Iatrogenic Immunodeficiency Associated Lymphoproliferative Disorders

Elizabeth L. Courville[1] and Aliyah R. Sohani[2]
[1]Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA
[2]Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

Definition

Iatrogenic immunodeficiency-associated lymphoproliferative disorders can be defined as lymphoid proliferations, plasmacytic proliferations, or lymphomas that arise as a consequence of iatrogenic immunosuppression. Such disorders are divided into **posttransplant lymphoproliferative disorders (PTLD)** arising in patients treated with immunosuppressive therapy for solid organ, bone marrow, or stem cell transplant and **other iatrogenic immunodeficiency-associated lymphoproliferative disorders** arising in patients treated with immunosuppressive drugs for autoimmune disease or conditions other than transplant (Bagg and Dunphy 2013; Gaulard et al. 2017; Swerdlow et al. 2017; Tsao and Hsi 2007). Immunosuppressive drugs reported as associated with lymphoproliferative disorders and lymphomas include methotrexate and antitumor necrosis factor alpha (anti-TNFα) therapy (e.g., infliximab, adalimumab, etanercept). These lymphoproliferative disorders are less well defined than PTLD.

Clinical Features

- **Incidence**: PTLD is rare with an overall frequency of <2% in the posttransplant population. In solid organ transplant recipients, the frequency depends on the organ transplanted, with kidney transplant recipients having a frequency of PTLD <1% and up to 20% in intestinal transplant recipients. After stem cell allografts, the frequency is approximately 1%.

  The exact incidence of other iatrogenic immunodeficiency-associated lymphoproliferative disorders is unknown. The incidence likely depends on the type of immunosuppressive agent and the underlying disorder being treated. Complicating determination of incidence is the likely baseline increased risk of lymphoma in patients with various autoimmune disorders.
- **Age**: All ages are affected. In solid organ or stem cell transplant recipients who are children, the frequency of developing PTLD is higher by two to five-fold.
- **Sex**: Both genders are affected.
- **Site**: In PTLD, involvement of lymph node, gastrointestinal tract, lungs, and liver is

H. V. Krieken (ed.), *Encyclopedia of Pathology*,
https://doi.org/10.1007/978-3-319-28845-1_4772-1

common. In nondestructive PTLD, the tonsil and/or adenoid are frequently involved.

In other iatrogenic immunodeficiency-associated lymphoproliferative disorders related to methotrexate use, nearly half arise in extranodal locations.

- **Treatment**: Treatment in PTLD is dependent on the subclassification of disease and extent of involvement. Nondestructive PTLD or polymorphic PTLD may be treated with a decrease in immunosuppressive therapy or anti-CD20 (rituximab) therapy alone while monomorphic PTLD is most often treated with chemotherapy.

  Some methotrexate-associated lymphoproliferative disorders regress after withdrawal of methotrexate, while most require chemotherapy. TNFα antagonist associated lymphoproliferative disorders rarely regress after drug discontinuation.
- **Outcome**: Outcome in PTLD is dependent on the subclassification of disease and location and degree of involvement. In general, monomorphic PTLD has a worse prognosis than polymorphic PTLD or nondestructive PTLD, although exceptions occur and some nondestructive PTLD (infectious mononucleosis-like) can be fatal.

