Post-transplant Lymphoproliferative Disorders

Definition

- Post-transplant lymphoproliferative disorder (PTLD) is a lymphoid proliferation or lymphoma that develops as a consequence of immunosupression in a recipient of a solid organ or bone marrow allograft.

Definition

- PTLDs comprise a spectrum ranging from early EBV-driven polyclonal proliferations resembling infectious mononucleosis to EBV-positive or EBV-negative lymphomas of predominantly B-cell or less often T-cell type.

Epidemiology

- The characteristics of PTLD appear to differ somewhat from one institution to another, probably as a result of different patient populations, allograft types, and immunosupressive regimens.
- The risk of lymphoma varies depending on the type of allograft and the immunosupressive regimen.

Epidemiology

- Among solid organ recipients, patients receiving renal allografts have the lowest frequency of PTLD (<1%).
- Those with hepatic and cardiac allografts have an intermediate risk (1-2%), and those receiving heart-lung or liver-bowel allografts develop PTLD at the highest frequency (5%).

Epidemiology

- The overall incidence of PTLD for solid organ transplant recipients is <2%. This risk is estimated to be 20 times that of the normal population for renal allograft recipients and 120 times normal for cardiac allograft recipients.

Epidemiology

- Marrow allograft recipients in general have a low risk of PTLD (1%), but those who receive HLA-mismatched or T-cell depleted BM and those who receive immunosupressive therapy for GVHD are at the highest risk for development of lymphoma – up to 20% for patients with more than one of this risk factors.

Aetiology

- The majority of PTLD are associated with EBV infection, and appear to represent EBV-induced monoclonal or, less often, polyclonal B-cell or rarely T-cell proliferations that occur in setting of decreased T-cell immune surveillance.

Aetiology

- About 20% of PTLD are EBV-negative; among renal allograft recipients up to 50%.
- EBV-negative cases tend to occur later than EBV-positive cases, and the majority of cases occurring >5 years after transplant are EBV-negative.

Aetiology

- The aetiology of EBV-negative PTLD is not known.
- Although these occur less frequently than EBV-positive cases, their frequency is still higher than would be expected in the normal population; in addition, some cases respond to decreased immunosupression. Thus, it is likely that they are also in some way related to decreased immune competence.

Aetiology

- The majority of PTLD in solid organ recipients are of host origin, reflecting escape of host EBV-positive cells from immune surveillance.
- A minority (<10% of the cases) are of donor origin, indicating that lymphoid cells transplanted with the allograft can survive and undergo malignant transformation in some cases.

Aetiology

- 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 marrow allograft recipients are of donor origin, as would be expected, since successful allografting results in an immune system that is exclusively of donor origin.

Sites of involvement

- In solid organ recipients immunosupressed with azathioprine-based regimens, PTLDs tend to involve extranodal sites, including the allograft and the CNS.
- Patients treated with cyclosporine-based or Tacrolimus-based regimens develop PTLDs that tend to involve lymph nodes and GI tract, less frequently CNS.

Sites of involvement

- The bone marrow, liver and lungs are often involved, but peripheral blood is rarely involved.
- The allograft is involved in aproximately 25% of the cases overall, and on biopsy specimens this may give rise to a differential Dx of rejection vs PTLD.

Sites of involvement

- BM allograft recipients tend to present with widespread disease involving nodal and extranodal sites, including liver, spleen, GI tract and lungs.

Clinical features

- The clinical features of PTLD at presentation are variable, and correlate with the type of immunosupression, type of allograft , and with morphologically defined categories.
- In solid organ recipients treated with azathioprine, the mean interval to PTLD following transplantation is 48 months. With cyclosporine A, it is 15 months.

Clinical features

- The majority of PTLD in bone marrow allograft recipients develop within the first 5 months.
- EBV-positive cases tend to occur earlier than EBV-negative cases, with a median interval of 6-10 months compared with 4-5 years for EBV-negative cases.

Clinical features

- PLasmacytic hyperplasia (PH) and infectious-mononucleosis like (IM-like) lesions may arise at any time, most often within the first 2 years after transplantation, but some as late as 5 years.

Clinical features

- The majority of both polymorphic and monomorphic PTLDs occur in the first year after transplantation; patients may present with lymphadenopathy in one or multiple sites, or with organ dysfunction, including the allograft, related to extranodal infiltrates.

Clinical features

- Monomorphic PTLD overlap clinically with polymorphic cases; however, late-occurring, EBV-negative cases are more likely to be monomorphic.

