11 Immunodeficiency-Associated Lymphoproliferative Disorders Other Than PTLD (in Primary Immune Deficiency, HIV, and Iatrogenic Conditions)

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1. What are the major subtypes of primary immune deficiency (PID)?

- *Common variable immune deficiency (CVID)* (see also Chap. 29).
  - The most common primary immune deficiency, with an incidence of 1 in 10,000 to 50,000.
  - It is not a single entity but rather a group of diseases with reduced serum levels of one or more of IgG, IgM, and IgA.
  - The disease first occurs in late childhood or more typically young adults and affects male and female equally.
  - The clinical presentation is broadly heterogeneous depending on the severity of the antibody deficiencies. The most common clinical manifestation is recurrent bacterial infection, which most commonly affects sinopulmonary and gastrointestinal systems. Other clinical presentation may include immune disorders, granulomatous disease, and lymphoproliferative disorders. Most cases are sporadic while only 10–25% have familiar history.

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  - The diagnosis is established by clinical presentation, laboratory evidence of reduction in one or several immunoglobulin isotypes with or without reduced B cells, and exclusion of the other primary immune disorders.
  - The etiology of the majority of cases (>90%) is unknown. Mutations in *ICOS*, *TACI*, *MSH5*, and *BAFFR* were found in a small number of CVID patients, which were thought to contribute to the diseases [1, 2].
- *Severe combined immunodeficiency (SCID)*
  - Represents a heterogeneous group of severe immune deficiency, primarily affecting cell-mediated immunity. All SCID patients have defect of T-cell immunity, and a fraction have additional defect in B-cell immunity.
  - Two major forms of SCID have been described: typical SCID and leaky SCID.
  - Typical SCID has low or absent T cells with marked compromise of both number and function of T cells.
  - Patients with typical SCID develop various symptoms from infancy including bacterial and viral respiratory infection, diarrhea and failure to thrive, lymphadenopathy, and underdeveloped thymus.
  - Patients with leaky SCID may show delayed onset of symptoms that include immune dysregulation, skin rash, granulomatous inflammation, lymphadenopathy, and hepatosplenomegaly.
  - Germline gene mutations involving lymphoid maturation and differentiation, T-cell receptor signaling, and cytokine signaling can be detected in SCID patients.
  - Diagnosis of SCID can be established by characteristic clinical presentation during infancy, numerical and/or functional T-cell defect, gene mutations, and *EBV*-associated lymphoproliferative disorders. Nearly 100% SCID patients develop *EBV*-associated lymphoproliferative disorders [3, 4].
- *Hyper IgM syndrome* (HIgM, also known as CD40 or CD40 ligand deficiency)
  - A group of rare disorders characterized by deficiency of either CD40 ligand on T cells (type 1 HIgM) or CD40 on T cells (type 3 HIgM).
  - All types of inherence including autosomal dominant, autosomal recessive, and X-linked may be seen in HIgM.
  - Impaired CD40 or CD40 ligand on T cells results in abnormal interaction of T cells with B cells and consequently impairs class switching from IgM to IgG and IgA in B cells.
  - Serum IgG and IgA levels are consistently low while IgM level is normal to high.
  - The disease onset occurs before 2 years of age and affected children usually present with neutropenia, thrombocytopenia, and recurrent opportunistic infection in respiratory and gastrointestinal tracts.
  - Patients have increased risk of *EBV*-associated large B-cell lymphoma and Hodgkin lymphoma. Some patients may develop large granular lymphocytic leukemia [5].
- *Ataxia-telangiectasia (AT)*
  - An autosomal recessive disorder primarily affecting young children. The incidence in Western countries is approximately 1 in 100,000 live births.
  - The disease is characterized by primary immunodeficiency and neurological defect with cerebellar degeneration.
  - Symptoms usually start to occur at around 1 to 4 years of age with progressive cerebellar ataxia, oculocutaneous telangiectasia, and dysarthria. Patients are highly susceptible to recurrent sinopulmonary infection and increased sensitivity of ionizing radiation.
  - Up to 20% of AT patients may develop malignancies, which are nearly all lymphoid leukemia and lymphoma.
  - AT is caused by mutations in *ATM* gene, which is a member of phosphotidyl inositol kinase (PI3K) family that functions as sensor for DNA repair.
  - Diagnosis of AT is based on family history, highly characteristic clinical presentation, and confirmation of biallelic mutations in *ATM* gene [6, 7].
- *Wiskott-Aldrich Syndrome (WAS)*
  - An X-linked primary immune disorder affecting male children. The incidence in Western countries is approximately 1 in 250,000 live male births. The onset of symptoms can be at variable ages, but thrombocytopenia is present at birth.
  - The disease is caused by mutations in *WAS* gene located at the short arm of the X chromosome, which carries important functions of actin polymerization and T-cell receptor signaling. Female carriers are asymptomatic.
  - Clinical manifestation includes frequent, recurrent infection, bleeding with thrombocytopenia and microthrombosis, severe eczema, and immune deficiency. The disease usually starts with skin rash, petechiae, and ecchymoses and progresses to recurrent bacterial, viral, and/or fungal infection, autoimmune disorders, internal bleeding, and thrombosis.
  - Hematologic malignancies develop in approximately 10–20% patients and may be lymphoid or myeloid neoplasms.
  - Diagnosis of WAS is based on family history, clinical presentation, and confirmation of either abnormal WAS protein expression or *WAS* gene mutations [8, 9].
- *X-linked lymphoproliferative disease (XLP)*
  - Also known as Duncan syndrome, XLP is an X-linked genetic disorder affecting male children. The incidence is approximately 1 to 2 in 1,000,000 male infants.

  - The disease is caused by a germline mutation at *SH2D1A* gene, which encodes a protein with key role in T-cell and NK-cell signaling. Cellular immunity with suppressed NK-cell function and humoral immunity with acquired hypogammaglobulinemia are affected.
  - These patients develop *EBV*-associated lymphoproliferative disorders due to impaired T-cell response to *EBV*. Symptoms of *EBV* infection appear sometime during childhood or adolescence. The gastrointestinal tract is the most common site of infection, but other extranodal and nodal site can also be affected. Most patients succumb to hepatic failure and/or hemophagocytic syndrome.
  - The disease spectrum includes infectious mononucleosis-like diseases, fatal *EBV*-associated infection, and high-grade B-cell lymphomas [10, 11].
- *Autoimmune lymphoproliferative syndrome (ALPS)*
  - Also known as Canale-Smith syndrome, ALPS is an acquired genetic disorder mainly affecting lymphoid system. The disease onset occurs at a medium age of 3 years, and symptoms include unexplained lymphadenopathy and splenomegaly and multilineage cytopenia.
  - The most common presentation of ALPS is asymptomatic lymphadenopathy and/or splenomegaly in children, many patients have an incidental finding of enlarged palpable peripheral lymph nodes. A blood work may also identify multilineage cytopenia. Symptoms related with cytopenia may include fatigue, pallor, easy bruising, and infection.
  - Patients may also present with autoimmune symptoms and autoantibodies such a rheumatoid factor, ANA, as well as a positive Coombs test.
  - The disease is caused by inherited or acquired mutations in a group of genes involving programmed cell death (apoptosis), with vast majority occurring in *FAS* genes. Other genes that may be involved include *FASLG*, *CASP10*, and *CASP8*.
  - The diagnosis is established based on clinical presentation of unexplained lymphadenopathy and/or splenomegaly for greater than 6 months, increased CD4 and CD8 double-negative T cells in blood, and germline mutations of one of the aforementioned genes involving apoptotic pathways [12–14].

2. How is autoimmune lymphoproliferative syndrome (ALPS) different from other PIDs? What are other entities that may mimic ALPS?

