Definitions and Pathology of PTLD

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Introduction

Definition

Post-transplant lymphoproliferative disorders (PTLDs) are defined by the World Health Organization as "lymphoid or plasmacytic proliferations that develop as a consequence of immunosuppression in a recipient of a solid organ or stem cell allograft" [1]. An association with Epstein-Barr virus (EBV) is frequent but not required. It is important to exclude other causes of lymphoid/plasmacytic proliferations that can occur in immunocompromised hosts, such as chronic inflammatory responses to infection or rejection in the allograft.

General Pathologic Features and Classification

The post-transplant lymphoproliferative disorders (PTLD) demonstrate a spectrum of pathologic appearances that vary in terms of their degree of resemblance to other reactive and neoplastic lymphoid and plasmacytic proliferations, in terms of their cytologic composition and cell(s) of origin, and in terms of whether or not they are associated with EBV. Specifically, it should be noted that EBV positivity is not required for the diagnosis of a PTLD, that about 20–40% of cases are EBV negative

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which is higher than seen in the past, and that the EBV negative cases include more monomorphic PTLD and more PTLD of T-cell origin [2–4]. Rare cases have been associated with HHV-8 [5]. Most, but not all, PTLDs in solid organ transplant patients are of host origin, whereas they are of donor origin in bone marrow/stem cell transplant patients. It is important to exclude other specific (or non-specific) lymphoid or plasmacytic proliferations prior to diagnosing PTLD, since transplant patients are also at risk for other infectious or inflammatory processes. In addition, infiltrates associated with rejection in the allograft should not be confused with PTLD.

In order to deal with this wide spectrum of PTLD, a consensus classification has evolved from those originally suggested by Frizzera et al., Nalesnik et al., Knowles et al., a Society for Hematopathology slide workshop, and others [6–13]. The current classification of the PTLD is part of the 2016 WHO classification of hematopoietic and lymphoid tumors (Table 2.1) [1, 14].

In brief, the non-destructive PTLDs show findings that could be seen in reactive proliferations in immunocompetent hosts: the *polymorphic PTLDs* are the most unique-appearing and demonstrate heterogeneous populations of lymphocytes and plasma cells with architectural destruction of the underlying tissues and are not easily categorized as one of the standard lymphomas that occur in immunocompetent hosts; the *monomorphic* PTLDs generally resemble one of the transformed B-cell

Table 2.1 WHO classification of PTLD [1, 14]

Non-destructive PTLDs
Plasmacytic hyperplasia
Infectious mononucleosis
Florid follicular hyperplasia
Polymorphic PTLD[a]
Monomorphic PTLDs[b]
B-cell neoplasms
Diffuse large B-cell lymphoma, NOS
Burkitt lymphoma
Plasma cell myeloma
Plasmacytoma
Other[c]
T-cell neoplasms
Peripheral T-cell lymphoma, NOS
Hepatosplenic T-cell lymphoma
Other
Classic Hodgkin lymphoma PTLD

[a]EBV-positive mucocutaneous ulcer which might resemble a polymorphic PTLD should be separately designated

[b]Classify according to lymphoma they resemble

[c]Indolent small B-cell lymphomas arising in transplant recipients are not included among the PTLDs, with the exception of EBV-positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

lymphomas, a plasma cell neoplasm, or T/NK-cell lymphoma; and *classic Hodgkin lymphoma* PTLDs fulfill the same criteria as those for classic Hodgkin lymphoma in immunocompetent hosts. *EBV-positive mucocutaneous ulcer* is another polymorphic proliferation that can be seen in the post-transplant setting and should be separately designated [15, 16]. It was introduced as a new provisional entity into the 2016 WHO classification [14, 17]. With the exception of EBV+ extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT lymphoma), the small B-cell lymphomas are not considered PTLD even if occurring in transplant patients. This is both for historical reasons and because the standardized incidence ratios are either not increased or only moderately elevated in solid organ transplant recipients [1, 18–20].

While one should try to categorize the PTLD as precisely as possible, and note if they are EBV positive or negative, there is a spectrum of changes ranging from the non-destructive lesions to polymorphic to B-cell monomorphic lesions making precise classification sometimes impossible and reproducibility questionable. Furthermore, individual patients may have different types of PTLD, sometimes clonally unrelated or even with a different cell of origin, either simultaneously at the same or different sites or subsequently. In some cases, recurrences may show evidence of progression from a less destructive or more polymorphic PTLD to one that is more lymphoma-like, including B-cell or T-cell monomorphic PTLD or even Hodgkin lymphoma [4, 21].