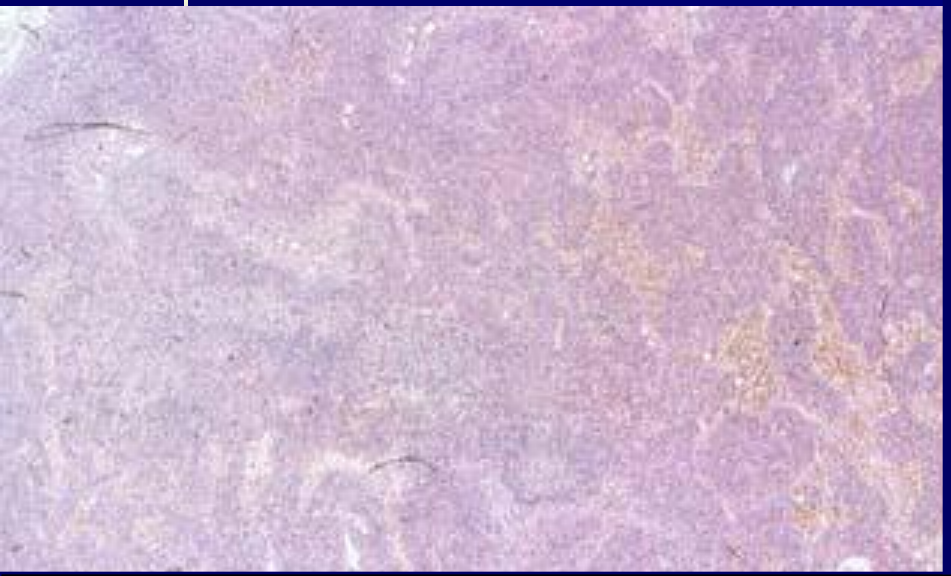
Morphologic Categories

- *"Early" lesions: Plasmacytic hyperplasia (PH) and Infectious-mononucleosis-like PTLD*:
  - These lesions are defined as a lymphoid proliferation in an allograft recipient, characterised by some degree of architectural preservation of the involved tissue, with preservation of the nodal sinuses or tonsillar crypts, and residual reactive follicles in some cases.

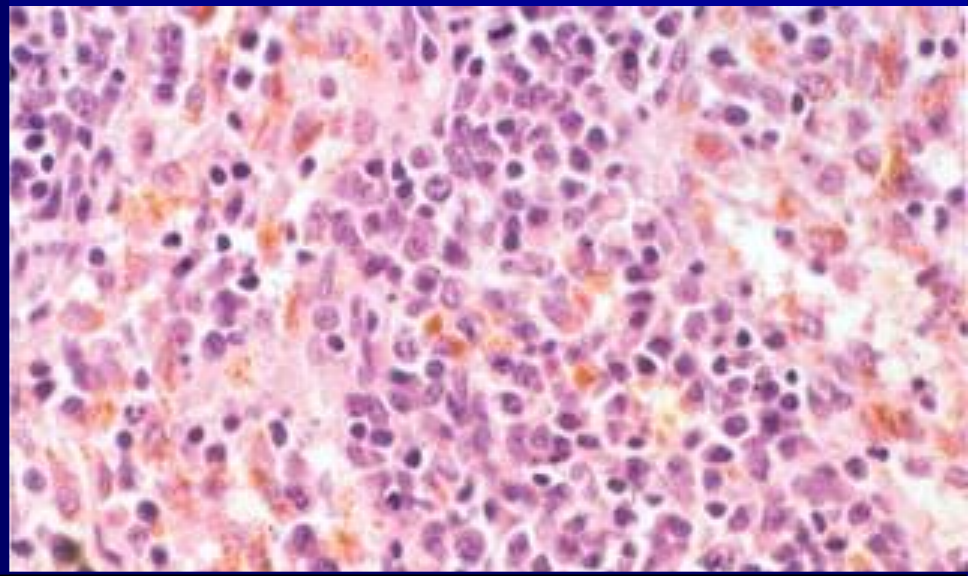
Morphologic Categories

- Plasmacytic hyperplasia is characterised by numerous plasma cells and rare immunoblasts, while the IM-like lesion has the typical morphologic features of IM, with paracortical expansion and numerous immunoblasts in a background of T cells and plasma cells.