- ALPS may be suspected when a child or young adult presents with unexplained lymphadenopathy and/or splenomegaly and cytopenia with or without symptoms. Many of the ALPS patients are initially asymptomatic in contrast to the other types of PIDs that recurrent infection is usually the initial presentation.
- The disease is characterized by the increase of CD4 and CD8 double-negative T lymphocytes in blood, bone marrow, and the lymphoid organs, which can be detected by flow cytometry and immunohistochemistry.
- ALPS can occasionally affect older adults, which are usually caused by acquisition of somatic mutations in later age. These patients may be difficult to recognize due to atypical clinical presentation and broader differential diagnosis.
- Other entities that may overlap with ALPS include Evan's syndrome, hemophagocytic lymphohistiocytosis, Castleman disease, and other benign and atypical lymphoproliferative disorders.
- The lymph node morphology from ALPS has its characteristic morphologic and phenotypic features, which is discussed in the next section [15, 16].
- An international workshop in 2010 proposed detailed diagnostic guidelines and algorithm for ALPS. A set of diagnostic criteria including major and minor criteria was listed. A definitive diagnosis requires the presence of two required criteria and one primary accessory criterion. A probable diagnosis requires the presence of two required criteria and one secondary accessory criterion [17]:
  - *Required*
    - Chronic (>6 months), nonmalignant, noninfectious lymphadenopathy or splenomegaly or both
    - Elevated CD3 + TCRab+ and CD4-CD8- double-negative T cells (≥1.5% of total lymphocytes or 2.5% of CD3+ lymphocytes) in the setting of normal or elevated lymphocyte counts
  - *Accessory*

    Primary
    - Defective lymphocyte apoptosis (in two separate assays)
    - Somatic or germline pathogenic mutation in *FAS, FASLG*, or *CASP10*

    Secondary
    - Elevated plasma sFASL levels (>200 pg/mL) or elevated serum or plasma vitamin B12 level (>1500 ng/L) or elevated plasma interleukin 18 level (>500 pg/mL)
    - Typical immunohistological findings as reviewed by an experienced hematopathologist
    - Autoimmune cytopenia (hemolytic anemia, thrombocytopenia, or neutropenia) and elevated immunoglobulin G level (polyclonal hypergammaglobulinemia)
    - Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity

3. What are the types of benign lymphoid proliferation associated with the PID? What are the morphologic and phenotypic features?

- *Follicular and paracortical hyperplasia*
  - This is commonly seen in CVID and less frequently in other types of PIDs.
  - Morphologically, the lymph nodes are indistinguishable from lymphoid hyperplasia in immune-competent individuals. The lymph nodes usually show follicular hyperplasia with highly activated germinal centers. Numerous tingible body macrophages may be present in germinal centers. The paracortex is usually expanded and contains a variable number of immunoblasts. Reed-Sternberg-like cells may be present.
  - *EBV*-infected lymphocytes are invariably present in the paracortical areas and can be demonstrated by EBER in situ hybridization [18].
- *Nodular lymphoid hyperplasia of gastrointestinal tract*
  - Nodular lymphoid infiltrate of the GI tract is commonly seen in CVID.
  - The lymphoid nodules are present in the lamina propria and may extend deep into the GI wall. Reactive-appearing lymphoid follicles may or may not present. The lymphoid nodules contain a mixture of B cells and T cells.
  - *EBV*-positive cells are usually present.
  - Clonal B-cell gene rearrangement may be detected in some patients.
  - The clinical course is usually self-limited, and the detection of B-cell clonality does not indicate disease progression or lymphoma [19, 20].
- *Lymphoproliferative disorders associated with ALPS*
  - The lymph nodes show prominent follicular hyperplasia with many enlarged, often irregularly shaped follicles. Large hyperplastic germinal centers contain many increased centroblasts and tingible body macrophages. Progressive transformation of germinal center (PTGC) is frequently seen.
  - The paracortex is expanded and contains increased CD4 and CD8 double-negative T cells admixed with phenotypically normal T cells, polyclonal plasma cells, and immunoblasts. These double-negative T cells may be difficult to visualize by CD4 and CD8 immunohistochemistry due to the mixture of normal helper and suppressor T cells.
  - Flow cytometry is more accurate to detect and enumerate the percentage of the double-negative T cells. The double-negative T cells range from 51% to 78% of alpha-beta T cells according to one study [15].
  - These lesions are usually not associated with *EBV*.
  - The spleen is usually moderately to massively enlarged, which shows expansion of both white pulp and red pulp. The white pulp shows features of follicular hyperplasia with expansion of marginal zone. The red pulp shows similar features to the paracortex in the affected lymph nodes containing numerous lymphocytes, immunoblasts, and polyclonal plasma cells.
  - The peripheral blood shows variable degree of lymphocytosis. The lymphocytes are usually small mature in morphology. The double-negative T cells are invariably increased in peripheral blood (2- to 67-fold over normal value) and can be easily detected by flow cytometry. Peripheral B lymphocytes may show coexpression of CD5, but these B cells are usually polyclonal [15].
- *Lymphoid hyperplasia associated with HIgM*
  - The most characteristic feature of the lymph node morphology is hyperplastic lymphoid follicles with absent germinal centers. IgM-positive plasma cells may be increased in the paracortical and/or medullary areas.
  - These lesions are usually not associated with *EBV*.
  - In extranodal sites, such as the intestinal tract and liver, IgM-positive plasma cells may accumulate.
  - IgG-positive B cells in blood are reduced or absent and can be demonstrated by flow cytometry analysis of blood B cells [5].
- *Fatal infectious mononucleosis*
  - This is primarily seen in SCID and XLP.
  - The lymph nodes are hyperplastic containing markedly expanded T zones. There are variable numbers of immunoblasts and Hodgkin-like cells, which are forming sheets in some cases.
  - *EBV*-positive cells are usually abundant.
  - The lymphadenopathy may be extensive and fulminant in progression. Some patients have associated uncontrolled hemophagocytic syndrome which results in severe progressive pancytopenia.
  - Although this condition is benign, many patients die from fulminant *EBV* infection and bone marrow failure [21].

4. What are the types of malignant lymphoproliferative conditions associated with the PID? What are the morphologic and phenotypic features?

- *Diffuse large B-cell lymphoma (DLBCL)*
  - DLBCL is the most common lymphoma in PIDs and occurs in nearly all types of PIDs (CVID, HIgM, WAS, AT, XLP, ALPS).

  - Morphologically, DLBCL in PIDs is similar to those of the immune-competent patients. Both centroblast and immunoblast morphologies can be present.
  - *EBV* can be demonstrated in many, but not all, cases.
  - There are insufficient data on histogenesis (germinal center vs. activated B-cell types) or MYC/BCL2 expression pattern in these lymphomas [22].
- *Hodgkin lymphoma*
  - Classic Hodgkin lymphoma (CHL) can arise from WAS and AT, and nodular lymphocyte-predominant Hodgkin lymphoma may arise from ALPS.
  - Classic Hodgkin lymphoma shows similar morphology to those from immune-competent population. The most frequent subtype is mixed cellularity followed by nodular sclerosis.
  - Most of these lesions are *EBV* positive.
  - Hodgkin-like lesions that phenotypically do not fulfill diagnostic criteria of CHL can also occur.
  - Nodular lymphocyte-predominant Hodgkin lymphoma in ALPS has similar morphologic and phenotypic features to those from immune-competent patients and is usually *EBV* negative [22, 23].
- *Lymphomatoid* granulomatosis
  - Patients with WAS have an increased incidence of lymphomatoid granulomatosis.
  - The primary sites of involvement are lung, skin, brain, and kidney.
  - The morphology and phenotype are similar to those arising from immune-competent population or other immunodeficient patients.
  - There are variable numbers of large B cells in an inflammatory background with reactive T lymphocytes, histiocytes, and granulocytes. The infiltrate is angiocentric and angiodestructive with often large areas of necrosis. The large B cells express common B-cell antigens, consistently express *EBV*, and variably express CD30. The background T lymphocytes are predominantly CD4+ with normal T-cell phenotype.
  - Clonal immunoglobulin gene rearrangement can be detected in higher-grade lesions (grades 2 and 3) [24, 25].
- *Burkitt lymphoma*
  - Burkitt lymphoma can be occasionally seen in AT, XLD, and ALPS.
  - The lymphoma shows similar morphology and phenotype to those of sporadic type and HIV-associated type.
  - Expression of *EBV* is variable from case to case.
  - Similar to that of the sporadic and HIV-associated types, confirmation of diagnosis requires evidence of rearrangement of *C-MYC* with either immunoglobulin heavy or light chains and absence of *BCL2* and *BCL6* translocations [15, 22].
- *T-cell neoplasms*
  - Peripheral T-cell lymphoma NOS, T-prolymphocytic leukemia, and T-lymphoblastic leukemia/lymphoma are increased in AT.
  - T-cell large granular lymphocytic leukemia is increased in HIgM.
  - Peripheral T-cell lymphoma NOS has been reported in ALPS.
  - These T-cell neoplasms show similar morphology and phenotype to those arising from immune-competent individuals. *EBV* expression is variable in these cases.
  - Diagnosis is based on the same criteria to those of the T-cell neoplasms in the general populations [26].

5. What are the diagnostic criteria for lymphoproliferative disorders associated with PIDs? What is the minimal and optimal ancillary work-up for diagnosis and subclassification of these conditions?

