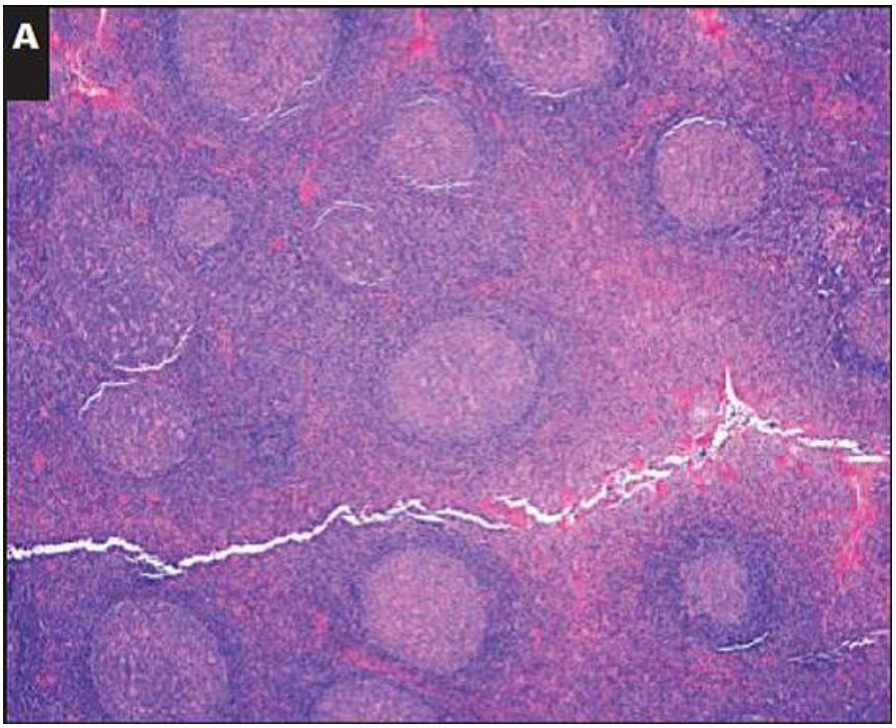

Figure 1. Florid follicular hyperplasia in tonsil. Many variably sized reactive follicles (H&E staining). (reproduced with permission from Hum Pathol. Vakiani E, Nandula SV, Subramaniyam S, et al. Cytogenetic analysis of B-cell posttransplant lymphoproliferations validates the World Health Organization classification and suggests inclusion of florid follicular hyperplasia as a precursor lesion. Hum Pathol. 2007;38:315-325).

The underlying lymph node and extranodal sites(tonsils and adenoids) diagnosed as FFH PTLD show markedly enlarged germinal centers (CD10+, BCL6+, BCL2-) containing numerous tingible-body macrophages and expanded follicular dendritic cell meshworks (CD21+). A variable number of follicles showed blurring of the dark zone-light zone boundary and attenuation or loss of the mantle zones. Interfollicular areas were only mildly expanded by small lymphocytes, scattered immunoblasts, and small clusters of polytypic plasma cells

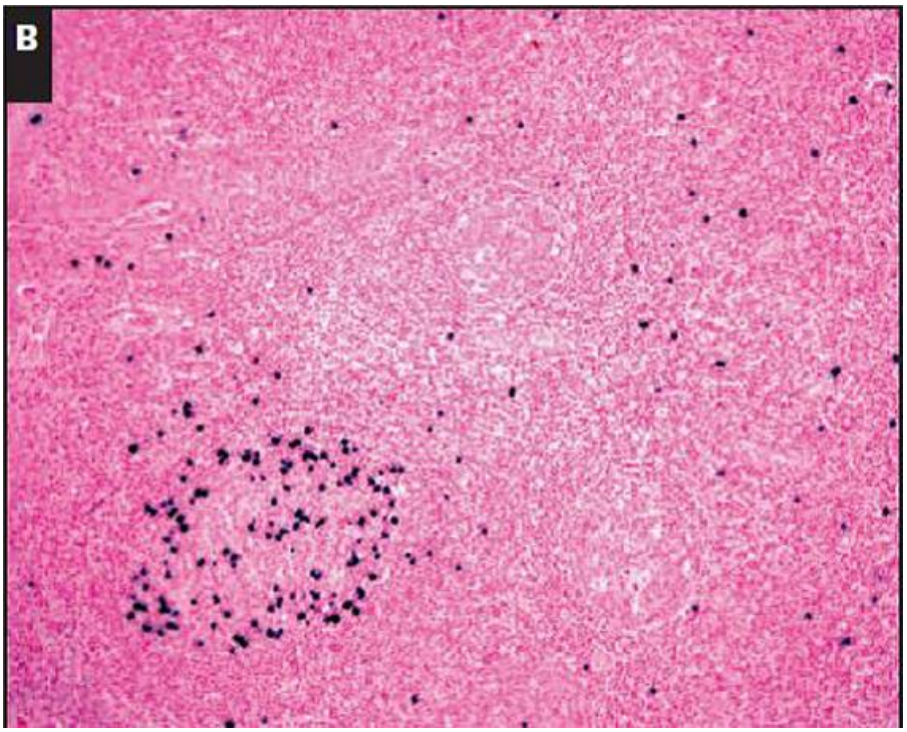

Figure 2. Florid follicular hyperplasia in tonsil. In situ hybridization withEpstein-Barr virus (EBV)-encoded RNA shows EBV-positive cells that are more numerous in a germinal center with occasional positive cells among the follicles (H&E staining). (From Vakiani E, Nandula SV, Subramaniyam S, et al. Cytogenetic analysis of B-cell posttransplant lymphoproliferations validates the World Health Organization classification and suggests inclusion of florid follicular hyperplasia as a precursor lesion. Hum Pathol. 2007;38:315-325).

Treatment

There is no consensus on the optimal treatment of PTLD. It is generally agreed that three major 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 IS, 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 ,2010. Xu, 2010).

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. The indolent behavior of early lesion of PTLD in a series and others may be related in part to the fact that they are almost always polyclonal and do not harbor alteration of oncogenes or tumor suppressor genes. Although clonal cytogenetic abnormalities have been rarely detected in FFH TLDs, they have also had good clinical outcome without aggressive therapy. In a study, two patients had adenotonsillar FFH PTLD, and one patient developed M-PTLD involving tonsils and adenoids, 8.5 years after PH at the same site (Opelz,2003. Opelz,2010. Vakiani,et al, 2007).

Genetics

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In a study, polymerase chain reaction analysis of the IGH gene found germline configuration in FFH PTLD. Clonal karyotypic abnormalities were detected in 2 (11.1%) of 18 FFH PTLD, and recurrent chromosome breaks at 1q11-21,14q32 were identified. (Vakiani, et al, 2007). Increased mTOR signaling in FFH PTLD suggests that this may be an early feature of the lymphoproliferative process in the posttransplant setting (Nelson, et al, 2012).

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