Plasmacytic Hyperplasia

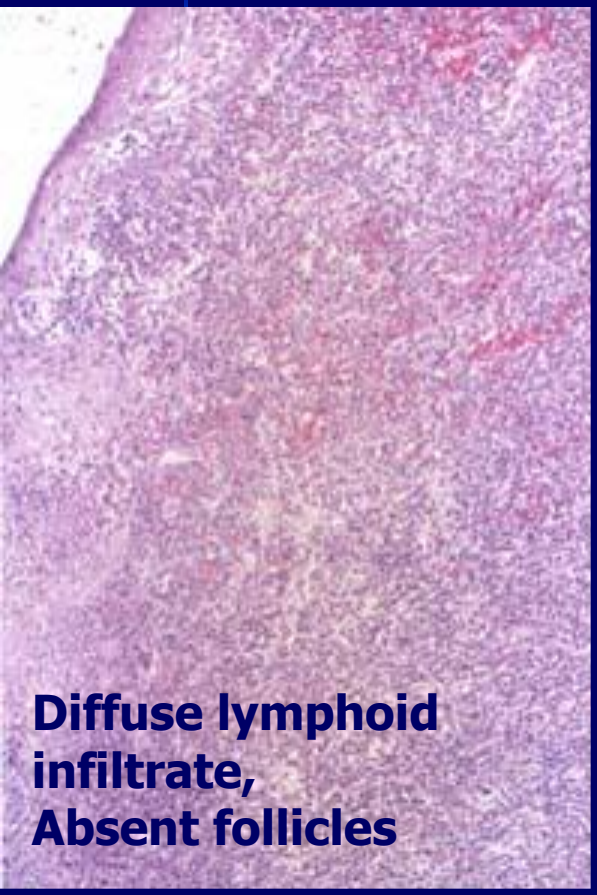


LN: intact architecture

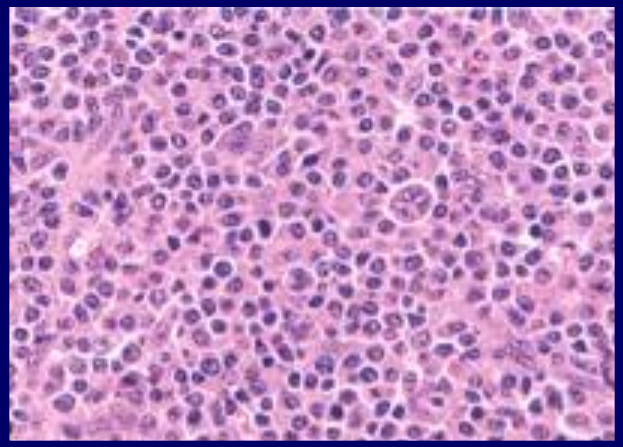


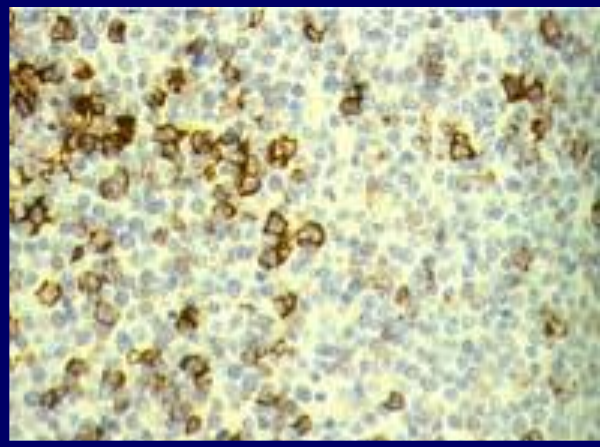
Numerous plasma cells

IM-like Lesion in a Tonsil

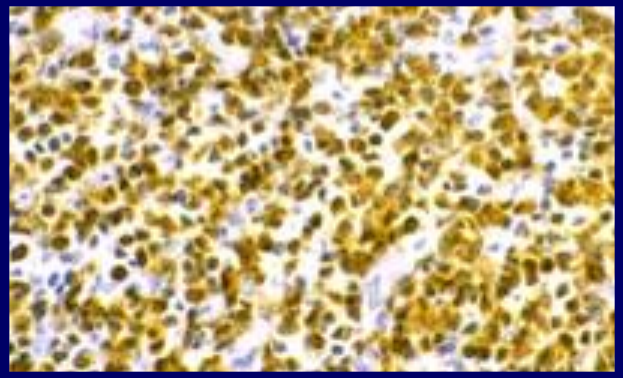


Diffuse lymphoid infiltrate, Absent follicles

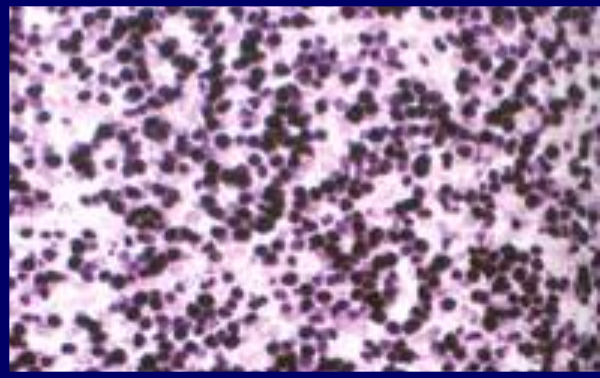




CD20



CD79a



EBER

Morphologic Categories

- These are 2 possibly overlapping lymphoid proliferations that differ from typical reactive follicular hyperplasia in having a diffuse proliferation of plasma cells and immunoblasts with incomplete effacement of the involved tissue.
- Some (Nalesnik et al) described "reactive plasmacytic hyperplasia", but they did not considered it a form of PTLD.

Morphologic Categories

- The same term was used by Knowles et al. and found that 3/8 cases they diagnosed as Plasmacytic Hyperplasia involved LNs, 4/8 involved Waldeyer´s ring and one involved the lung; the latter cases may correspond to what others have called IM-like lesions.

Morphologic Categories

- Plasmacytic Hyperplasia and IM-like lesions occur at a younger age than the other PTLDs and are often seen in children or in adult solid organ recipients who had no prior EBV infection.
- They involve LN (Plasmacytic Hyperplasia) or tonsils and adenoids (IM-like) more often than true extranodal sites, and often regress spontaneously or with reduction in immunosupression.

Morphologic Categories

- However, IM-like lesions can be fatal, as can infectious mononucleosis in other settings. They may be followed by polymorphic or monomorphic PTLD in some cases.

Morphologic Categories

- *Polymorphic PTLD*
  - Synonyms: Polymorphic B-cell Hyperplasia, polymorphic B-cell lymphoma.
  - Defined as destructive lesions composed of immunoblasts, plasma cells, and intermediate-sized lymphoid cells, that efface the architecture of LNs or form destructive extranodal masses.

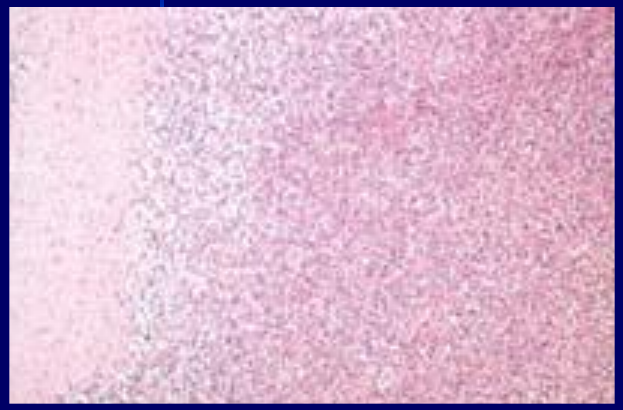
Morphologic Categories

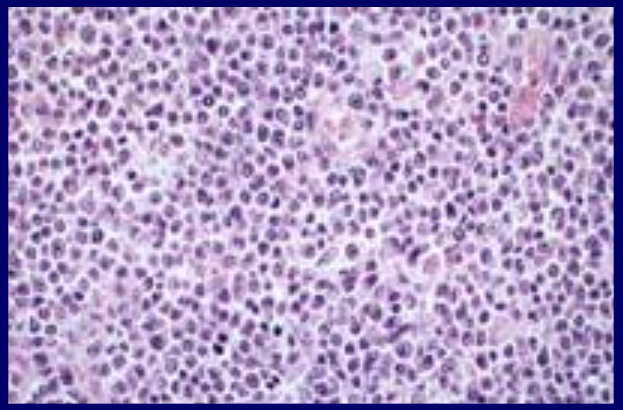
- In contrast to early IM-like lesions, the tissue architecture is effaced, but in contrast to most lymphomas, they show the full range of B-cell maturation, from immunoblasts to plasma cells, with small and medium-sized lymphocytes and cells with irregular nuclei resembling centrocytes.