- Each entity should be worked up similarly to its corresponding disease in immune-competent individuals. The diagnostic criteria are essentially identical.
- However, EBER should be performed in all cases, and *EBV* serology is recommended in all patients.
- A thorough clinical history should be obtained for any overt or underlying immune deficiency. Severe PIDs such as SCID, WA, and AT arise at an early age, and usually the diagnoses have already been established at the time when the LPDs arise. Other more indolent PIDs, such as CVID and ALPS, primary etiologies may be inconspicuous at the time of LPDs. Careful assessment of clinical presentation, proper interaction with clinicians, and thorough assessment of biopsied specimens are essential for elucidating the underlying causes.
- In clinical practice, diagnosis of CVID is usually delayed due to its broad heterogeneity of the disease presentation. Patients presented with recurrent mild infection are often treated symptomatically without further work-up of underlying etiology.
- The presence of hypogammaglobulinemia of two or more isotypes points toward CVID. Demonstration of impaired functional antibody response confirms the diagnosis.
- Patients with ALPS usually present with asymptomatic enlargement of lymph nodes and/or the spleen, many of

which are incidental findings. These patients are often accompanied by unexplained multilineage cytopenia. The current diagnostic criteria do not require biopsy of lymph node. However, lymph node biopsy is necessary if lymphoma is suspected. The characteristic lymph node morphology and increase of CD4 and CD8 double-negative T cells in the expanded paracortex help to confirm the diagnosis of ALPS.

6. What is an adequate specimen for the diagnosis of lymphoproliferative disorders associated with PID? When is it appropriate to seek external consultation?

- Diagnosis of LPD in PIDs universally requires tissue biopsy. Excisional biopsy of an enlarged lymph node is the preferred choice, although in certain cases needle core biopsy may be sufficient to reach a diagnosis if sampled appropriately.
- Clinical tests include *EBV* serology, and quantitative *EBV* DNA tests are necessary in addition to the standard work-up on biopsied tissue samples.
- In certain conditions, such as CVID and ALPS, additional tests such as serum gamma globulin quantitation and flow cytometry analysis of blood and tissue are readily available on site or at major reference laboratories and are very useful for initial screening to rule out/rule in these diseases.
- Genetic testing for constitutional or acquired mutations at genomic level is only offered by several specialty pediatric genomic laboratories in the country. The genomic analysis on the constitutional mutations can be performed on blood samples, while for acquired mutations, testing additional tissue sample may be necessary.

7. What are the benign lymphoproliferative disorders associated with human immunodeficiency virus (HIV) infection?

- *HIV-related benign lymphadenopathy (HIV-BNL)*
  - Persistent generalized lymphadenopathy is one of the most common findings in HIV patients. The lymphadenopathy is often accompanied by systemic symptoms such as fever, fatigue, night sweat, and weight loss. The frequency of HIV-BNL has considerably declined as the disease is now effectively controlled by combination antiretroviral therapy (cART).
  - The lymphadenopathy consists of progressive conditions spanning through a series of four morphological patterns (stages): florid follicular hyperplasia, mixed follicular hyperplasia and follicular involution, follicular involution, and lymphocyte depletion. These stages advance in synergy with the decreasing CD4 count, degree of viremia, and the HIV disease progression in the untreated HIV+ individuals.
  - Nearly all biopsied lymph nodes from living individuals have the morphology of florid follicular hyperplasia and mixed follicular hyperplasia. The follicular involution and lymphocyte depletion are only seen in terminal stages of HIV infection that are exceedingly rare in the post-cART era [27–29].
- *Benign lymphoepithelial cyst (BLC)*
  - These lesions affect salivary glands, most commonly parotid gland, and accounts for 25% of salivary glands enlargements in HIV patients. Besides HIV patients, the condition often occurs in patients with autoimmune disorders such as Sjögren syndrome and other autoimmune sialadenitis. Bilateral salivary glands are usually affected, which often lead to lymphadenopathy in the regional lymph nodes.
  - The lesions are composed of epithelium-lined cysts in a background of lymphoid follicular hyperplasia. The prolonged lymphocytic proliferation results in epithelial metaplasia and duct calcification that in turn results in duct obstruction and cyst formation.
  - Histologically, there are multiple nodules consisting of hyperplastic lymphoid tissue that are surrounded by multiple cysts. The lymphoid tissue shows features of HIV lymphadenopathy with large hyperplastic follicles and highly proliferative germinal centers. The cysts are lined by columnar, cuboidal, or squamous epithelium and are filled with clear or pink amorphous material.
  - Surgical excision is typically performed on these patients for symptomatic relief and to rule out lymphoma [30, 31].
- *Multicentric Castleman disease (MCD)*
  - HIV patients have an increased risk of developing MCD.
  - Evidence of HHV8 infection can be found in nearly all MCD in these patients; otherwise, the lesions are similar in morphology and phenotype to MCD in immune-competent population.
  - HHV8+ Kaposi sarcoma is often in concurrence with MCD. In fact, most patients would have developed Kaposi sarcoma prior to the Castleman disease.
  - Most MCD cases are of the plasma cell variant or mixed variant types. The histological features of MCD

are similar to those from non-HIV patients; however, a more prominent follicular hyperplasia and hyalinization as well as greater numbers of interfollicular plasma cells may be seen.
  - The risk of developing lymphoma in HIV patients who have MCD increases 15-fold as compared to those who have no MCD [32, 33].

8. What are the morphologic stages of HIV-related benign lymphadenopathy?

- *Florid follicular hyperplasia (FFH)*
  - Florid follicular hyperplasia is the first stage of HIV-BNL and is the most common lymph node finding in HIV patients.
  - The lymph nodes are usually moderately enlarged and are characterized by numerous hyperplastic lymphoid follicles with geographical shapes. Bizarre-shaped follicles such as "dumbbell-like" and other irregularly shaped follicles are commonly seen. The germinal centers are massively enlarged and are highly proliferative with numerous, often sheets, of centroblasts and abundant tingible body macrophages. Mantle zones are attenuated or absent, resulting in "naked" germinal centers.
  - Accompanying the hyperplastic follicles, clusters of monocytoid B cells are nearly always present. These clusters may be located next (abut) to the follicles, next to sinusoids, or isolated in the T zones.
  - Follicle lysis, once considered as a specific feature of HIV lymphadenopathy and later was found in other hyperplastic lymph nodes, consists of "bleeding" inside the follicles and invasion of the lymphoid follicles by small lymphocytes with effacement of the mantle zones [34–36].
- *Mixed follicular hyperplasia and follicular involution (MFHFI)*
  - When the disease progresses, some of the hyperplastic follicles regress with involuted germinal centers. The interfollicular areas are expanded more than what is seen in FFH.
  - The involuted follicles at this phase consist of less than 50% of all follicles [34–36].
- *Follicular involution (FI)*
  - At this phase, most follicles are regressed and small in size. Remnants of germinal centers are composed largely of hyalinized follicular dendritic cells with prominent hyalinized blood vessels. The interfollicular areas are further expanded between the small regressed follicles, but the cellular components are reduced.
  - Histiocytes and plasma cells preside over lymphocytes.
  - Follicular dendritic cells are markedly decreased [34–36].
- *Lymphocyte depletion (LD)*
  - This morphology represents the late stage of HIV lymphadenopathy and is usually not observed in living individuals. Much of the data were collected from autopsy cases.
  - Lymph nodes from this type are usually small in size and show absence of germinal centers and scant lymphoid elements in interfollicular areas. The lymph node parenchyma is composed of connective tissue stromal cells, medullary cords, and sinusoids.
  - Follicular dendritic cells (FDC) are virtually absent.
  - CD4-positive T cells are markedly decreased to absent, reflecting progression to the late stage of the disease.
  - The progression of morphological features from the initial follicular hyperplasia to the late stages of follicular involution and lymphocytic depletion correlates the destruction of FDC meshwork leading to loss of the normal lymphoid follicles. During clinical latency of the disease, the FDC meshwork serves as a barrier to keep the viral particles contained in the lymphoid tissue, which correlates with low viral counts in the blood. As the disease progresses and FDC meshwork degenerates, the capacity to containing the virus decreases and the blood viral count consequently rises [34–36].