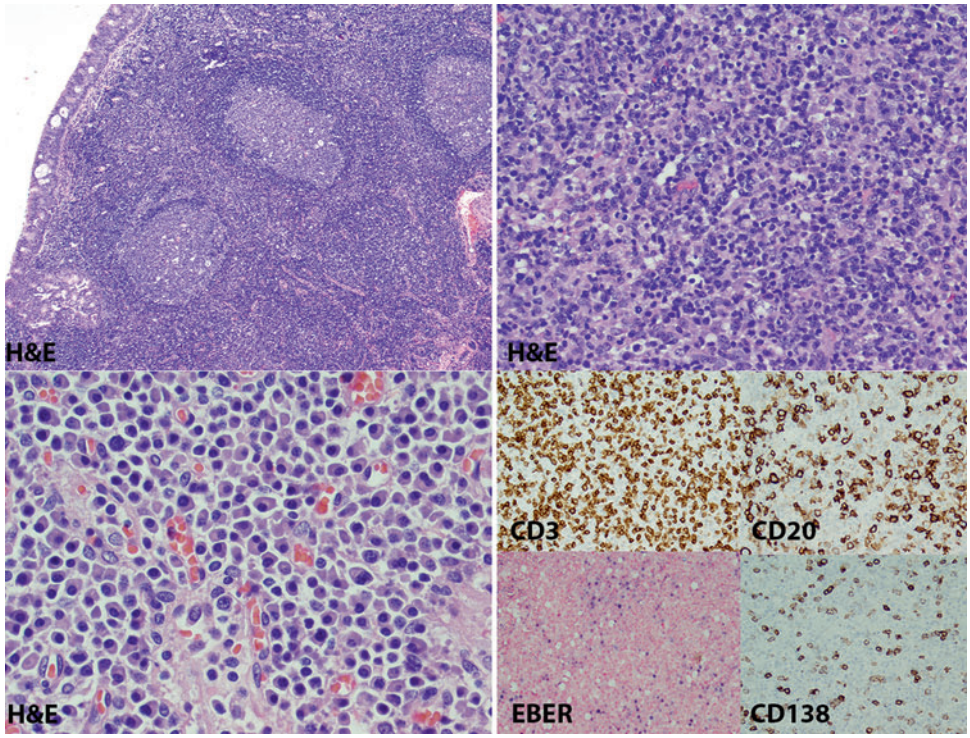
Macroscopy

PTLD is characterized by lymphadenopathy or extranodal mass lesions. The cut surface of a lymph node in early lesions of PTLD will be unremarkable (similar to that of a reactive lymph node), while that of a lymph node with monomorphic PTLD can show characteristic features of lymphoma (e.g., obliteration of the hilus, fleshy homogenous cut surface, or bands of fibrosis).

Microscopy

Posttransplant Lymphoproliferative Disorders (PTLD)

PTLD is subclassified based on morphologic and immunohistochemical features into the following categories: nondestructive PTLD (previously termed "early lesions"), polymorphic PTLD, monomorphic PTLD, and classic Hodgkin lymphoma PTLD (Figs. 1, 2, and 3). Nondestructive PTLD is characterized by mass-forming lymphoid proliferations with preservation of the nodal or extranodal architecture and shows a pattern of plasmacytic hyperplasia, florid follicular hyperplasia, or infectious mononucleosis-like features (follicular hyperplasia with paracortical expansion and numerous immunoblasts). In contrast, polymorphic PTLD is characterized by effacement of the normal lymph node architecture or formation of destructive extranodal masses by a polymorphous infiltrate composed of small lymphocytes, intermediate-sized lymphocytes, immunoblasts, and plasma cells. Polymorphic PTLD may show areas of geographic necrosis. By definition, the morphology of polymorphic PTLD does not meet the criteria for a recognized type of lymphoma described in immunocompetent hosts. When the lymphoproliferative process *does* meet the diagnostic criteria for a B-cell or T/NK-cell lymphoma or plasma cell neoplasm as described in an immunocompetent individual, this is categorized as monomorphic PTLD with further designation as the lymphoma or plasma cell neoplasm it resembles. EBV-positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue has recently been recognized as a distinct type of monomorphic PTLD, usually occurring late after transplant in a solitary cutaneous/subcutaneous location (Gibson et al. 2011). With that exception, the remainder of the small B cell lymphomas are not considered PTLD in current classifications. Among monomorphic B cell PTLD, cases are further classified as diffuse large B cell lymphoma (DLBCL), Burkitt lymphoma, plasmacytoma, or, rarely, plasma cell myeloma depending on the conventional criteria fulfilled. Monomorphic T/NK-cell PTLD most commonly fit conventional criteria for peripheral T cell lymphoma, not otherwise specified (PTCL, NOS), or hepatosplenic T cell lymphoma, and less commonly other types of T/NK cell lymphomas. Classic Hodgkin lymphoma PTLD fits the morphologic and immunophenotypic criteria for classic Hodgkin lymphoma as in an