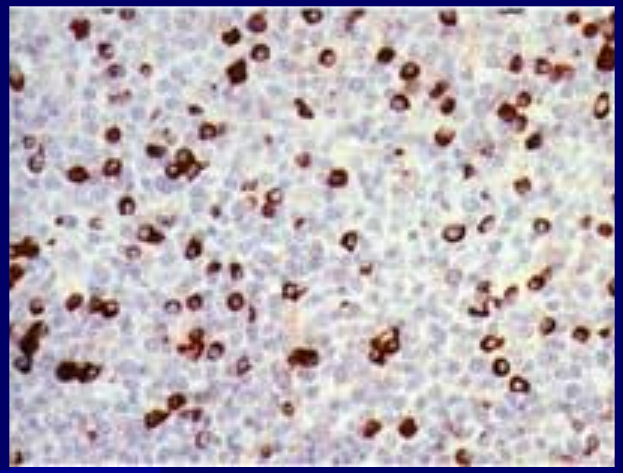
Morphologic Categories

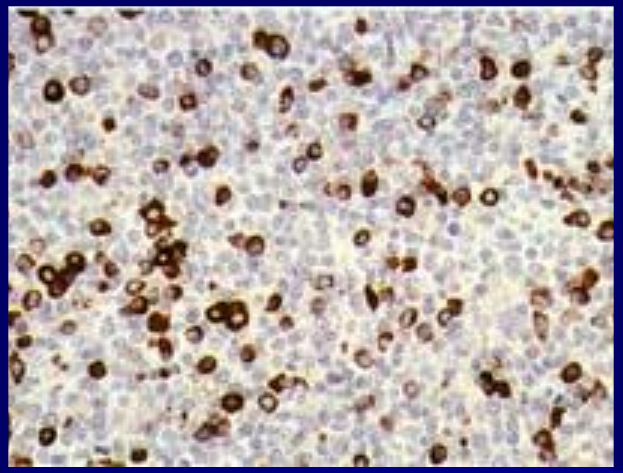
- Overall the impression is often that of "mixed small and large cell" lymphoma, resembling the "polymorphic immunocytoma" of the Kiel classification.
- There may be areas of necrosis and scattered large cells (atypical immunoblasts); numerous mitoses may be present.

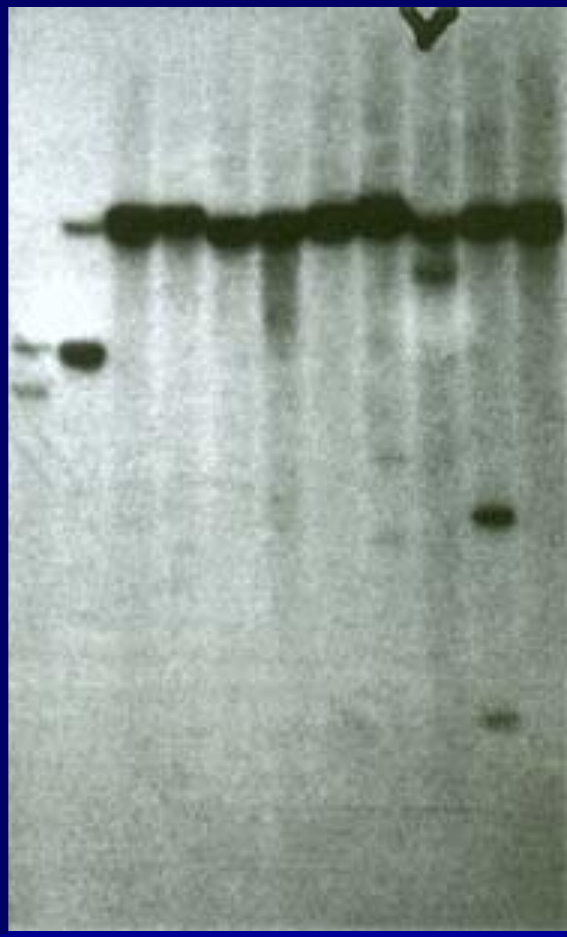
Polymorphic PTLD











Kappa

Lambda

Southern Blot for heavy chain J region shows a clonal band

Show polyclonal pattern

Morphologic Categories

- This category was one time subdivided into "polymorphic B-cell hyperplasia" and "polymorphic B-cell lymphoma" based on the presence of atypical immunoblasts and necrosis, but it is now felt that attempting to distinguish between these is not practical or necessary, since both are typically monoclonal and have similar clinical features.

Morphologic Categories

- Some cases have areas that appear more monomorphic in the same or other tissues; thus, there may be a continuous spectrum between these lesions and the monomorphic PTLD.
- The frequency of polymorphic PTLD ranges from 20 to over 80% of the cases.
- Reduction in immunosupression leads to regression in a variable number of the cases; others may progress and require treatment for lymphoma.

Morphologic Categories

- *Monomorphic PTLD*
  - Monomorphic B-cell PTLD: these have sufficient architectural and cytologic atypia to be diagnosed as lymphoma on morphologic grounds, and have expression of B-cell associated antigens.
  - These tumours should be classified as B-cell lymphomas, but the term PTLD should also appear in the diagnosis.