Differential Diagnosis

Before diagnosing a PTLD, it is important to exclude the possibility of some other type of lymphoid or plasmacytic proliferation that simply happens to be occurring in a patient post-transplantation or, if the biopsy is from the allograft, exclude the possibility of rejection. Features that would favor the diagnosis of a PTLD over rejection (and over many, but not all, other types of inflammatory infiltrates) include the presence of expansile nodules or a mass lesion, numerous transformed cells, lymphoid atypia, a very B-cell-rich infiltrate, extensive serpiginous necrosis in the infiltrate, a high proportion of plasma cells and finding numerous EBV+ cells. Not all of these features, however, will be present in a PTLD, and one must also be aware of cases with both rejection and a PTLD. Diagnosis, thus, of the PTLD requires a multiparameter approach that also must take into account the clinical setting. Non-destructive lesions without a high proportion of transformed cells at extranodal sites other than the tonsils or spleen, even if EBV+, are generally not diagnosed as a PTLD, but rather as an inflammatory process, such as EBV hepatitis or EBV enteritis. Nevertheless, these extranodal infiltrates may precede PTLD, be associated with PTLD at other sites, and get treated like a PTLD with reduction in immunosuppression, frequently with resolution [22–24].

It should be noted that finding a small proportion of EBV-positive cells in a lymphoid proliferation is not pathognomonic of a PTLD. Likewise, although the subject is too extensive to review here, there are transplant patients with chronically

elevated peripheral blood EBV loads who never develop a PTLD, although in some settings it may put them at higher risk for one [25, 26]. Following peripheral blood EBV loads has been useful in trying to recognize the earliest signs of a PTLD so they can be treated more successfully; however, the findings are not absolute, and the best way to monitor EBV loads remains to be determined [25, 27, 28]. This topic is covered in more detail in Chaps. 6, 11, and 17.

Multiparameter Approach to the Diagnosis of PTLD

The diagnosis and classification of PTLD require handling nodal or extranodal biopsies of potential cases using a standard protocol that provides for histologic sections and fresh material for flow cytometric immunophenotypic studies (if possible) (Table 2.2). In some instances, sending fresh tissue for classical cytogenetic studies may also be of interest, and if possible, snap freezing a small portion of tissue may be worthwhile for certain molecular studies [29, 30].

Adequate evaluation requires morphologic review, at least limited immunophenotypic studies, and an Epstein-Barr virus-encoded RNA (EBER) in situ hybridization stain to assess EBV status (immunostain for EBV-LMP1 is satisfactory if positive). Depending on these results and those of classical cytogenetic studies (if performed), genotypic studies (usually looking for a demonstrably clonal B-cell or T-cell population), and/or cytogenetic fluorescence in situ hybridization (FISH) studies (looking for one of the lymphoma-associated translocations or numerical abnormalities) may be required to arrive at a precise diagnosis. Gene expression profiling studies have provided interesting new information about PTLD but are not of diagnostic or prognostic utility at the current time [31, 32]. Mutational studies are also of interest, but again are not a part of current clinical practice.

Non-destructive PTLDs

The non-destructive PTLDs are defined as lymphoid/plasmacytic proliferations in the post-transplant setting that do not efface the underlying architecture, usually do produce mass lesions, and do not have another explanation, such as a specific non-EBV-associated infectious disorder. These lesions were previously known as “early

Table 2.2 Recommendations for tissue-based diagnosis of PTLD

1.	Excisional biopsy preferred over fine needle aspiration or needle core, when feasible.
2.	Histopathologic and immunophenotypic evaluation, similar to “lymphoma workup” in an immunocompetent host.
3.	EBER in situ hybridization stain for EBV essential.
4.	Molecular/cytogenetic testing often helpful and essential in a subset of cases.
5.	Diagnosis requires categorization of PTLD based on the 2016 WHO classification and statement of whether the PTLD is EBV+. Cases of M-PTLD must be evaluated and classified based on the type of lymphoma they most closely resemble.

PTLD"; however, the name was changed because there was confusion with PTLD of varied types that occurred "early" after transplantation. In fact, these non-destructive lesions may occur many months to years after transplantation [33]. There are three types of non-destructive PTLDs that are currently recognized. It is advisable to use these diagnoses cautiously given the non-specificity of the histologic/immunophenotypic findings, at least in the absence of extensive EBV. Some, however, have specifically argued that transplant patients can have enlarged tonsils with marked follicular hyperplasia and EBV+ cells who do not have a PTLD and never develop one [34]. In contrast to many PTLDs that occur in extranodal sites, the classic non-destructive cases are found most commonly in lymph nodes and tonsils. In the absence of underlying tissue destruction in a biopsy of an extranodal site, particularly if there is a paucity of EBV+ cells (defined in one study of children after small bowel transplantation as not more than 15 EBV+ cells/"field") [24], the diagnosis of a PTLD should only be made with great caution. As noted above, even if there is EBV positivity, non-destructive infiltrates, such as in the liver or bowel, are conventionally designated as EBV hepatitis or EBV enteritis, respectively.

Plasmacytic Hyperplasia (PCH)

Histopathology

Lymph nodes demonstrate intact sinuses with a proliferation of predominantly small lymphocytes and plasma cells with few transformed cells[1] (Fig. 2.1a, b). Caution is advised as, especially if EBV cannot be documented, the changes are totally non-specific.

Ancillary Studies

PCH either is usually non-clonal or at best only has a very small clonal population sometimes only documentable with EBV terminal repeat Southern blot analysis (Fig. 2.1c, d). Cytogenetic or oncogene abnormalities are not expected.