9. What is the differential diagnosis of HIV-related benign lymphadenopathy?

- When typical HIV-BNL morphology is seen in a lymph node biopsy, a potential HIV infection should be suspected and further clinical investigation such as HIV serology and viral DNA test should be suggested.
- However, none of the morphologic features in HIV-BNL are unique to HIV infection, and many other diseases may share similar morphology.
- Nonspecific follicular hyperplasia is a very common finding in lymph node biopsy that may or may not have a known etiology at the time of biopsy. Follicular hyperplasia is a response of lymph node to regional antigen stimulation that can be caused by infection, autoimmune disorders, hypersensitivity, among others. When assessing such cases, a thorough review of clinical history should be performed in order to elucidate possible causes [37].
- Acute *EBV* infection (infectious mononucleosis) can occasionally mimic early stages of HIV-related lymph-

adenopathy when follicular hyperplasia is prominent. However, acute *EBV* infection typically has variously expanded paracortical zone with increased immunoblasts.
- Atypical mycobacterial infection may show regressed follicles and lymphocyte-depleted morphology with increased background fibrosis that leads to a morphological picture similar to the late stages of HIV-BL of follicular involution and lymphocytic depletion.
- Hyaline vascular Castleman disease has regressed, hyalineized germinal centers that mimic follicular involution in the late stage of HIV lymphadenopathy. However, increased vasculature is usually absent in HIV cases.
- Classic Hodgkin lymphoma, especially lymphocyte-depleted type, may resemble lymphocyte-depleted stage of HIV lymphadenopathy. Careful morphologic assessment and review of relevant immunohistochemical stains can readily differentiate between them. One should be aware that a lymphoma like CHL may develop in a lymph node previously affected by the HIV-related benign lymphadenopathy.

10. What are the common types of lymphomas associated with HIV?

- *Diffuse large B-cell lymphoma, NOS*
  - DLBCL in HIV patients is more likely to present with high-stage disease and extranodal site involvement. Some unusual sites such as the anorectal, orbit, and heart are more likely seen at the presentation in HIV DLBCL, although the CNS and gastrointestinal tract are the most common extranodal sites of involvement.
  - The histopathologic features of DLBCL in HIV patients are similar to those of the DLBCL in immune-competent population. Both centroblast and immunoblast types may be present although immunoblast type is more common in HIV DLBCL.
  - Phenotypically, germinal center-type DLBCL (GC-DLBCL) is about twice as common as activated B-cell type DLBCL (ABC-DLBCL). Patients with GC-DLBCL usually have moderate CD4 counts in mildly immunodeficient state, while those with ABC-DLBCL are more likely to have low CD4 counts with more severe immunodeficient state.
  - Similar to DLBCL in the general population, ABC-DLBCL has unfavorable outcomes as compared to GC-DLBCL [38].
- *Primary central nervous system lymphomas (PCNSL)*
  - PCNSL is the most common extranodal lymphoma in HIV patients, comprising approximately 20% of all AIDS-related lymphomas.
  - Most patients who develop PCNSL are young homosexual male who have low CD4 counts. These patients often have concurrent other AIDS-defining illnesses with various degrees of systemic symptoms, which may mask the neurologic symptoms caused by the lymphoma. Surgical biopsy is invariably necessary to differentiate between lymphoma and infection.
  - Histologically, the lymphoma may diffusely replace brain tissue or focally infiltrate perivascular space. When present at only perivascular location, the diagnosis may be difficult due to small sample size, necrosis, and sparsity of involved blood vessels. The diagnosis can be confirmed by the presence of large B cells surrounding and infiltrating the blood vessel walls.
  - Nearly all HIV-related CNS lymphomas are *EBV* positive [39].
- *HIV-related Burkitt lymphoma (HIV-BL)*
  - HIV-BL accounts for 15% of HIV-associated lymphoma and involves lymph node as well as extranodal sites.
  - HIV-BL shows the similar histologic features to the sporadic type with proliferation of monomorphic, intermediate-sized lymphoma cells. In some cases, the lymphoma cells may show plasmablastic morphology. The rapid proliferation of the tumor cells results in numerous mitosis and increased tingible body macrophages exhibiting the characteristic histomorphologic "starry-sky" pattern.
  - Similar to sporadic BL, the tumor cells express B-cell markers and germinal center markers CD10 and BCL6 and are consistently negative for BCL2.
  - Translocations of *MYC* are the molecular hallmark of Burkitt lymphoma, with t(8;14) being the most common.
  - Approximately 50% of the cases are *EBV* positive [40, 41].
- *Plasmablastic lymphoma*
  - Plasmablastic lymphoma occurs primarily in HIV patients but can also occur in other immunosuppressive conditions such as posttransplantation, iatrogenic medication, and aging.
  - The lymphoma nearly always arises from extranodal sites, most commonly from the oral cavity followed by the gastrointestinal tract, skin, bone, nasal cavity, CNS, liver, and lung.
  - The tumor cells are large in size with immature morphology and varying degrees of plasmacytic differen-

tiation with prominent nucleoli and basophilic cytoplasm. Mitotic figures are common and tingible body macrophages may be present.
  - Plasmablastic lymphoma expresses CD138, CD38, and MUM1/IRF4 and is negative or weakly positive for CD20, PAX5, and CD45. CD56 is typically negative, and if positive, a differential diagnosis of plasma cell neoplasm should be considered. The proliferation index is usually greater than 90%.
  - The vast majority of plasmablastic lymphomas are positive for *EBV*.
  - Approximately 50% cases harbor *MYC* translocation [42].
- *Primary effusion lymphoma (PEL)*
  - PEL is a *human herpesvirus* 8 (HHV8)-driven lymphoma seen almost exclusively in HIV patients and to a lesser extent in individuals in other types of immunodeficiencies.
  - The classic cases develop in body cavities with no solid tumor component.
  - The lymphoma cells are very large in size but show highly variable morphology ranging from immunoblastic, plasmablastic to large bizarre anaplastic morphology.
  - The lymphoma expresses a limited set of antigens including CD138 and MUM1/IRF4 but is negative in nearly all pan-B-cell and pan-T-cell antigens.
  - All cases are positive for *EBV* in addition to HHV-8.
  - The prognosis is dismal with an overall survival of <6 months.
  - A solid variant (extracavitary) with similar morphological and immunophenotypic features to cavitary PEL was also described. These lesions are solid masses involving extranodal sites other than body cavities. Patients with extracavitary lesions have relatively higher CD4 counts and have slightly better prognosis than the cavitary type [43, 44].
- *Classic Hodgkin lymphoma (CHL)*
  - CHL is not considered an AIDS-defining entity. The incidence of CHL in HIV patients is not increased as compared to the incidence in the general population.
  - However, CHL in HIV individuals may often have atypical clinical features with more aggressive clinical behavior and unfavorable subtypes. Although the nodular sclerosis type is still the most common subtype, the frequency of mixed cellularity type and lymphocyte-depleted type are higher than those from immune-competent populations.
  - cART treatment also alters the frequencies of subtypes. In the pre-cART era, most cases of HIV CHL were mixed cellularity subtype, whereas after the introduction of cART therapy, a paradoxical increase in the incidence of nodular sclerosis subtype is observed.
  - Patients of mixed cellularity subtype usually present with an advanced disease and bone marrow involvement, whereas patients of nodular sclerosis subtype are more likely to present with a limited disease confined to the mediastinum.
  - Lymphocyte-depleted CHL was considered more frequent in HIV patients, and many of the cases are *EBV* positive. However, the "depletion" of the background lymphocytes is often a result of reduced CD4 T cells in the late stage of HIV infection, which may provide a "lymphocyte-depleted" appearance.
  - The Hodgkin and Reed-Sternberg cells in HIV CHL have similar phenotype to those from the immune-competent individuals; however, evidence of *EBV* expression is present in nearly all HIV CHL [45, 46].
- *Polymorphic B-cell lymphoproliferative disorders (PTLD-like)*
  - Rare cases of polymorphic PTLD-like lesions were reported in HIV patients. These lesions have similar morphologic, phenotypic, and genotypic features to the polymorphic PTLD seen in patients who receive solid organ transplantation.
  - The affected lymph nodes or extranodal masses show effacement of architecture with a polymorphous infiltrate containing scattered large lymphocytes admixed with inflammatory cells in the background.
  - B-cell clonality as well as *EBV* infection can be demonstrated in some, but not all, cases.
  - In contrast to the bona fide HIV-associated lymphomas, these polymorphic infiltrates often show more limited disease distribution and lack of consistent genetic alterations.
  - Due to the small number of reported cases, the clinical behavior and outcome are unknown [47].

11. What are the common genetic abnormalities and what are the main viral and molecular driving factors in HIV-associated lymphomas?

- The most common genetic alterations in conventional NHL are also present in HIV-associated lymphomas. Translocations such as *MYC*, *BCL6*, and mutations of *TP53* play similar roles in HIV-associated lymphomas. *TP53* mutations are seen in increased frequencies in multiple types of HIV-associated lymphomas.