Morphologic Categories

- The infiltrates are characterised by nodal architectural effacement and/or invasive, tumoural growth in extranodal sites, with confluent sheets of transformed cells.
- All or most cells in the infiltrate are large, transformed, blastic cells with prominent nucleoli and basophilic cytoplasm, in contrast to the full range of maturation seen in lesions characterised as polymorphic PTLD.

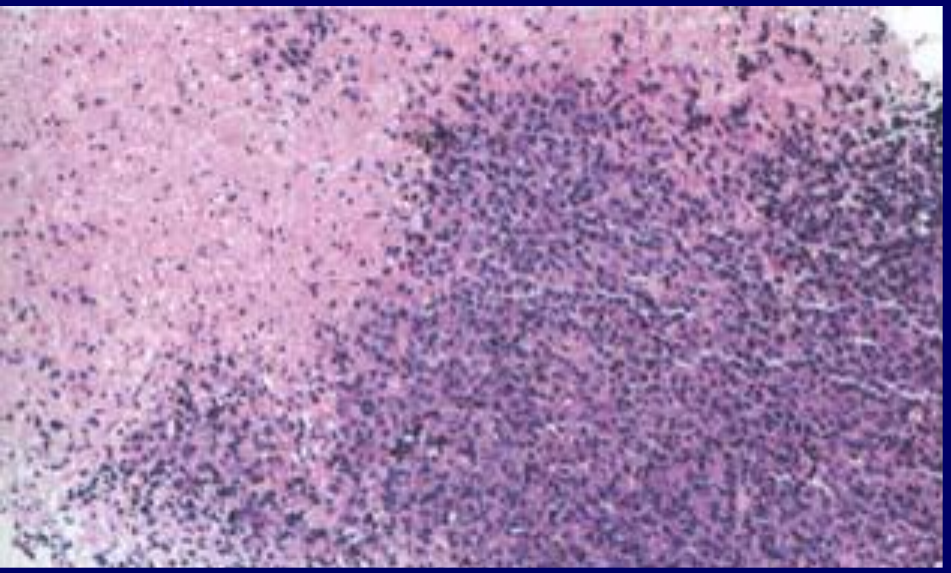
Morphologic Categories

- It is important to recognize that there may be plasmacytoid or plasmacytic differentiation.
- Thus, the term *monomorphic* does not mean complete cellular monotony, only that most of the cells appear to be transformed.

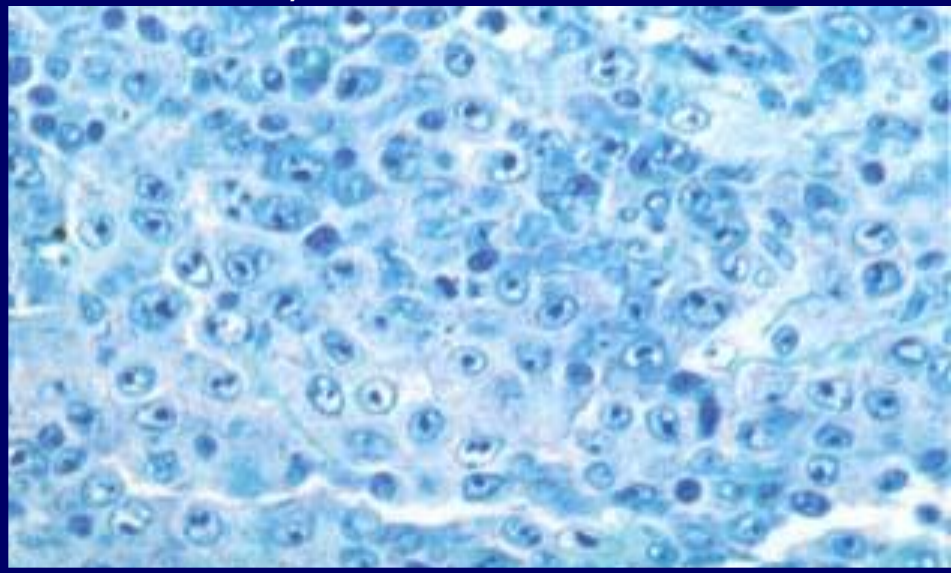
Morphologic Categories

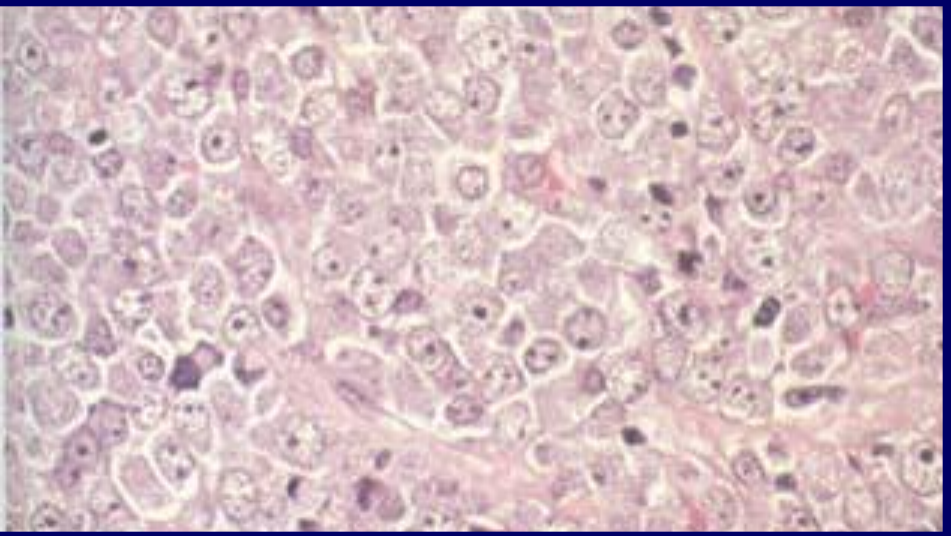
- Diffuse large B-cell lymphoma and Burkitt lymphoma: the majority of monomorphic B-PTLDs fall into the category of diffuse large B-cell lymphoma.
- Most would be subclassified as the immunoblastic variant, although some are centroblastic. Some cases show features of the anaplastic variant. A minority of the cases have morphologic features of Burkitt lymphoma.