Iatrogenic Immunodeficiency Associated Lymphoproliferative Disorders, Fig. 1 Non-destructive PTLD (left panel). The upper left panel is an example of florid follicular hyperplasia in an adenoid. There were numerous secondary follicles with germinal centers. By EBER in-situ hybridization, there were frequent EBV positive cells (not shown). The bottom left panel is an example of plasmacytic hyperplasia in a lymph node from a different patient. This high power view shows sheets of plasma cells. The plasma cells were polytypic by immunohistochemical stains for kappa and lambda light chains. **Polymorphic PTLD (right panel)**. This example of polymorphic PTLD arising in a lymph node shows effacement of the nodal architecture by a polymorphous infiltrate of small T lymphocytes (highlighted by CD3 immunohistochemical stain), B lymphocytes of various sizes (highlighted by CD20 immunohistochemical stain), and plasma cells (highlighted by CD138 immunohistochemical stain). This PTLD is EBV positive by EBER in situ hybridization

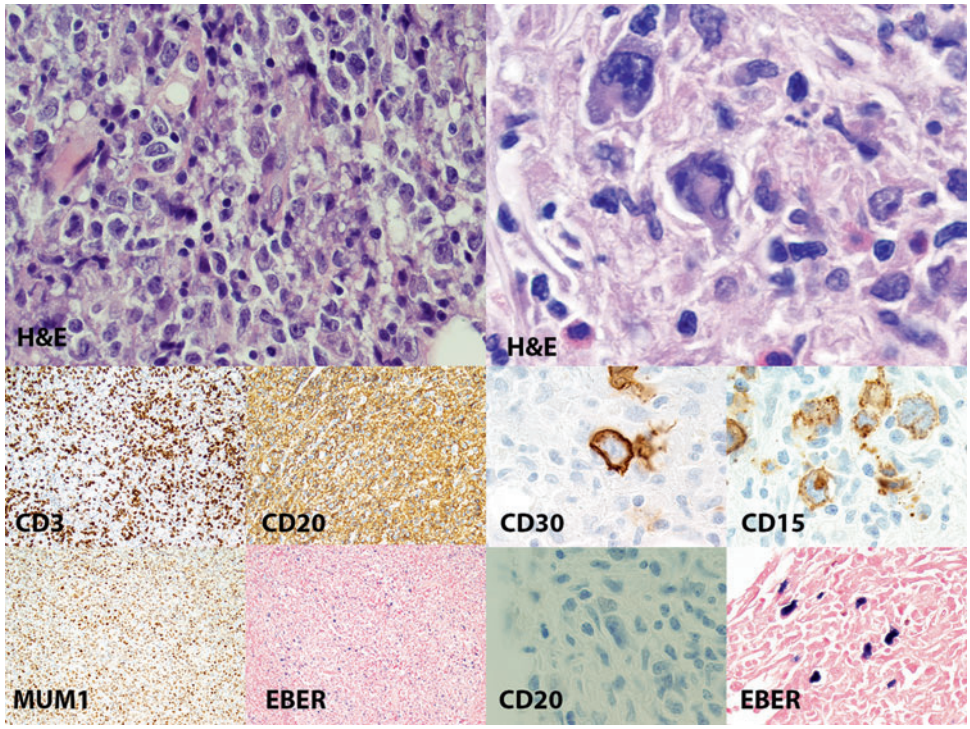
immunocompetent host and usually shows features of the mixed cellularity type.

Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders

Methotrexate-associated lymphoproliferative disorders are most commonly diffuse large B cell lymphoma or classic Hodgkin lymphoma. Less common are follicular lymphoma, Burkitt lymphoma, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, or peripheral T cell lymphoma. Polymorphic or lymphoplasmacytic proliferations resembling polymorphic PTLD comprise up to 20% of cases.

In one study evaluating 18 patients treated with immunomodulatory agents (e.g., anti-TNFα, anti-CD11a, anti-interleukin-2 receptor, or anti-interleukin-1 receptor therapies) for a variety of autoimmune disorders, cases ranged from atypical lymphoid proliferations (7 cases) to overt lymphomas (Hasserjian et al. 2009). For patients with Crohn disease treated with a TNFα inhibitor in combination with immunomodulators, there is an association with hepatosplenic T cell lymphoma (Deepak et al. 2013), although not all studies have shown in increased risk. In these cases, the hepatosplenic T cell lymphoma shows the same features as that arising in immunocompetent individuals.

EBV-positive mucocutaneous ulcer is a recently recognized entity occurring in patients with iatrogenic immunosuppression or age-



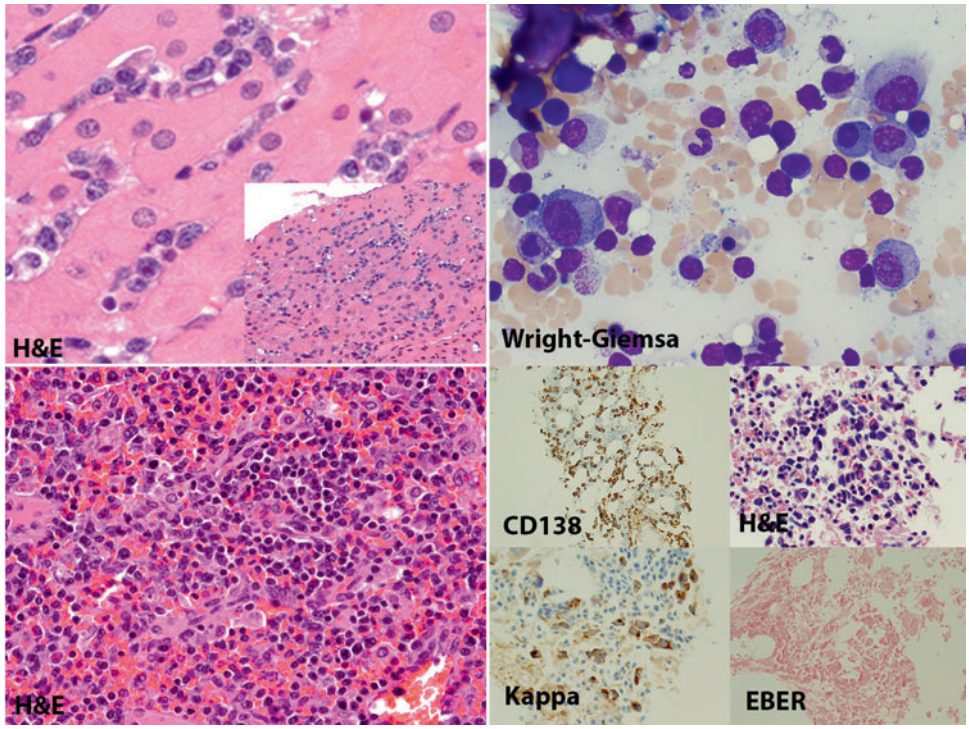
Iatrogenic Immunodeficiency Associated Lymphoproliferative Disorders, Fig. 2 Monomorphic PTLD (diffuse large B cell lymphoma) (left panel). This example of monomorphic PTLD arising in a lymph node has the morphology and immunophenotype of diffuse large B cell lymphoma. There is effacement of the nodal architecture by a diffuse infiltrate of intermediate to large sized atypical lymphoid cells with vesicular chromatin and prominent nucleoli. The atypical lymphoid cells are predominantly B lymphocytes (highlighted by CD20 immunohistochemical stain) with background T lymphocytes (highlighted by CD3 immunohistochemical stain). This case has a non-germinal center immunophenotype by the Hans criteria, being negative for CD10 and BCL6 and positive for MUM1 (shown). EBV is positive by EBER in situ hybridization. **Classic Hodgkin lymphoma PTLD (right panel)**: Features of classic Hodgkin lymphoma are present including large atypical lymphoid cells (Reed-Sternberg cells and variants) in a background of small lymphocytes, eosinophils, and histiocytes. The Reed-Sternberg cells and variants are positive for CD30 immunohistochemical stain, CD15 immunohistochemical stain, and EBV (by EBER in situ hybridization), but lack expression of CD20