- Evidence of *EBV* infection can be demonstrated in all HIV-associated lymphoma types ranging from 40% to nearly 100%. Increased serum cytokines such as IL6 and IL10 are observed in *EBV*-positive cases suggesting an association of cytokine network dysregulation with *EBV*-associated lymphomas [48].
- *MYC* rearrangement is present in 100% Burkitt lymphoma, nearly all plasmablastic lymphoma, and a small percentage of DLBCL in HIV patients. The *MYC* breakpoints in Burkitt lymphoma are similar in HIV and sporadic types and are usually within first intron, first exon or 5′ of first exon. The breakpoints in immunoglobulin heavy chain gene in t(8;14) typically involve switch regions. These patterns are different from endemic type. Approximately 25% of HIV-associated DLBCL also harbors *MYC* rearrangement. *MYC*-rearranged cases tend to have higher proliferation rate, but it is unclear whether *MYC* rearrangement portends unfavorable clinical outcome [41, 49, 50].
- *BCL6* rearrangement can be detected in 20% of systematic HIV-associated DLBCL and 40% of HIV-associated CNS lymphomas. *BCL6* translocation partners with immunoglobulin heavy chain gene in most cases and with various other genes in the remaining cases. Except for rare cases of double-hit lymphoma, *BCL6* and *MYC* translocations are mutually exclusive indicating different pathogenic mechanisms between lymphomas with these two translocations [51].
- *TP53* mutations can be detected in 40% of HIV-DLBCL and 60% of HIV-BL.
  - *TP53* is a tumor suppressor gene and is typically inactivated by loss of heterozygosity with a missense or nonsense mutation.
  - Mutations of *TP53* are detected across all tumor types, but high-grade lymphomas associated with HIV appear to have relatively higher frequency of mutations.
  - Most mutations accumulate between exon 5 to exon 9 and are missense or nonsense mutations. Most mutated cases also show loss of heterozygosity resulting in inactivation of the gene by loss of function of both alleles.
  - Other cases show intact second allele, and in these cases *TP53* may be inactivated through alternative mechanisms [51].
- Similar to lymphoproliferative processes in other immune deficiency conditions, *EBV* expression is a consistent finding in HIV-associated lymphomas.
  - *EBV* can be found in nearly all classic Hodgkin lymphoma and CNS lymphoma, 60–70% plasmablastic lymphoma, approximately 50% Burkitt lymphoma, and approximately 40% systemic DLBCL in HIV patients.
  - Nearly all HIV+ individuals are seropositive for *EBV*, and many have evidence of *EBV* reactivation.
  - Clonal *EBV* genomes were found in HIV-BL and HIV-CHL, which suggest that *EBV* infection is an early event.
  - The pathogenesis of *EBV* in HIV-associated lymphoma was considered similar to that of lymphomas in congenital and iatrogenic immune deficiencies. It was hypothesized that the compromised immunity in HIV infection was prone to *EBV* reactivation and polyclonal expansion of the *EBV*-infected B cells.
  - The proliferation of *EBV*-infected lymphocytes was unstable and susceptible to genetic alterations such *MYC* translocation and mutations in oncogenes and tumor suppressor genes, which resulted in malignant transformation to lymphoma [49, 52].

12. What is the definition of iatrogenic immunodeficiency-associated lymphoproliferative disorder (IA-LPD)?

- Iatrogenic immunodeficiency-associated lymphoproliferative disorder (IA-LPD) comprises of reactive and neoplastic lymphoid proliferations that arise in patients treated with immunosuppressive and immunomodulatory drugs for autoimmune disorders and conditions other than posttransplant setting.
- Some drugs used to treat autoimmune diseases are also used in posttransplant setting (i.e., tacrolimus, mycophenolate), and it is unclear whether these agents play a direct causative role.
- This is further complicated by the fact that many autoimmune disorders have inherent risk in developing lymphoma.
- *EBV*-associated mucocutaneous ulcer is a newly described entity that can be seen after immunotherapy or can be associated with age-related immune senescence [53].

13. Which clinical conditions and therapies are associated with IA-LPD?

- Based on the underlying diseases, IA-LPDs can be grouped into two categories based on the offending agents:
  1. LPDs associated with therapy of autoimmune/chronic inflammatory disorders
  2. LPDs associated with therapy of hematologic malignancies
- The common diseases in the former category are rheumatoid arthritis, inflammatory bowel disease, psoriasis and psoriatic arthritis, systemic lupus erythematosus, and ankylosing spondylitis.

- In the setting of hematologic malignancies, IA-LPDs are more commonly reported in certain leukemias and lymphomas including chronic lymphocytic leukemia/small lymphocytic lymphoma and plasma cell myeloma, although rare cases have been reported in a wide variety of neoplastic hematologic disorders [53].

14. How common is the IA-LPD?

- While the association of various chemotherapeutic agents and immune modulators with lymphoproliferative disorders is well established, the exact frequency of IA-LPD is not known. There are various small series and case reports in the literature which are indicative of rarity of these diseases. It appears that the prevalence of IA-LPD is on the rise due to the increasing use of immunomodulatory agents in many autoimmune and rheumatologic conditions.
- Several factors affect the frequencies of these disorders including underlying diseases and their severity and the types of immunosuppressive therapy. Many of the reported patients used multiple immune suppressive agents, which prevented clear understanding of the role of each individual agent.

  However, it is generally believed that the incidence of LPDs increases 8–10 folds in patients treated with multiple immunosuppressive agents as compared to those treated with single agent [54, 55]. A large meta-analysis of 18 studies of patients with inflammatory bowel disease reported a significantly increased risk of lymphoma among patients taking thiopurines [56].
- The absolute risk was highest in patients older than 50 years of age [56].

15. Which therapeutic agents are associated with IA-LPD?

- The major classes of drugs associated with IA-LPDs are antimetabolites, methotrexate, purine analogues (fludarabine), and immunomodulators (Table 11.1).
- In the broad class of antineoplastic drugs, secondary LPDs are most common in CLL/SLL patients treated with fludarabine and cyclophosphamide.
- Other chemotherapeutic agents that may result in secondary LPDs include alemtuzumab, chlorambucil, cyclosporine, bendamustine, bortezomib, doxorubicin, melphalan (used in conditioning for autologous stem cell transplant), and vincristine (Table 11.1). Many of these agents are used in combination which precludes understanding of the precise role of individual drug in association of secondary LPDs [57].

16. What is the median interval from initiation of therapy to the diagnosis of IA-LPD?

- The time interval from initiation of therapy to diagnosis of LPD varies considerably ranging from 6 weeks to 24 years, with the median intervals from 24 months to 55 months [57, 58].
- IA-LPDs arising after treatment of autoimmune and other chronic inflammatory disorders have a shorter median

Table 11.1 List of common immune modulators and biologic agents that are associated with IA-LPD

Name	Class	Mechanism	Common indications
Methotrexate	Antimetabolite	Inhibition of DHFR	Leukemia, lymphoma, autoimmune disorders
Azathioprine	Antimetabolite	Inhibits nuclei acid synthesis	Renal transplant, RA, UC, CD, lupus nephritis
6-Mercaptopurine	Antimetabolite	Inhibits nuclei acid synthesis	ALL, CD
Infliximab	Cytokine inhibitor	TNF-α inhibitor	UC, CD, psoriatic arthritis
Adalimumab	Cytokine inhibitor	TNF-α inhibitor	RA, AS, UC, CD, psoriatic arthritis
Etanercept	Cytokine inhibitor	TNF-α inhibitor	RA, psoriasis, AS
Anakinra	Cytokine inhibitor	IL-1Ra inhibitor	RA
Tocilizumab	Cytokine inhibitor	IL-6R inhibitor	RA, juvenile idiopathic arthritis
Abatacept	Selective co-stimulation modulator	Blocks binding of the CD80/CD86 in APC to CD28 on T cells	RA, juvenile idiopathic arthritis
Tofacitinib	JAK-STAT pathway inhibitor	Inhibits JAK1, JAK3	RA, IBD, psoriasis

DHFR dihydrofolate reductase, *RA* rheumatoid arthritis, *UC* ulcerative colitis, *CD* Crohn's disease, *ALL* acute lymphoblastic leukemia, *AS* ankylosing spondylitis, *IBD* inflammatory bowel disease, *APC* antigen-presenting cell

interval (24 months) as compared to those arising after chemotherapy for malignancies (55 months). However, more data with large multi-institutional studies are necessary to confirm these observations.