Infectious Mononucleosis (IM) PTLD

Histopathology

Although underlying architectural features are retained, there is a polymorphous lymphoplasmacytic proliferation often in lymph nodes or tonsils/adenoids with more numerous transformed cells/immunoblasts than seen in PCH (Fig. 2.2a, b). Distinction from infectious mononucleosis in the normal host is impossible.

[1] Transformed lymphoid cells are relatively large, usually with a round to oval nucleus with one or more nucleoli and basophilic cytoplasm as seen on a Wright-Giemsa-type stain. They resemble lymphocytes that have been exposed to a mitogen.

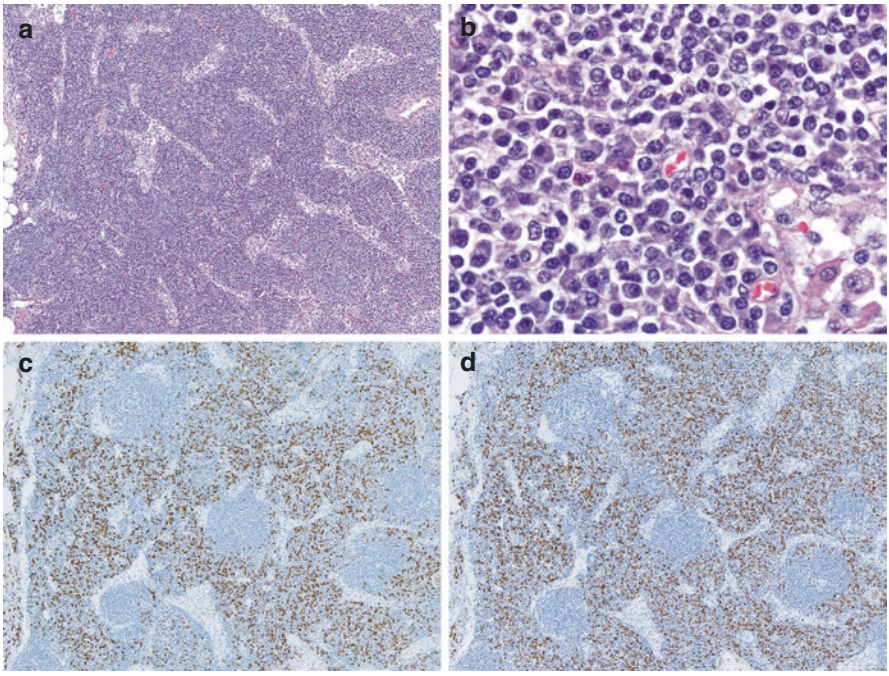

Fig. 2.1 Plasmacytic hyperplasia, lymph node. (**a**) Note there is architectural preservation with many open sinuses. (**b**) There are many plasma cells and some small lymphocytes but few transformed cells. Note the open sinus at the lower right. The (**c**) kappa and (**d**) lambda immunohistochemical stains demonstrate polytypic plasma cells. The scattered follicles are negative. (Unless otherwise noted all figures are hematoxylin and eosin stained sections)

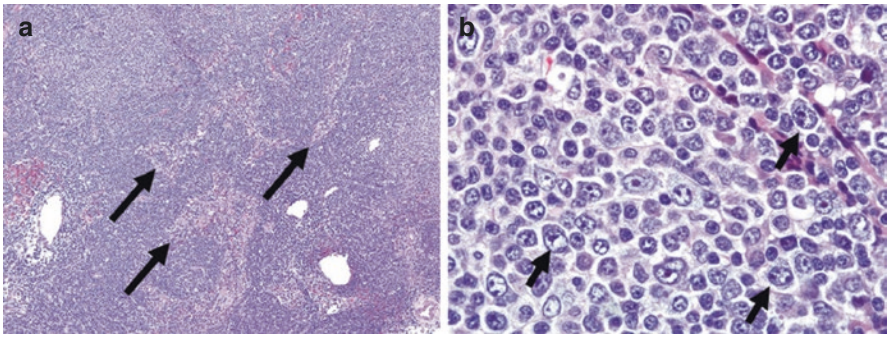

Fig. 2.2 Infectious mononucleosis PTLD, lymph node. (**a**) There is a more florid mostly diffuse proliferation in this lymph node that still demonstrates intact paler sinuses (arrows). (**b**) The proliferation is polymorphic and includes more transformed cells/immunoblasts (arrows) than in plasmacytic hyperplasia. The plasma cells were polytypic

Ancillary Studies

IM PTLD are typically EBV positive and do not demonstrate phenotypic aberrancies. Some cases have small clonal or oligoclonal lymphoid populations, and occasional cases are reported with simple clonal cytogenetic abnormalities [21, 30].

Florid Follicular Hyperplasia

Histopathology

These cases are indistinguishable from non-specific florid follicular hyperplasias in the normal host but should be mass-forming lesions. They are reported not to have significant expansion of interfollicular areas and few interfollicular immunoblasts/transformed cells. Distinction from totally non-specific FH may be impossible especially in the absence of significant numbers of EBV+ cells or other abnormalities, and there will be a gray zone between these cases and IM PTLD.