DLBCL, immunoblastic

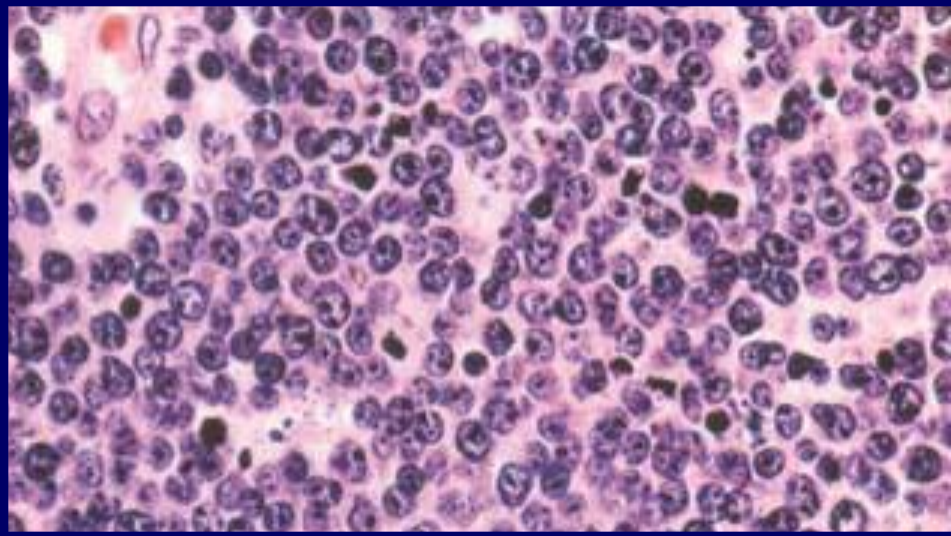


DLBCL, immunoblastic





DLBCL, centroblastic



Atypical Burkitt

Morphologic Categories

- Plasma cell myeloma: rare transplant patients develop plasma cell myeloma. These may be EBV-positive or negative; most reported cases have failed to regress with decreased immunosupression.

Morphologic Categories

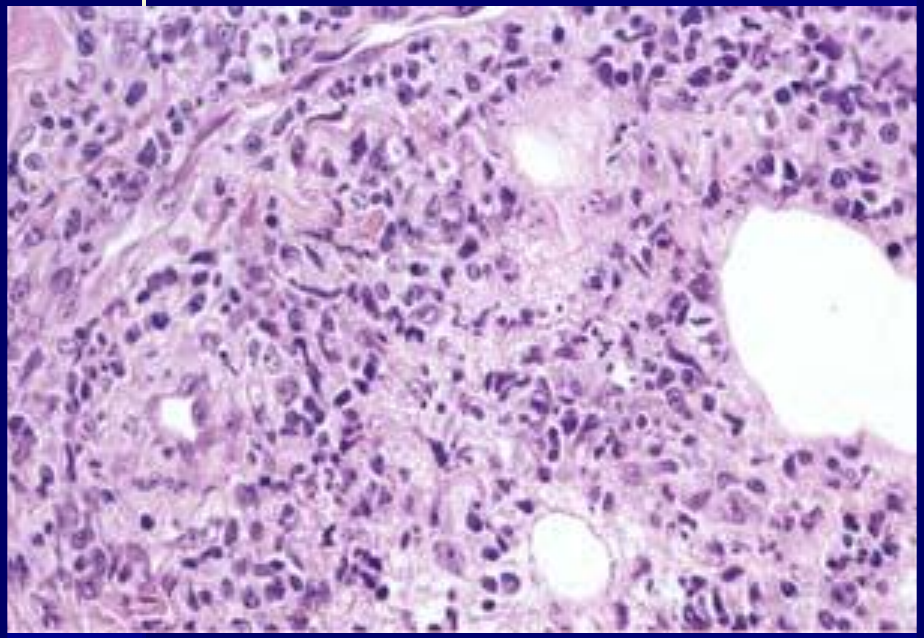
- Plasmacytoma-like PTLD: rare extramedullary plasmacytic neoplasms, which appear to be similar to extramedullary plasmacytoma in the non-immunocompromised host, have been reported in the post-transplant setting.
- They may occur in the GI tract, LN, or other extranodal sites.
- Clinical behaviour not well studied.

Morphologic Categories

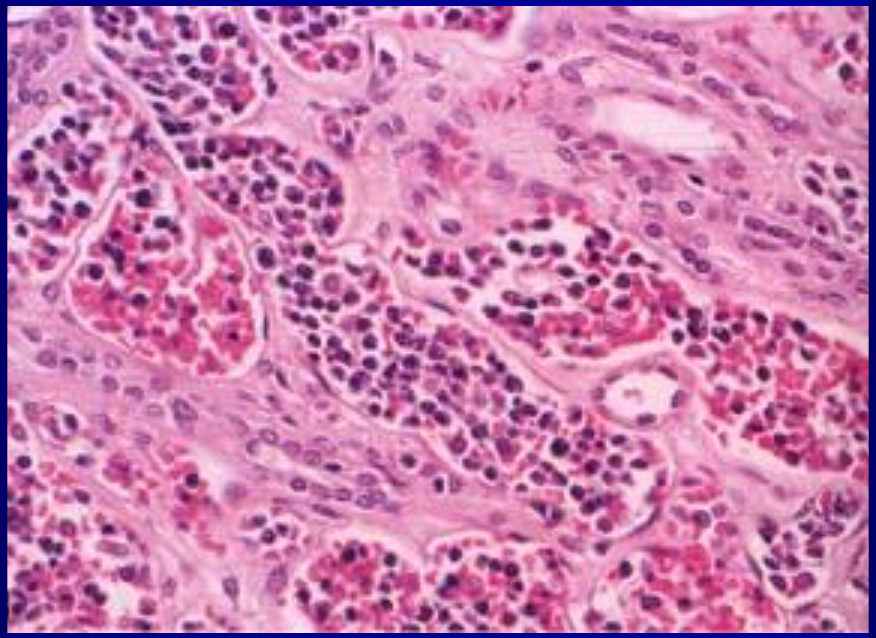
- *Monomorphic T-cell PTLD*
  - Similarly to the monomorphic B-PTLDs, monomorphic T-PTLDs have sufficient atypia and monomorphism to be recognised as neoplastic, and should be classified in the T-cell neoplasms category.
  - The frequencies of T-cell origin cases reported range from 4 to 14%.