17. What are the types of IA-LPD?

- Lymphoproliferative disorders in the setting of prior therapy can present as overt lymphomas and polymorphic lymphoid proliferations. In general, polymorphic LPDs are less common than lymphomas (10% vs 90%).
  - The polymorphic LPDs can be nodal (atypical follicular hyperplasia, atypical paracortical T-cell hyperplasia, aberrant T-cell phenotypes, and abnormal extrafollicular proliferation of B cells) or extranodal.
  - The iatrogenic lymphomas are dominated by diffuse large B-cell lymphoma and classic Hodgkin lymphoma. Other less commonly reported lymphomas include Burkitt lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, peripheral T-cell lymphoma, and marginal zone lymphoma [58, 59].
- *Polymorphic lymphoid proliferation associated with iatrogenic immune suppression (IA-PLP)*
  - IA-PLP encompasses a wide spectrum of morphological changes that include atypical follicular hyperplasia, paracortical hyperplasia, atypical lymphohistiocytic proliferation, and lymphoid proliferation with Hodgkin-like cells.
  - *EBV*-positive cases may show areas of geographic necrosis.
  - The infiltrating lymphocytes exhibit a spectrum of differentiation (small lymphocytes, centroblasts, immunoblasts, and plasma cells). Some cases show florid follicular hyperplasia or polymorphous paracortical hyperplasia with prominent vascular proliferation. However, many of these lymphoid proliferations do not fulfill the diagnostic criteria for either reactive lesions or neoplastic proliferations.
  - Clonal immunoglobulin heavy chain (*IGH*) gene rearrangement may be detected, but the clonal peaks are usually small and are accompanied by a polyclonal background.
  - Most of these lesions regress following discontinuation of the offending drugs [60, 61].
- *Dasatinib-associated reactive follicular hyperplasia*
  - Patients treated with dasatinib have been reported to develop florid reactive follicular hyperplasia that regresses after discontinuation of the drug. The patients often present with solitary or regional lymphadenopathy.
  - This entity shows distinctive morphological features. The lymph nodes can be markedly enlarged but nodal architecture is preserved. The follicles are hyperplastic with features akin to progressive transformation of germinal centers (PTGC). However, unlike typical PTGC, the displaced mantle zone forms a cuff around capillaries. This feature is reminiscent of Castleman's disease, but other features of Castleman's disease are absent [62, 63].
- *Diffuse large B-cell lymphoma, NOS (DLBCL)*
  - DLBCL is the most common LPD in patients treated with methotrexate (MTX). Up to 40% cases show an extranodal presentation.
  - A few cases of cutaneous DLBCL have been reported after prolonged MTX administration. A case of MTX-associated LPD was reported at the injection site of MTX [64].
  - These cases show sheets of large centroblast or immunoblast lymphocytes and express a B-cell phenotype with CD20, CD79a, PAX5, BOB1, and OCT2.
  - *EBV* has been reported in up to 79% cases.
  - CD30 is more frequently expressed; otherwise, the morphology and phenotype are identical to the DLBCL in immune-competent population [58, 65, 66].
- *Classic Hodgkin lymphoma associated with iatrogenic immune suppression (IA-CHL)*
  - Diagnosis of CHL in iatrogenic clinical setting is challenging as *EBV*+ polymorphic LPD often contains Hodgkin-like cells. For accurate diagnosis, the lesions should have unequivocal morphologic and phenotypic features of CHL.
  - The histologic morphology is similar to those arising from immune-competent population with large single or multinucleated HRS cells in a background of lymphocytes, plasma cells, eosinophils, and histiocytes.
  - Up to 80% cases express EBER. The HRS cells lack a complete B-cell phenotype with frequent but not universal expression of CD15. If the large cells express strong B-cell markers, a diagnosis of T-cell/histiocyte-rich B-cell lymphoma should be entertained.
  - In terms of microenvironment, IA-CHL shows a predominance of CD163+ histiocytes with a M2 phenotype. Increased number of M2 histiocytes were reportedly associated with a worse prognosis in non-immunodeficiency-associated CHL. Prognostic significance of this finding in CHL in iatrogenic setting is unknown.
  - Subtyping of IA-CHL arising after therapy is usually difficult, although it appears that mixed cellularity is more frequent than nodular sclerosis subtype. This is the opposite of CHL in immune-competent population.
  - IA-CHL requires treatment with combination chemotherapy. Regression of CHL after cessation the offending drugs was reported only in rare cases [67].
- *EBV-positive mucocutaneous ulcer (EBV-MCU)*

  - *EBV*-MCU is a recently recognized B-cell lymphoproliferative disorder and was initially reported by Dojcinov, et al. in 2010 [68].
  - The disease presents as ulcerated lesions in gingiva or other mucocutaneous locations and is associated with immunosuppressive therapy (56%), age-related immune senescence (40%), as well as primary immune deficiencies (4%).
  - Iatrogenic medications that may increase risk of developing *EBV*-MCI are methotrexate, azathioprine, cyclosporine, mycophenolate, and tacrolimus.
  - Histologically, these lesions show polymorphic infiltrate with scattered atypical large B cells in a background of abundant T cells. The B cells may show HRS cell-like morphology and are usually positive for CD30 and EBER [68, 69].
- *Extranodal marginal zone lymphoma (ENMZL) and small B-cell lymphoma with plasmacytic differentiation*
  - In 2011, Gibson et al. described four cases of *EBV*+ marginal zone lymphoma arising after organ transplant [70]. Subsequently, similar cases arising after iatrogenic therapy were reported.
  - These lesions are nearly always positive for *EBV*, which suggests underlying immunodeficiency when expressed in mature B-cell neoplasms. ENMZL has been reported in patients with rheumatoid arthritis after treated with immunosuppressives such as methotrexate.
  - These cases frequently involve the skin and subcutaneous tissue [71].
- *EBV+ B-cell lymphoproliferative disorders of the central nervous system*
  - These lesions range from polymorphic *EBV*+ lymphoid proliferations to *EBV*+ diffuse large B-cell lymphoma and were reported after mycophenolate therapy for various autoimmune disorders.
  - They can regress with mycophenolate withdrawal with or without additional therapy.
  - Almost all the cases occur when mycophenolate is administrated alone without calcineurin inhibitors. It appears that calcineurin inhibitors have a protective effect [72, 73].
- *Peripheral T-cell lymphomas*
  - Hepatosplenic T-cell lymphoma (HSTCL), extranodal NK−/T-cell lymphoma, and breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) may arise after immunosuppressive/immunomodulator therapy.
  - Up to 20% cases of HSTCL are reported in young patients treated with immunosuppressive/immunomodulator therapy for inflammatory bowel disease. Rare cases have also been reported in rheumatoid arthritis and sarcoidosis after treatment with thiopurines and TNF-α inhibitors. An FDA study reported 25 cases of iatrogenic HSTCL, of which 24 had undergone treatment with TNF-α inhibitor followed by a second immunomodulator (azathioprine, 6-mercaptopurine, or methotrexate) [74].

Case Presentations

Case 1

Learning Objectives

1. To become familiar with the clinical presentation and pathologic diagnosis of nodular lymphoid hyperplasia of gastrointestinal (GI) tract in patient with common variable immunodeficiency syndrome.
2. To become familiar with the application of laboratory evaluations to diagnose common variable immunodeficiency syndrome and associated nodular lymphoid hyperplasia of the gastrointestinal tract.
3. To be familiar with other types of benign and neoplastic lymphoid proliferations associated with primary immunodeficiency.

Case History

A 31-year-old female with history of recurrent respiratory infection presented with chronic diarrhea. Upper and lower gastrointestinal endoscopy demonstrated multiple polypoid lesions in the stomach, duodenum, ileum, and large intestine resembling what could be seen in familial adenomatous polyposis.

Histologic Findings

- H&E sections of upper and lower GI endoscopic biopsies demonstrated nodular lymphoid proliferation in the lamina propria (Figs. 11.1 and 11.2).
- In the small intestine, villous atrophy was noted, resembling the features seen in celiac disease. Some lymphoid nodules contained germinal centers.
- Immunohistochemical analysis performed on section of colonic biopsy showed mixed B cells and T cells within lymphoid nodules with B cells in the center surrounded by T cells.

Differential Diagnosis

- Nodular lymphoid hyperplasia of the gastrointestinal tract
- Follicular lymphoma of the gastrointestinal tract
- Mantle cell lymphoma of the GI tract
- Familiar adenomatous polyposis with lymphoid aggregates
- Nodular lymphoid hyperplasia of the GI tract associated with primary immunodeficiency

Ancillary Studies

- EBER ISH was positive in rare cells.
- *IGH* and *TCR* gene rearrangement analyses were negative for clonal rearrangement of the genes.