related immune senescence (Dojcinov et al. 2010). EBV-positive mucocutaneous ulcers are characterized by isolated sharply circumscribed ulcers involving oropharyngeal mucosa, skin, and gastrointestinal tract; the lymphoid infiltrate shows a polymorphous background and scattered Reed-Sternberg and Hodgkin-like cells (Fig. 4). These lesions frequently show a self-limited, indolent course.

Immunophenotype

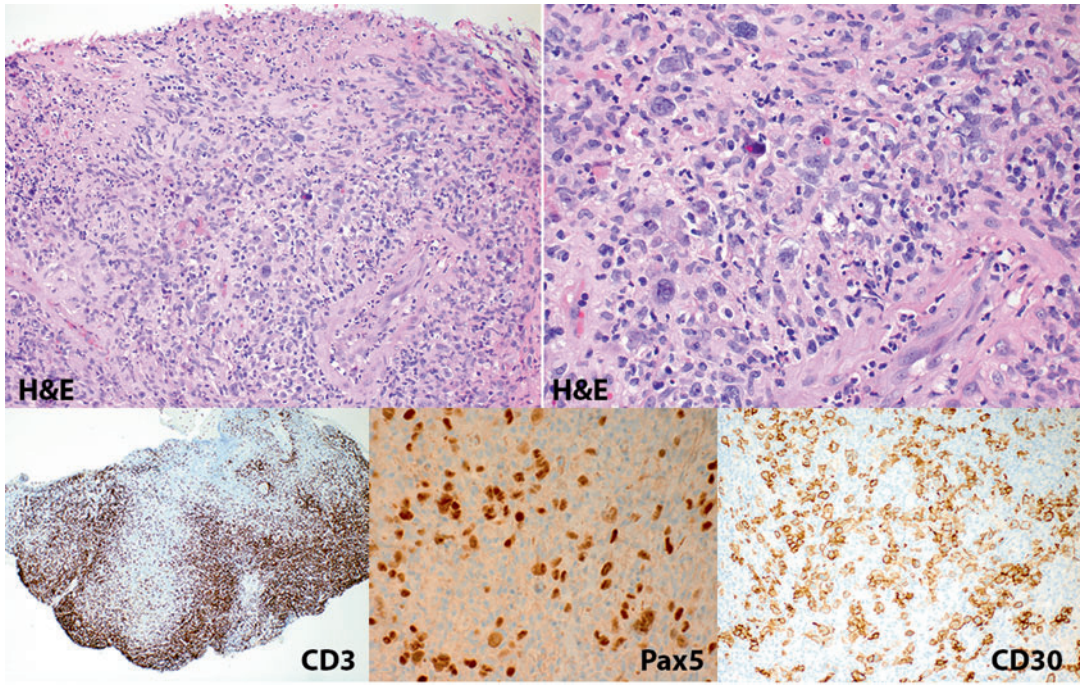
Posttransplant Lymphoproliferative Disorders (PTLD)

The majority of PTLD are composed predominantly of B cells and therefore stain with B-cell markers such as CD19, CD20, Pax5, and CD79a. Plasmacytic components of the proliferations can be identified by CD138 and immunohistochemical stains for kappa and lambda cytoplasmic light chains. Almost all nondestructive PTLD and polymorphic PTLD are positive for Epstein-Barr