Ancillary Studies

Immunophenotypic studies are non-diagnostic, and most cases fail to demonstrate a clonal lymphoid population by any method. Occasional cases are reported to demonstrate simple clonal cytogenetic abnormalities [30].

Polymorphic PTLD

Polymorphic (P) PTLDs traditionally are destructive polymorphic lymphoplasmacytic proliferations that do not fulfill the criteria for a typical lymphoma as seen in immunocompetent hosts. These PTLDs are common in children after solid organ transplantation but form a minority of the PTLDs observed in adults. They are also more commonly seen in the first few years after transplantation (especially when associated with primary EBV infection in children) but may still be observed in late-onset cases years after transplantation. When originally defined, ancillary studies were very limited so P-PTLDs were defined in terms of their polymorphism (lymphoid cells of varied size and shape and at different maturational stages) in contrast to the more uniform transformed cell proliferations that defined the monomorphic (M) PTLD. With the increasing use of more ancillary studies, many classic P-PTLDs may have at least some features that do suggest a traditional lymphoma, such as easily identified clonal plasma cells in addition to B-cell clones identified by molecular studies. In addition, some M-PTLDs share features commonly associated with P-PTLD such as pleomorphism or more numerous smaller lymphocytes (see below) so that there is now more of a gray zone between these two categories of PTLD, and it is clear that there is a lack of uniformity in the way P-PTLD is used. There is also a gray zone between some P-PTLD and IM-PTLD, particularly in tonsils. Cases of EBV+ mucocutaneous ulcer should be separately designated.

Histopathology

There is destruction of the underlying lymph node or other parenchymal tissue architecture by a diffuse polymorphic proliferation of lymphocytes of varying size, shape, and degree of transformation plus plasma cells (Fig. 2.3a, b). The transformed cells/immunoblasts may be "atypical" and resemble classic Reed-Sternberg cells (Fig. 2.3c). The infiltrates may be angiocentric and angiodestructive and, in the lung, may resemble lymphomatoid granulomatosis. Geographic (serpiginous) areas of necrosis are seen in about one third of cases. The separately designated EBV+ mucocutaneous ulcers are ulcerated polymorphic proliferations in the skin, oral mucosa, or intestine, often with many large transformed cells and Reed-Sternberg-like cells with admixed lymphocytes, histiocytes, plasma cells and eosinophils, and a rim of smaller lymphocytes at their periphery [17]. Angioinvasion and necrosis may also be present. Some more closely resemble a diffuse large B-cell lymphoma.

Ancillary Studies

Typically, immunophenotypic studies demonstrate an admix of variably sized B cells and heterogeneous T cells (Fig. 2.3d, e). Major light chain restricted B-cell populations are not expected; however, light chain restricted plasma cell populations are found in some cases that most people would still include in this category, and genotypic studies will demonstrate variably sized B-cell clones in virtually all cases. *BCL6* mutations that in part are physiologic are reported in some polymorphic PTLD; however, while abnormalities in tumor suppressor genes and oncogenes have been reported, they are much less common than in M-PTLD [8, 32, 35, 36]. Some cases have cytogenetic abnormalities [29, 30]. Many, but not all, cases are EBV+ (Fig. 2.3f).

EBV+ mucocutaneous ulcer typically has prominent large CD20+, IRF4/MUM1+, and CD30+ B cells that may be CD15+, as well as admixed EBV− T cells that are most dense at the periphery of the lesion [15]. Monoclonal immunoglobulin rearrangements are seen in less than half of the cases, and there are often oligoclonal or restricted T-cell populations. They typically lack EBV DNA in the peripheral blood [16].

Monomorphic PTLD

The monomorphic PTLD are a heterogeneous group of lymphoid/plasmacytic proliferations that fulfill the criteria for one of the lymphomas or plasma cell neoplasms that are recognized in the immunocompetent host. While EBV+ MALT lymphomas are now accepted as a form of M-PTLD, other small B-cell lymphomas are not [1, 20]. While classically defined as being composed predominantly of numerous transformed lymphoid cells at one maturational stage (hence monomorphic), they may show pleomorphism, have plasmacytic differentiation, be composed of sheets of