Morphologic Categories

- T-PTLDs appear to span the spectrum of T-cell neoplasms, including subcutaneous paniculitis-like T-cell lymphoma, hepatosplenic gamma-delta T-cell lymphoma, NK/T-cell lymphomas, T-cell large granular lymphocytic leukemia, and peripheral T-cell lymphoma, unspecified.
- Some cases may be CD30+.



Subcutaneous panniculitis-like
T cell lymphoma



Hepatosplenic T cell lymphoma

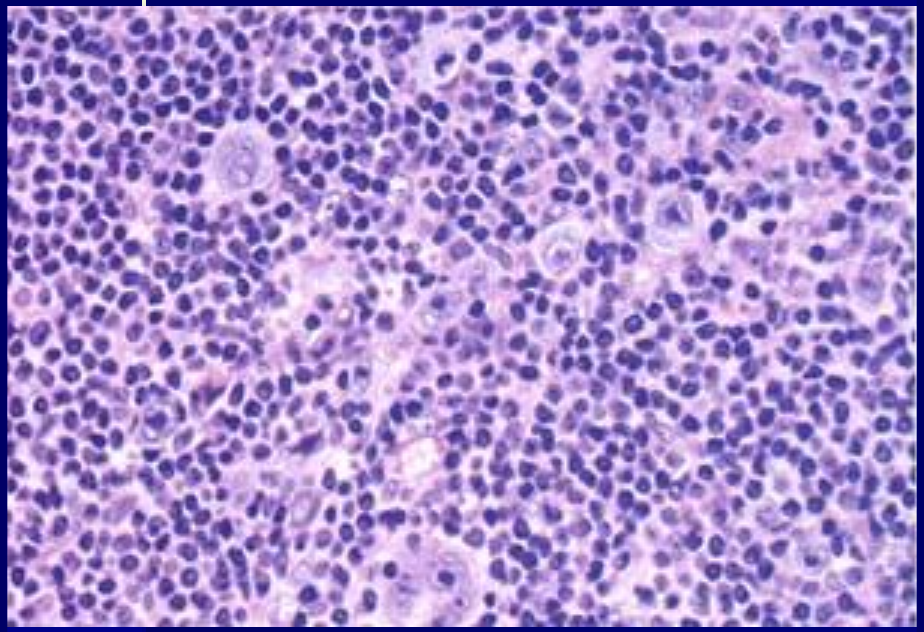
Morphologic Categories

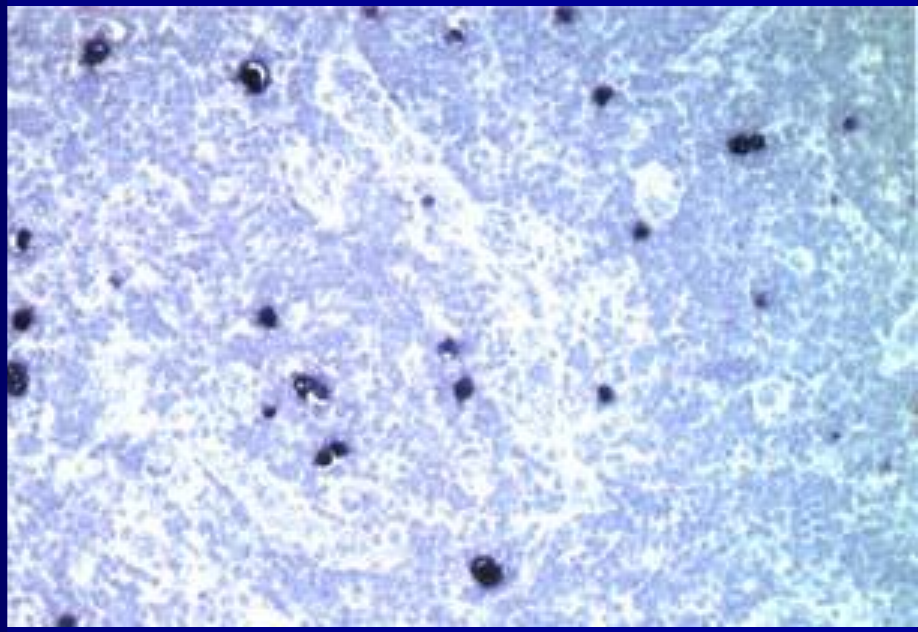
- The interval to lymphoma development is typically longer for the T-PTLDs than for the B-cell cases, and patients are less likely to respond to decreased imunosupression.
- Many reported cases of T-PTLD are EBV-negative, but some are EBV-positive.