Iatrogenic Immunodeficiency Associated Lymphoproliferative Disorders, Fig. 3 Monomorphic PTLD (hepatosplenic T cell lymphoma) (left panel). The upper left panel shows liver involvement with sinusoidal expansion by an atypical lymphoid infiltrate composed of medium sized cells with slightly dispersed nuclear chromatin and inconspicuous or small nucleoli. Low power view is shown in in-set. The bottom left panel shows involvement of the splenic red pulp, with expansion by an atypical lymphoid infiltrate. Immunohistochemical stains (not shown) demonstrated that the atypical lymphoid infiltrate was composed of CD3 positive T cells with aberrant loss of the pan-T cell antigen CD5. **Monomorphic PTLD (plasma cell myeloma) (right panel)**. Monomorphic PTLD with the morphology of plasma cell myeloma shares the same diagnostic features as plasma cell myeloma diagnosed in an immunocompetent individual. Wright-Giemsa stained aspirate smears show multiple enlarged atypical plasma cells with prominent nucleoli, present in a background of normal hematopoiesis. On the bone marrow trephine core, the increased plasma cells are highlighted by CD138 immunohistochemical stain. In this case, the plasma cells were kappa light chain restricted (kappa immunohistochemical stain shown) with only rare lambda light chain positive cells. EBV was negative by EBER in situ hybridization.

Virus (EBV), with in situ hybridization for EBV RNA (EBER ISH) a more sensitive method of detection than EBV immunohistochemical staining. The immunophenotype of monomorphic PTLD follows that of the disorder arising in immunocompentent hosts. Therefore, as in an immunocompetent host, monomorphic B-cell PTLD with the morphology of Burkitt lymphoma shows positivity for B-cell markers as well as CD10 and BCL6, but lacking BCL2, and with a high proliferative index by Ki-67 immunohistochemical stain of nearly 100%. Monomorphic B-cell PTLD with the morphology of DLBCL includes both those with a germinal center type and nongerminal center type immunophenotype as defined by immunohistochemical parameters in the Hans criteria. In contrast to DLBCL arising in immunocompetent hosts, such separation has not yet been shown to have prognostic significance in the posttransplant setting. Approximately two-thirds of monomorphic B-cell PTLD are positive for EBV by EBER-ISH, and there is an association of a nongerminal center immunophenotype with EBV positivity. EBV status as a prognostic indicator or predictor of treatment response has not been shown (Luskin et al. 2015). In



Iatrogenic Immunodeficiency Associated Lymphoproliferative Disorders, Fig. 4 EBV positive mucocutaneous ulcer arising in oral mucosa (gum lesion). Images from H&E stained sections demonstrate some of the characteristic features of EBV positive mucocutaneous ulcer including an ulcerated surface (top of left-sided H&E image), and Reed-Sternberg-like and Hodgkin-like large atypical lymphoid cells interspersed in a mixed inflammatory background. CD3 immunohistochemical stain highlights T-lymphocytes concentrated in the base of the ulcerative lesion. The large atypical lymphoid cells are positive for B cell markers including Pax5, as well as CD30. These large atypical lymphoid cells were also positive for EBV (not shown)

monomorphic B/plasma-cell PTLD, a clonal B cell or plasma cell population is identified by flow cytometric immunophenotyping in most cases. Polymorphic PTLD may or may not have a clonal B cell population by flow cytometry, whereas nearly all cases of nondestructive lesions of PTLD show polytypic B cells and plasma cells. Monomorphic T/NK-cell PTLD share the same immunophenotype as the T/NK-cell lymphoma arising in an immunocompetent host it resembles and similarly the same immunophenotypic criteria for classic Hodgkin lymphoma as in an immunocompetent host must be met to diagnose classical Hodgkin lymphoma PTLD. Classic Hodgkin lymphoma PTLD is usually EBV positive, while monomorphic T/NK-cell PTLD and monomorphic PTLD resembling plasma cells neoplasms are usually EBV negative.

Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders

Typically, in iatrogenic immunodeficiency-associated lymphoproliferative disorders, the immunophenotype of the lymphoma resembles that of the lymphoma arising in an immunocompetent individual. In the setting of patients treated with immunomodulatory agents (anti-TNFα and others), unusual immunophenotypic features have been noted in a subset (Hasserjian et al. 2009). There is an association with EBV in methotrexate-

associated lymphoproliferative disorders (with EBV positivity in about half the cases), and there may be an association between EBV and B-cell derived lymphomas/lymphoproliferative disorders arising in patients treated with immunomodulatory agents.

Molecular Features

By molecular studies, clonal immunoglobulin heavy chain gene rearrangements or clonal T-cell receptor (TCR) gene rearrangements are expected to be seen in monomorphic B-cell PTLD and monomorphic T-cell PTLD, respectively. Polymorphic PTLD is expected to demonstrate clonally rearranged immunoglobulin genes, although with less predominant clones than in monomorphic B-cell PTLD. Nondestructive lesions and Hodgkin lymphoma type PTLD are likely to show polyclonal populations by gene rearrangement studies. Results of molecular studies need to be interpreted with caution and in the context of morphologic and immunophenotypic findings. For example, T cell clonality is not synonymous with T-cell malignancy and a reactive clonal T cell response can be seen in B-cell PTLD. A negative immunoglobulin heavy chain gene rearrangement study does not exclude monomorphic B-cell PTLD as there is a significant false-negative rate for this assay. Very small monoclonal B-cell populations can be seen in nondestructive PTLDs.

The genetic features of both PTLD and other iatrogenic immunodeficiency-associated lymphoproliferative disorders have yet to be fully elucidated. Genetic changes reported in PTLD include alterations in *MYC* and *BCL6*, *TP53* mutations, DNA hypermethylations, aberrant somatic hypermutation, and microsatellite instability (Courville et al. 2016; Morscio et al. 2013). As in Burkitt lymphoma arising in immunocompetent individuals, monomorphic B-cell PTLD with Burkitt lymphoma morphology are characterized by translocations involving *MYC* and, most commonly, the immunoglobulin heavy chain gene.

Differential Diagnosis

Posttransplant Lymphoproliferative Disorders (PTLD)

The differential diagnosis for PTLD depends on the morphology and immunophenotype, that is, on the subclassification. For nondestructive PTLD, the main differential is with lymphoid proliferations with other known explanations or other nonspecific chronic inflammatory processes, such as chronic tonsillitis. Distinction between monomorphic B cell PTLD and polymorphic PTLD is not well defined and can be difficult, and the main distinction lies in the number of large, transformed cells. Differential diagnoses for monomorphic B, T, and plasma cell PTLD include those that would be considered for the lymphoproliferative disorders they resemble arising in the immunocompetent host. Classical Hodgkin lymphoma PTLD has the additional differential of polymorphic PTLD with Reed-Sternberg/Hodgkin-like cells lacking the diagnostic immunophenotype of classic Hodgkin lymphoma.

Other Iatrogenic Immunodeficiency-Associated Lymphoproliferative Disorders

In a subset of cases, the differential lies between a lymphoproliferative disorder and a frank lymphoma. For most cases in which the diagnosis of lymphoma is straightforward, the question remains as to whether the lymphoma is directly related to the iatrogenic immunosuppression, the underlying autoimmune disorder, both, or neither (that is, the lymphoma arose by an unrelated mechanism). The distinction between these possibilities cannot be made on a case-by-case basis.

References and Further Reading

Bagg, A., & Dunphy, C. H. (2013). Immunosuppressive and immunomodulatory therapy-associated

lymphoproliferative disorders. *Seminars in Diagnostic Pathology, 30*(2), 102–112. https://doi.org/10.1053/j.semdp.2012.08.005.