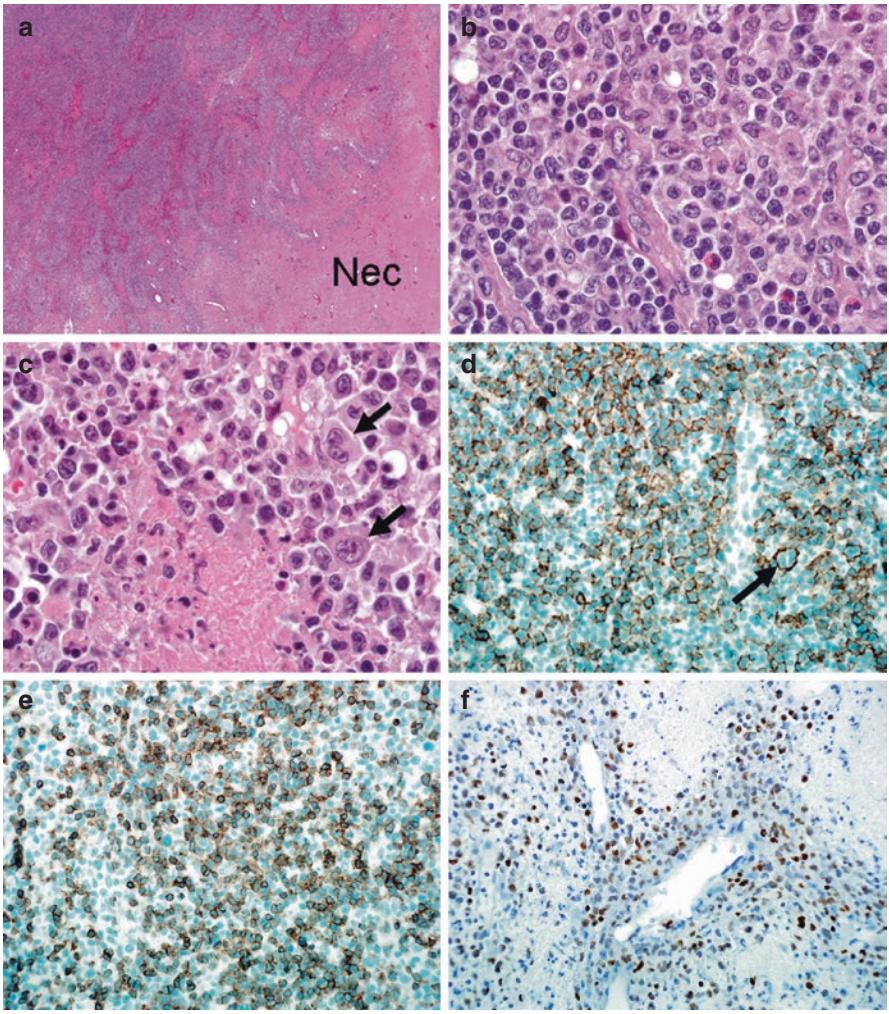

Fig. 2.3 Polymorphic PTLD, lymph node. (**a**) There is diffuse architectural effacement and extensive areas of eosinophilic geographic necrosis (Nec). (**b**) The lymphoid cells vary in size and shape and degree of transformation. There are also admixed histiocytes and eosinophils. (**c**) Atypical immunoblasts are seen especially around the necrotic areas (arrows). (**d**) There are many CD20+ B cells including the atypical/Reed-Sternberg-like cells (arrows). (**e**) There are also many admixed CD3+ T cells. (**f**) Many of the cells are EBV+ as seen in this EBER in situ hybridization stain

light chain restricted plasma cells, or, in the case of monomorphic T-cell PTLDs, be composed of quite heterogeneous T-cell populations as long as they would fulfill the criteria for a lymphoid neoplasm. They are all expected to be monoclonal, and it is among the monomorphic T-cell PTLDs that the greatest frequency of EBV negative cases will be found (about 70%). M-PTLD is the predominant pathology observed in adult transplant recipients.

Monomorphic B-Cell PTLD

The majority of the monomorphic PTLD resemble one of the types of diffuse large B-cell lymphoma, not otherwise specified, with smaller numbers resembling Burkitt lymphoma, plasma cell myeloma, or another type of plasma cell neoplasm. Cases of the new provisional entity, Burkitt-like lymphoma with 11q aberration, may be over-represented among transplant patients, but are not common [1, 37].

Histopathology

The most common monomorphic B-cell M-PTLDs are of the diffuse large B-cell lymphoma (DLBCL), not otherwise specified type, and are usually composed of sheets of large transformed cells growing with an infiltrative and/or destructive pattern and sometimes showing angiocentricity (Fig. 2.4a, b). There may be pleomorphism, and plasmacytic differentiation may be present in some cases. These cases do not have uniform morphologic features, and some B-cell M-PTLD may fulfill the criteria for one of the other large B-cell lymphomas, such as intravascular large B-cell lymphoma or plasmablastic lymphoma (Fig. 2.5) [38, 39]. Less frequently, they are of Burkitt type and composed of sheets of intermediate-sized transformed cells with amphophilic cytoplasm and a starry sky appearance due to the scattered tingible body macrophages that contain phagocytized apoptotic debris (Fig. 2.6). Some may resemble a Burkitt lymphoma but lack *MYC* translocations and have 11q aberrations [37]. Other cases are composed of a sheet of plasma cells as seen in plasma cell myeloma or a non-myelomatous plasmacytoma (Fig. 2.7a, b). These two situations must be distinguished just as they would be in an immunocompetent host, with an expected different approach to therapy [40–42].

