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Review Article

Posttransplant lymphoproliferative disorder following kidney transplant

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ABSTRACT

Posttransplant lymphoproliferative disorder (PTLD) is an important complication of kidney transplant and their presentations ranging from indolent polyclonal proliferations to aggressive lymphomas and involving various organs. There is scarce data on PTLD in live donor renal transplantation. This study highlights variable presentation of PTLD and involvement of many organ systems and higher incidence of late onset monomorphic PTLD at tertiary care center in north India over last 25 years.

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1. Introduction

Posttransplant lymphoproliferative disorders (PTLD) are, clinically and histopathologically, heterogeneous lymphoid disorders ranging from indolent polyclonal proliferations to aggressive lymphomas that complicate solid organ and bone marrow transplantation. Risk factors for PTLD include viral infections, degree of immunosuppression, recipient age and race, allograft type, and host genetic variations. The incidence vary from 1% in renal transplants, to 1.8, 2.2 and 9.4% in heart, liver and heart–lung transplants respectively.[1–3]

The pathogenesis of PTLD is multifactorial. EBV plays an important role in driving the proliferation of EBV-infected B cells. It is mow widely perceived that EBV is not solely responsible for the "neoplastic" state, and that accumulation of different aberrations in protooncogenes and suppressor genes, and hypermethylation of suppressor genes are integral parts of the pathogenesis.[3]

It is known that the risk of developing PTLD increases with the use of certain drugs such as tacrolimus and OKT3, especially when they are combined.[4] Despite the fact that immunosuppressive drugs are an established risk factor, it is still not well-understood whether the risk is due to the cumulative dose or peak levels of immunosuppressive drugs. The cumulative dose, however, is more likely to be the incriminating factor.[5]

The clinical manifestations may vary from nonspecific symptoms in the form of fever, sweats, malaise, weight loss, and features of primary EBV infection in some patients, to sudden enlargement of tonsils, lymph nodes, or other extranodal lymphoid organs. Other organs such as the central nervous system, bone marrow, spleen, lung, small intestine, liver, and kidney may also be affected[3]

The two basic principles of current standard PTLD treatments are reconstitution of anti-EBV/antitumor immune responses in form of reduction in immunosuppression, and, if this is not sufficient, antineoplastic immuno-/chemotherapy

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(+/− radiotherapy). Balancing immune reconstitution versus the risk of graft rejection is therefore challenging and requires expert guidance and interdisciplinary cooperation of transplant physicians and oncologists. Outcome of PTLD treatment has improved drastically after the introduction of *Rituximab* (anti-CD20 antibody) into standard regimens of PTLD treatment.[6]

The current classification of PTLD is based on the 2008 WHO classification of lymphoid neoplasms.[7] It divides PTLD into four major categories: early lesions, polymorphic PTLD, monomorphic PTLD, and Hodgkin's disease/Hodgkin-like PTLD. These are often difficult to differentiate, a clear separation is not always possible (Table 1).

1 *Early lesions*: Early lesions form one end of the spectrum of PTLD and mostly develop within one year after transplantation. They show oligo- or polyclonal proliferations of EBV-positive B cells and the underlying tissue architecture is preserved. The B cells may either have a predominantly immunoblastic phenotype (infectious mononucleosis like early lesion PTLD) or a plasma-cell phenotype (plasmacytic hyperplasia early lesion PTLD). Early lesions more frequently involve tonsils, adenoids or lymph nodes than true extranodal sites.[7]
2 *Polymorphic PTLD*: Polymorphic PTLDs affect nodal and extranodal tissues and show loss of tissue architecture and necrosis. Polymorphic PTLDs are composed of a mixed population of immunoblasts, plasma cells, intermediate sized lymphoid cells (incorporating a full range of B cell morphology and differentiation).[8] The majority of the lesions exhibit EBV latency type II or III (expressing EBER and EBV-LMP-1 with variable expression of EBV-EBNA2 and other viral antigens). A variable proportion of cases show regression in response to reduction in immune suppression while other cases may progress and require chemotherapy.[7] While polymorphic PTLD can easily be differentiated from early lesions in lymph nodes, this can be very difficult in extranodal PTLD.
3 *Monomorphic*: *PTLD* can be either of B cell or T cell lineage and resemble the typical types of non-Hodgkin lymphomas (NHLs) seen in immunocompetent patients, and they are usually monoclonal. They disturb the tissue architecture and spread to other organs. They are classified according to the WHO classification of lymphomas in immunocompetent patients. Monomorphic B-PTLDs show features of different morphologic variants of diffuse large B cell lymphoma (DLBCL) in immunocompetent patients (iDLBCL) (immunoblastic, centroblastic, or anaplastic), Burkitt's lymphoma (BL), or plasmablastic lymphoma (PL). Almost all cases display a clonal pattern of *IGH* rearrangement, and EBV-positive cases show episomal EBV genome. mPTLDs can be EBV-negative, tend to be more aggressive, and only rarely respond to a reduction in immune suppression.[7,9]
4 *Hodgkin's disease/Hodgkin-like PTLD*: Classical Hodgkin's disease and Hodgkin-like PTLD also belong to monomorphic PTLDs, but due to their special histological and clinical features, they represent a separate group within the WHO classification.

Table 1 – Classification of PTLDs.

Types	Categories of PTLD WHO (2008)
Early lesions	• Reactive plasmacytic hyperplasia • Infectious mononucleosis – like
PTLD polymorphic	• Polymorphic PTLD
PTLD monomorphic *(classified according to lymphoma classification)*	B cell lymphomas • Diffuse Large B Cell Lymphoma (DLBCL) • Burkitt Lymphoma (BL)/BLL • Plasma cell myeloma • Anaplastic large cell lymphoma T cell lymphomas • Peripheral T cell lymphoma (NOS) • Hepatosplenic lymphoma • Others • T/NK-cell PTLD • Anaplastic large cell lymphoma
Others	• Classical Hodgkin lymphoma type PTLD

2. Aims

The majority of the literature reports on PTLD are derived from cadaveric transplants. There are no major studies reporting the occurrence and characteristics of PTLD after live donor renal transplants. This single-centre study is carried out to analyse clinicopathological and immunohistochemical features of PTLD cases developing in live related/unrelated HLA-matched renal allograft recipients during last 24 years.

3. Materials and methods

Seventeen cases of PTLD were identified in the last 24 years. The treatment profile and follow-up records of all the allograft recipients are maintained at renal transplant follow-up clinic held twice weekly at our centre. The follow-up protocol includes twice monthly follow-up visits for initial 6 months and subsequently at monthly intervals. The variables studied were patient age, sex, type of transplant, type of immunosuppression received, posttransplant latency period, EBV serology, treatment received, follow-up and outcome. Formalin-fixed and paraffin-embedded tissue sections stained with haematoxylin and eosin (H & E), periodic acid Schiff, and reticulin were reviewed. Fine needle aspiration cytology (FNAC) smears stained with McGrunwald–Giemsa, H & E and Papanicolaou stains were also evaluated. The lesions were classified as WHO 2008 classification.[4] The immunohistochemistry was performed using indirect technique with labelled streptavidin. The 2monoclonal antibodies (Dako) used were CD3, CD20, CD30 and CD 45 Ro, kappa and lambda light chain. CD 56 and EBV serology by EBNA2 monoclonal antibody DAKO was done in available material as and when required.

4. Results

Seventeen cases of PTLD were observed during last 24 years (from 1989 to 2012) out of total 2770 transplant patients at SGPGIMS, a tertiary care center in North India. All the seventeen patients received either live related or unrelated renal

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