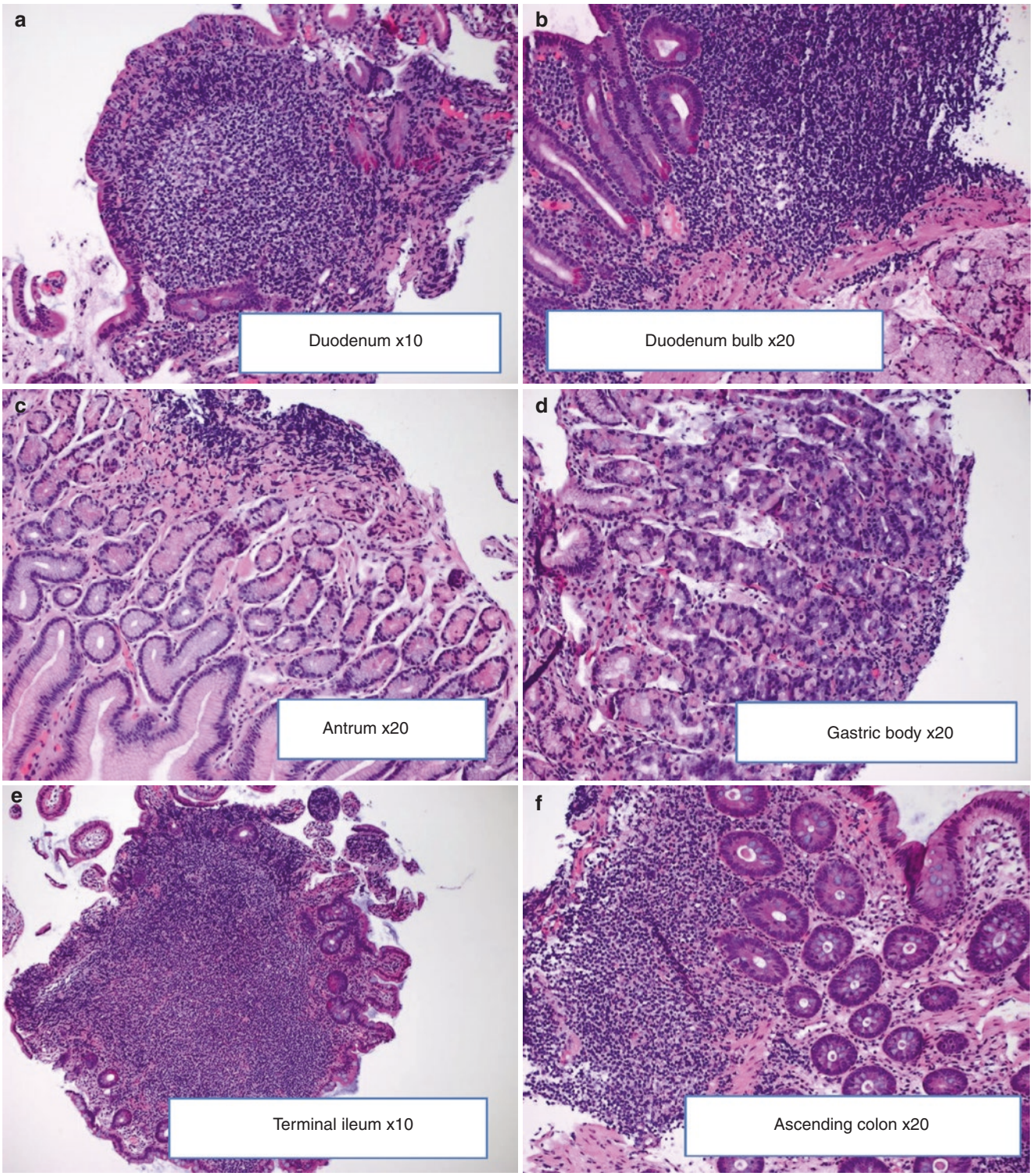

Fig. 11.1 Nodular lymphoid hyperplasia of the gastrointestinal tract associated with common variable immunodeficiency (Case 1). H&E sections of upper and lower GI endoscopic biopsies demonstrate nodular lymphoid proliferation in the lamina propria in duodenum (**a**, **b**), stomach (**c**, **d**), ileum (**e**), and ascending colon (**f**). Note villous atrophy in the small intestinal mucosa (**a**, **b**) and germinal center in lymphoid nodules (**a**)

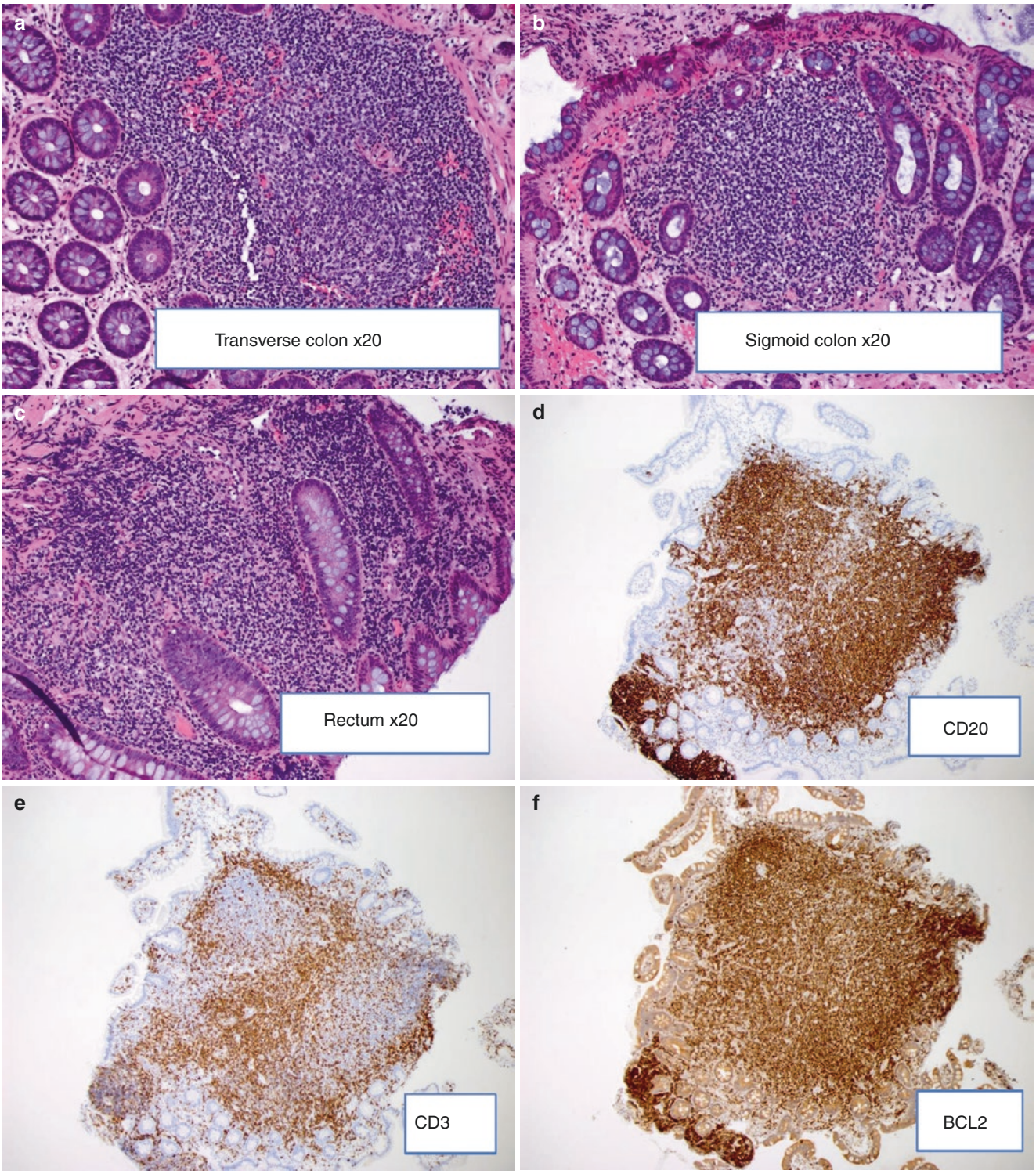

Fig. 11.2 Nodular lymphoid hyperplasia of the gastrointestinal tract associated with common variable immunodeficiency (Case 1). H&E sections of lower GI endoscopic biopsies demonstrate nodular lymphoid proliferation in the lamina propria in the transverse colon (**a**), sigmoid colon (**b**), and rectum (**c**). Immunohistochemical analysis performed on section of colonic biopsy showed mixed B cells (**d**) and T cells (**e**) within lymphoid nodules with B cells in the center surrounded by T cells. Image (**f**) is BCL2 stain that is positive in mantle zone and surrounding T cells, highlighting a small reactive germinal center at upper center (negative for the stain)

- Laboratory evaluations demonstrated serum immunoglobulin levels as follows: IgG = 600 mg/dl, IgA = 34 mg/dl, and IgM = 36 mg/dl.
- Anti-HIV 1 and 2 antibodies were not detected. Stool culture was negative for any pathogenic microorganisms.