Ancillary Studies

Most cases are CD20 positive. Except in cases that lack immunoglobulin expression, immunophenotypic studies should show light chain class restriction and a

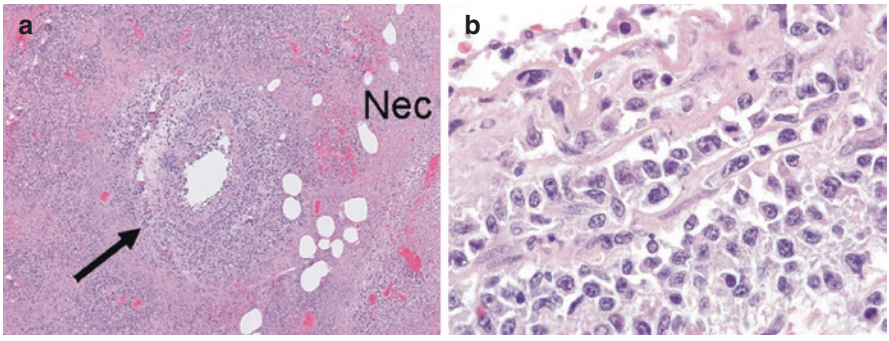

Fig. 2.4 Monomorphic B-cell PTLD, diffuse large B-cell lymphoma, not otherwise specified type, small intestine. (**a**) Note the angioinvasion (arrow) and foci of eosinophilic necrosis (Nec). (**b**) There are numerous transformed cells that marked as B cells in the vessel wall. Even here the cells are not completely monotonous

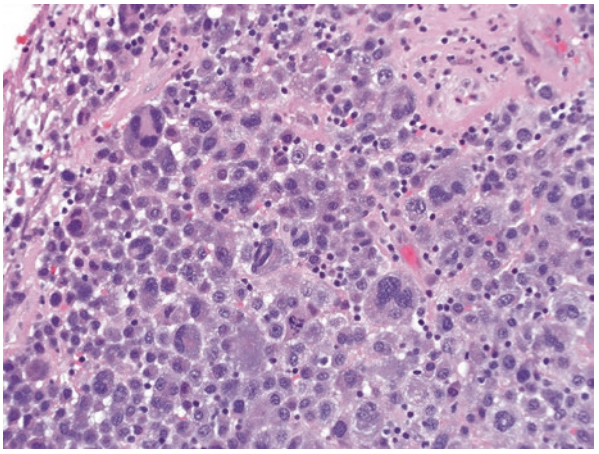

Fig. 2.5 Monomorphic B-cell PTLD, plasmablastic lymphoma type, sinus contents. Note the anaplastic-appearing plasmacytic cells that were CD20−, CD138+, kappa+, and EBV+

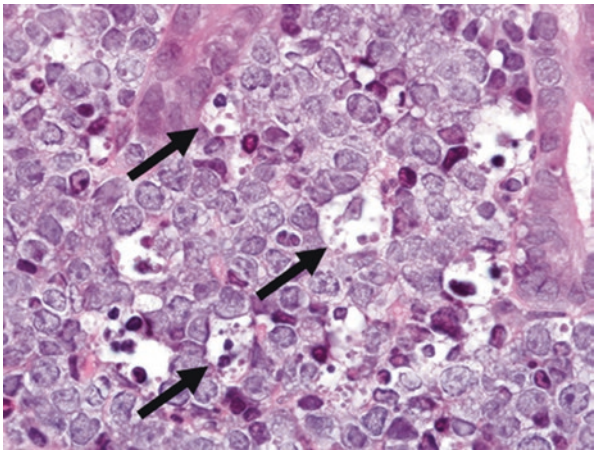

Fig. 2.6 Monomorphic B-cell PTLD, Burkitt lymphoma type, duodenum. There is a diffuse proliferation of transformed lymphoid cells and a starry sky appearance from the scattered tingible body macrophages (arrows). The cells had a typical Burkitt lymphoma phenotype (CD10+, BCL6+, BCL2−, Ki-67 numerous positive cells) and a *MYC* translocation

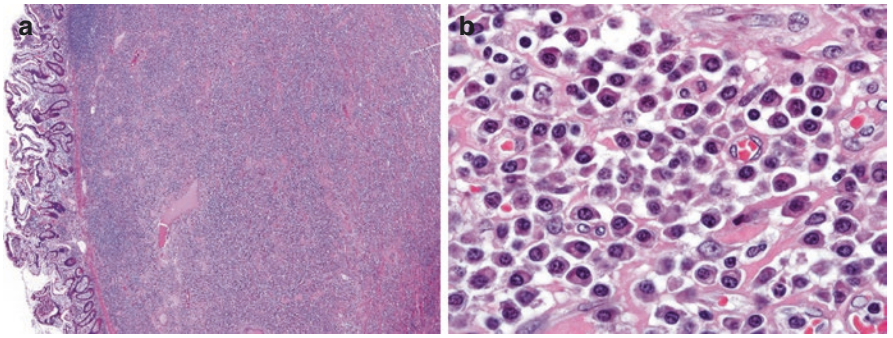

Fig. 2.7 Monomorphic B-cell PTLD, plasmacytoma type, small intestine. (**a**) Note the large mass lesion. (**b**) In most areas the mass was composed of a sheet of monotypic plasma cells. Cases like this must be distinguished from visceral involvement by plasma cell myeloma

more detailed phenotype like that seen in the neoplasms they resemble. The DLBCL may have either a germinal center type or non-germinal center phenotype with the former phenotype more common among the EBV-negative cases [43]. The prognostic importance of this distinction in the post-transplant setting is not well-established, but it still might have therapeutic implications. Burkitt lymphomas usually have a CD20+, CD10+, BCL6+, and BCL2− phenotype. The plasma cell neoplasms usually lack B-cell-associated markers and are CD138+ with cytoplasmic light chain class restriction. EBV is present in a majority of cases but a significant minority is negative.