Morphologic Categories

- *Hodgkin lymphoma (HL) and HD-like PTLD:*
  - Both classical HL and cases of HL-like PTLD have been reported in allograft recipients.
  - Because RS-like cells may be seen in polymorphic PTLD, the diagnosis of HL should be based on both classical morphologic and immunophenotypic features.

Hodgkin lymphoma-like PTLD





EBER

Morphologic Categories

- An increased incidence of classical HL has been reported after allogenic BM transplantation, with an observed-to expected incidence ratio of 6.2.
- Rarely, allograft recipients develop polymorphic, HL-like lesions in nodal or extranodal sites, similar to those that develop in patients treated with methotrexate for rheumatoid arthritis or psoriasis.

Morphologic Categories

- HL-like PTLD are similar to both methotrexate-related HL and HL in HIV infection in that they are virtually always EBV-positive.
- Some cases have responded to therapy for HL, while others have been clinically aggressive.
- Given the small number of reported cases, further study is required to determine their spectrum of clinical behaviour.

Immunophenotype

- *Plasmacytic hyperplasia and IM-like lesions*
  - Immunophenotypic studies show an admixture of polyclonal B cells, plasma cells, and T cells.
  - Immunoblasts are typically EBV-LMP(+).

Immunophenotype

- *Polymorphic PTLD*
  - Immunophenotyping shows a mixture of B and T cells, surface and cytoplasmic Ig may be either polytypic or monotypic.
  - EBV-LMP1 and EBNA2 are detectable in the immunoblasts in the majority of the cases.

Immunophenotype

- *Monorphic B-cell PTLD*
  - Immunophenotypic studies show B-cell associated antigens (CD19, CD20, CD79a), with monotypic immunoglobulin (often with expression of gamma or alpha heavy chain) in 50% of the cases.
  - EBV-associated Ags EBNA2 and LMP1 are expressed in the majority of the cases.

Morphologic Categories

- Many express antigens usually associated with T cells, specifically CD43 and CD45RO, which are upregulated in EBV-infected B cells, and are expressed by some conventional B-cell lymphomas. They do not indicate T lineage in this setting.
- Many cases are CD30(+), with or without anaplastic morphology.

Immunophenotype

- *Monomorphic T-cell PTLD*
  - T-cell cases are recognised by expression of pan-T cell antigens, may express CD4 or CD8, CD56 or CD30, and either $\alpha\beta$ or $\gamma\delta$ T-cell receptors.
  - They are variably EBV-positive.

Immunophenotype

- *HL and HL-like PTLD*
  - Classical HL cases have expressed CD15 and CD30.
  - Cases diagnosed as HL-like PTLD more often have an atypical immunophenotype with B-cell antigen expression; virtually all cases are EBV-positive.

Genetic features

- *Antigen receptor genes and EBV: Plasmacytic hyperplasia and IM-like lesions*
  - Ig genes are polyclonally rearranged.
  - EBV is present in many but not all of the cases of nodal PH.
  - EBV-negative PH may represent nonspecific lymphoid hyperplasia or a reaction to an infection other than EBV, and should not be considered PTLD.

Immunophenotype

- Extranodal and nodal IM-like cases are typically EBV-positive and may have small monoclonal or oligoclonal bands on Southern blots probed for episomal EBV genomes.
- The significance of oligoclonality or a small clonal band is unknown.

Genetic features

- *Polymorphic PTLD*
  - Molecular genetic studies virtually always show clonal rearrangements of Ig genes and/or EBV genomes, but cytogenetics and oncogene studies (*MYC, RAS, TP53*) show no mutations.
  - Early sudies reporting polyclonality were based on Ig light chains detection in paraffin blocks.

Genetic features

- Later studies using molecular genetic analysis confirmed that most poly- and monomorphic lesions are in fact monoclonal.
- In some cases tumours at different sites in the same patient may be clonally distinct.
- In most cases that lack Ig gene rearrangements, clonal episomal EBV genomes can be detected.

Genetic features

- EBV in PTLD is reported to be exclusively of type A.
- Detection of EBV by EBER ish is a useful tool in the differential Dx of PTLD vs rejection in allografts.
- Most cases of polymorphic PTLD contain numerous EBER positive cells. Rare positive cells should not be seen in PTLD.

Genetic features

- *Monomorphic B-PTLD*
  - Ig gene rearrangement in virtually all cases, and the majority contain EBV genomes (if present, are in clonal episomal form).

Genetic features

- *Monomorphic T-PTLD*
  - Most reported cases show clonal T-cell receptor gene rearrangement.
  - About 25% have clonal episomal EBV genomes.

Genetic features

- *Oncogenes*
  - In polymorphic PTLD, one study showed no mutations of the RAS or TP53 genes, and no rearrangement of the MYC gene. Monomorphic B-PTLD frequently showed such abnormalities, similar to de-novo DLBCL.
  - Mutations of the BCL6 gene were described in 40% of polymorphic cases and 90% of monomorphic cases; were associated with failure to respond to decreased immunosupression.

Prognosis and predictive factors

Early and IM-like lesions tend to regress with reduction of immune supression, and if this can be accomplished without graft rejection, the prognosis is excellent, particularly in children.

Polymorphic and less often monomorphic PTL may regress with reduction in immune supression. The proportion of cases that do not regress require cytotoxic chemotherapy.

Prognosis and predictive factors

- Overall the mortality of PTLD in solid organ allograft recipients is aprox 60%, while that of marrow allograft recipients with PTLD is 80%.
- Anti-CD20 therapy has been useful in abrogating PTLD development in some cases, particularly in the marrow allograft setting.

Prognosis and predictive factors

- Monitoring for evidence of reactivation of EBV infection may provide an early warning of PTLD development.
- With an early diagnosis, prompt reduction of immune suppression, and careful administration of chemotherapy or radiation therapy, the prognosis for all types of PTLD has improved.