Courville, E. L., Yohe, S., Chou, D., Nardi, V., Lazaryan, A., Thakral, B., et al. (2016). EBV-negative monomorphic B-cell post-transplant lymphoproliferative disorders are pathologically distinct from EBV-positive cases and frequently contain TP53 mutations. *Modern Pathology, 29*(10), 1200–1211. https://doi.org/10.1038/modpathol.2016.130.

Deepak, P., Sifuentes, H., Sherid, M., Stobaugh, D., Sadozai, Y., & Ehrenpreis, E. D. (2013). T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-alpha) inhibitors: Results of the REFURBISH study. *The American Journal of Gastroenterology, 108*(1), 99–105. https://doi.org/10.1038/ajg.2012.334.

Dojcinov, S. D., Venkataraman, G., Raffeld, M., Pittaluga, S., & Jaffe, E. S. (2010). EBV positive mucocutaneous ulcer – a study of 26 cases associated with various sources of immunosuppression. *The American Journal of Surgical Pathology, 34*(3), 405–417. https://doi.org/10.1097/PAS.0b013e3181cf8622.

Gaulard, P., Swerdlow, S. H., Harris, N. L., Sundstrom, C., & Jaffe, E. S. (2017). Other iatrogenic immunodeficiency-associated lymphoproliferative disorders. In S. H. Swerdlow, E. Campo, N. L. Harris, E. S. Jaffe, S. A. Pileri, H. Stein, & J. Thiele (Eds.), *WHO classification of tumours of haematopoietic and lymphoid tissues* (Revised 4th ed., pp. 462–464). Lyon: IARC.

Gibson, S. E., Swerdlow, S. H., Craig, F. E., Surti, U., Cook, J. R., Nalesnik, M. A., … & Bacon, C. M. (2011). EBV-positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the posttransplant setting: A distinct type of posttransplant lymphoproliferative disorder? *The American Journal of Surgical Pathology, 35*(6), 807–815. https://doi.org/10.1097/PAS.0b013e3182190999.

Hasserjian, R. P., Chen, S., Perkins, S. L., de Leval, L., Kinney, M. C., Barry, T. S., … & O'Malley, D. P. (2009). Immunomodulator agent-related lymphoproliferative disorders. *Modern Pathology, 22*(12), 1532–1540. https://doi.org/10.1038/modpathol.2009.131.

Luskin, M. R., Heil, D. S., Tan, K. S., Choi, S., Stadtmauer, E. A., Schuster, S. J., … & Reshef, R. (2015). The impact of EBV status on characteristics and outcomes of posttransplantation lymphoproliferative disorder. *American Journal of Transplantation, 15*(10), 2665–2673. https://doi.org/10.1111/ajt.13324.

Morscio, J., Dierickx, D., Ferreiro, J. F., Herreman, A., Van Loo, P., Bittoun, E., … & Tousseyn, T. (2013). Gene expression profiling reveals clear differences between EBV-positive and EBV-negative posttransplant lymphoproliferative disorders. *American Journal of Transplantation, 13*(5), 1305–1316. https://doi.org/10.1111/ajt.12196.

Swerdlow, S. H., Webber, S. A., Chadburn, A., & Ferry, J. A. (2017). Post-transplant lymphoproliferative disorders. In S. H. Swerdlow, E. Campo, N. L. Harris, E. S. Jaffe, S. A. Pileri, H. Stein, & J. Thiele (Eds.), *WHO classification of tumours of haematopoietic and lymphoid tissues* (Revised 4th ed., pp. 453–462). Lyon: IARC.

Tsao, L., & Hsi, E. D. (2007). The clinicopathologic spectrum of posttransplantation lymphoproliferative disorders. *Archives of Pathology & Laboratory Medicine, 131*(8), 1209–1218. https://doi.org/10.1043/1543-2165(2007)131[1209:TCSOPL]2.0.CO;2.