Genotypic studies can be used to confirm the monoclonality of these PTLDs; however, they are usually unnecessary for diagnostic purposes. Caution is advised as clonal T-cell receptor rearrangements may also be present in the absence of a coexistent T-cell PTLD [44]. Among the common types of PTLD, the B-cell M-PTLDs are the ones most likely to demonstrate abnormalities of tumor suppressor genes (e.g., *TP53*), oncogenes (*N-RAS*), perhaps *BCL6* mutations, aberrant somatic hypermutation (e.g., of *MYC* or *RHO/TTF*), and translocations such as of *MYC* (a feature of Burkitt lymphomas) [8, 32, 35]. Cytogenetic abnormalities, including some (not universally agreed upon) recurrent abnormalities, are more common than in the other types of B-cell-rich PTLD [29, 30]. In addition to finding some recurrent abnormalities associated with conventional lymphomas, such as involving *MYC*, trisomies 9 and 11 have been found by some with trisomy 11 also associated with other EBV-associated neoplasms [29, 45]. EBV+ PTLDs have been reported to have fewer genetic/mutational abnormalities than EBV− cases which may show more features like the DLBCL in immunocompetent hosts which they resemble [46, 47]. Nevertheless, at least limited differences are reported between even EBV- PTLD and DLBCL arising in immunocompetent hosts, with more differences found in comparison with the EBV+ PTLD [36]. Although not consistently found, at least two gene expression profiling studies have shown differences between EBV+ and EBV− PTLD, consistent with mutational differences [31, 36, 46, 48].

Monomorphic T/NK-Cell PTLD

Monomorphic T/NK-cell PTLDs account for only about 7–15% of PTLD in Western countries and appear to be more common in Japan [4]. They are defined as post-transplant lymphoid proliferations that fulfill the criteria for one of the T/NK-cell neoplasms recognized in the WHO classification and hence are often not composed of monomorphic large transformed cells [1]. The T/NK-cell PTLDs most commonly resemble peripheral T-cell lymphoma, not otherwise specified, with cases of hepatosplenic T-cell lymphoma another one of the more common types seen. Many of the recognized peripheral T-cell lymphomas have been described in the post-transplant setting including, among others, T-cell lymphoblastic leukemia/lymphoma, T-cell large granular lymphocyte leukemia, adult T-cell leukemia/lymphoma, mycosis fungoides, Sézary syndrome, and cutaneous and other anaplastic large cell

lymphomas (ALK+ and ALK−) [4]. Occasional lymphomas of natural killer cells, including extranodal NK/T cell lymphoma, nasal type, are also reported. Only about one third of T-cell PTLD are EBV positive.

Histopathology

The histopathology of the T/NK-cell PTLD is very variable but should be the same as for the varied T-cell lymphomas seen in immunocompetent hosts. These cases may be confused with polymorphic PTLD or other reactive proliferations because many T/NK-cell lymphomas can appear heterogeneous and include many admixed reactive elements. Some features to look for, in addition to a destructive growth pattern, include prominent cytologically atypical lymphoid cells or, in some cases, very numerous transformed lymphoid cells (like in other monomorphic PTLD) (Fig. 2.8a). A discussion of the histopathology of T-cell lymphomas is beyond the scope of this chapter [1].

Ancillary Studies

Ancillary studies are critical in the diagnosis of the T-cell PTLD. Immunophenotypic studies are useful to exclude findings that would suggest one of the other types of PTLD (e.g., abnormal B cells); to document that the cells of concern mark as T cells (pan-T-cell and T-cell subset marker expression) or natural killer (NK) cells (surface CD3−, CD5−, CD56+); and, in some cases, to demonstrate a population with an aberrant T-cell phenotype (e.g., "loss" of one or more pan-T-cell markers) or expansion of a T-cell subset that is either usually not present in large numbers or is present on cells that clearly appear neoplastic based on their cytologic features and growth pattern (Fig. 2.8b). For example, finding that an intrasinusoidal neoplastic T-cell infiltrate in the liver lacks T-cell receptor beta chain expression and is positive with TIA-1 but not granzyme B helps make the diagnosis of a hepatosplenic T-cell

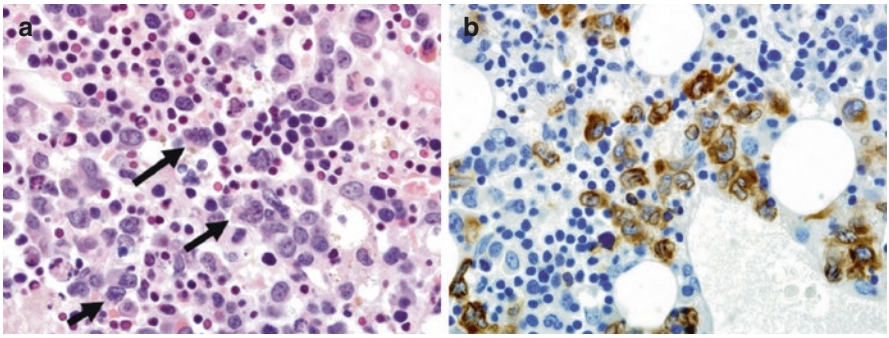

Fig. 2.8 Monomorphic T-cell PTLD, peripheral T-cell lymphoma, not otherwise specified type (cytotoxic), bone marrow. (**a**) There is a patchy interstitial infiltrate composed of very large cells with irregular nuclear contours (arrows) in the marrow biopsy. (**b**) The very abnormal cells are more easily seen in this CD3 immunohistochemical stain that identifies T cells (and natural killer cells). A clonal T-cell receptor beta chain rearrangement was documented by Southern blot analysis. EBV was not detected

lymphoma type T-PTLD. Molecular studies (PCR analyses looking for clonal T-cell receptor gene rearrangements) are also very important to help identify the presence of a clonal T-cell population remembering that clonal populations can be seen in the setting of infectious mononucleosis [49] and in some B-cell PTLD [44] and that natural killer cell neoplasms will be negative. Both chromosomal abnormalities and oncogene and epigenetic modifier gene mutations are commonly found and reported to be similar to those in T-cell lymphomas arising in immunocompetent hosts [50].

Classic Hodgkin Lymphoma PTLD

Classic Hodgkin lymphoma PTLD is strictly defined and must fulfill the criteria for classic Hodgkin lymphoma in an immunocompetent host. Caution is advised as cells resembling Reed-Sternberg cells are seen in many different types of PTLD, most of which are not of Hodgkin type. So-called "Hodgkin-like" PTLDs are no longer included with the classic Hodgkin PTLD and are to be categorized in whatever other PTLD category they best fit in [51].

Histopathology

Post-transplant classic Hodgkin lymphoma most typically shows at least partial architectural effacement by a proliferation of variable numbers of small lymphocytes, plasma cells, eosinophils, and histiocytes, together with diagnostic Reed-Sternberg cells and Reed-Sternberg variants (Fig. 2.9). Most cases in the transplant setting fulfill the criteria for the mixed cellularity type. Whether post-transplant Hodgkin lymphoma has any unique features is difficult to assess given the difficulty sometimes in distinguishing it from other PTLD with Hodgkin-like features.

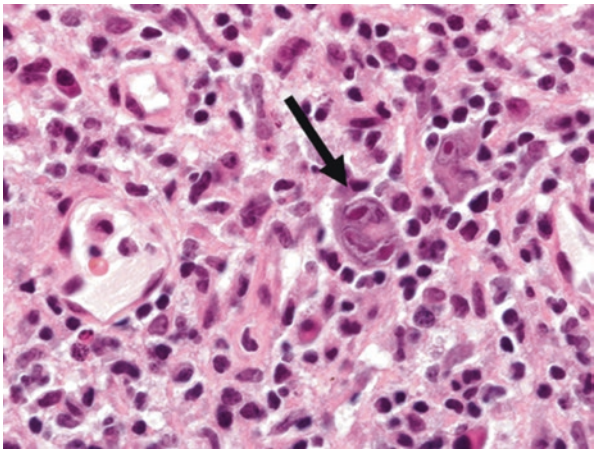

Fig. 2.9 Mixed cellularity classic Hodgkin lymphoma PTLD, lymph node. There are Reed-Sternberg cells (arrow) in a sea of small lymphocytes and some plasma cells. The Reed-Sternberg cells were CD20−, CD15+, and CD30+

Ancillary Studies

Immunohistochemical studies are critical, particularly given the resemblance of many other types of PTLD to classic Hodgkin lymphoma. In the most definite cases, the Reed-Sternberg cells are CD15+, CD30+, CD20−, and CD45− with the majority of the surrounding small lymphocytes of T-cell type. It is expected that, as in immunocompetent hosts, the Reed-Sternberg cells are also either OCT2 (POU2F2) or BOB.1 (POU2AF1) negative – a feature that may be helpful in the presence of some CD20 staining or an absence of CD15 expression. The neoplastic cells should also be weakly positive for PAX5 in most cases and positive for IRF4/MUM1. Almost all cases have been EBV+. Genotypic studies may demonstrate clonal B cells in some cases.

Take-Home Pearls

- The PTLDs include many different types of lymphoid and plasmacytic proliferations that are associated with the Epstein-Barr virus in about 60–80% of cases. Some cases may be driven by other forms of chronic antigenic stimulation.
- Classification of the PTLD is important and is best accomplished by working up potential cases as one would a potential lymphoma. Categorization requires knowledge about the WHO criteria both for the PTLD and for lymphomas in general.
- In spite of one's best efforts, some cases may be difficult to categorize because there are gray zones between the different types of PTLD, particularly those of non-destructive, polymorphic, and monomorphic B-cell types.
- There is no sharp border between a PTLD and an overt lymphoma in the post-transplant setting.
- It is always important to exclude the possibility of some other type of lymphoplasmacytic proliferation including rejection prior to making the diagnosis of a PTLD. In rare cases there may be both rejection and a PTLD.

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