Final Diagnosis

Nodular lymphoid hyperplasia of the gastrointestinal tract associated with common variable immunodeficiency

Take-Home Messages

1. Nodular lymphoid hyperplasia of the gastrointestinal tract can be seen in patient with common variable immunodeficiency.
2. The diagnosis relies on histologic examination and laboratory evaluations.
3. The disease is benign, and the treatment involves immunomodulators.

Case 2

Learning Objectives

1. To become familiar with the clinical presentation and pathologic diagnosis of *EBV*-positive lymphoproliferative disorder associated with another hematolymphoid neoplasm, in particular chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
2. To become familiar with the morphologic spectrum of *EBV*-positive lymphoproliferative disorders associated with CLL/SLL
3. To be familiar with the pathogenesis of *EBV*-positive lymphoproliferative disorder associated with CLL/SLL or other indolent B-cell lymphoma/leukemia.

Case History

A 62-year-old male with remote history of CLL/SLL presented with fever, fatigue, and weight loss. Physical examination and radiologic evaluation revealed generalized lymphadenopathy and liver mass. Laboratory data showed pancytopenia.

Histologic Findings

- H&E sections of inguinal lymph node biopsies demonstrated nodal architecture effaced by diffuse proliferation of small- to medium-sized lymphocytes. Vague nodular areas consistent with proliferation centers were noted (Fig. 11.3a, b).
- Immunohistochemical analysis showed that the majority of lymphoid cells were positive for CD20 and negative for CD3 (Fig. 11.3c, d). The latter stain exhibited scattered positive cells consistent with reactive T cells.
- The majority of lymphoid cells were positive for CD5 and CD23 (Fig. 11.3e, f), suggesting that B cells coexpressed these two antigens.
- H&E section of liver biopsy showed mixed inflammatory cell infiltrate including small lymphocytes, plasma cells, histiocytes, and eosinophils with scattered large lymphoid cells (Fig. 11.4a).
- Immunohistochemical analysis showed the findings as below: the large cells were positive for CD30 (Fig. 11.4b) and CD15 (partial) (Fig. 11.4c) and negative for CD45 (Fig. 11.4d). CD68 stain highlighted many histiocytic cells in the background (Fig. 11.4e).

Differential Diagnosis

- Richter transformation of CLL, DLBCL type
- Richter transformation of CLL, classic Hodgkin lymphoma type
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive DLBCL type
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive cHL type
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive cHL-like
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive polymorphic type

Ancillary Studies

- EBER ISH revealed scattered positive lymphoid cells, most being large (Fig. 11.4f).
- Flow cytometric analysis of lymph node biopsy demonstrated monoclonal B-cell population with CD5 and CD23. However, the tests on liver mass biopsy were negative.
- *IGH* gene rearrangement analysis was positive for clonal rearrangement of the gene on lymph node section and the section of liver mass. The amplicon size and breakpoint sequences were different between the two biopsies.
- Bone marrow biopsy showed the lymphomatous involvement with morphologic features similar to those seen in the liver biopsy (Fig. 11.5). Flow cytometric analyses were negative. *IGH* gene rearrangement analysis was positive for clonal rearrangement of the gene with amplicon size and breakpoint sequences identical to that seen in the liver mass.

Final Diagnosis

***EBV*-positive B-cell lymphoproliferative disorder associated with iatrogenic immunodeficiency related to CLL therapy or CLL itself.**

Take-Home Messages

1. Patients with CLL and corresponding therapy could develop B-cell lymphoproliferative disorders.
2. This category of LPD could demonstrate a spectrum of histologic features.

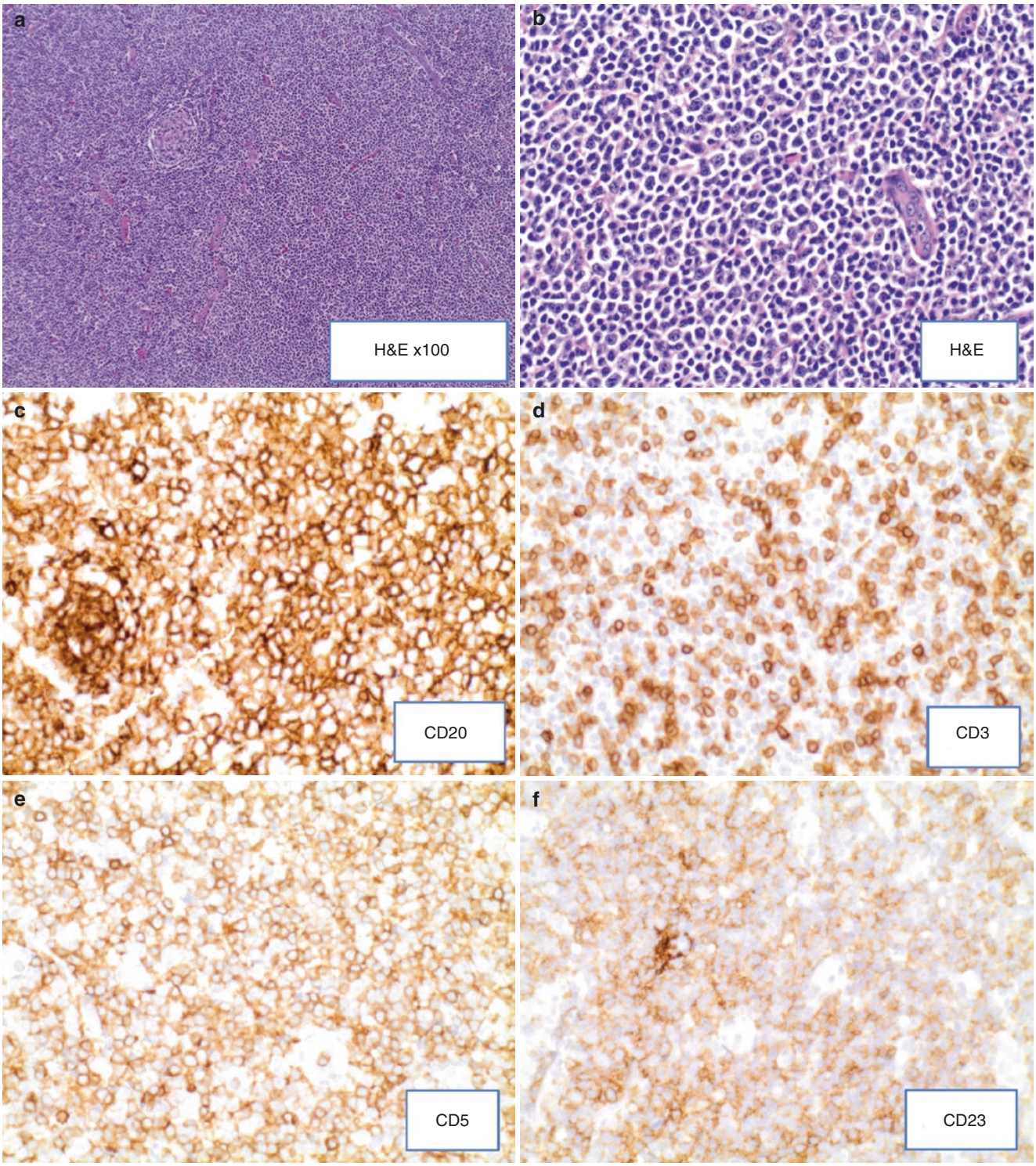

Fig. 11.3 Small lymphocytic lymphoma (Case 2). H&E section of inguinal lymph node biopsies demonstrates nodal architecture effaced by diffuse proliferation of small- to medium-sized lymphocytes (**a**, **b**). Note the size and morphology of lymphoid cells that are consistent with history of CLL/SLL. (**c**) CD20 stain. Note the weak staining in the majority of lymphoid cells. (**d**) CD3 stain. Note the scattered positive cells consistent with reactive T cells. The majority of lymphoid cells are positive for CD5 (**e**) and CD23 (**f**), suggesting coexpression of these two antigens in B cells

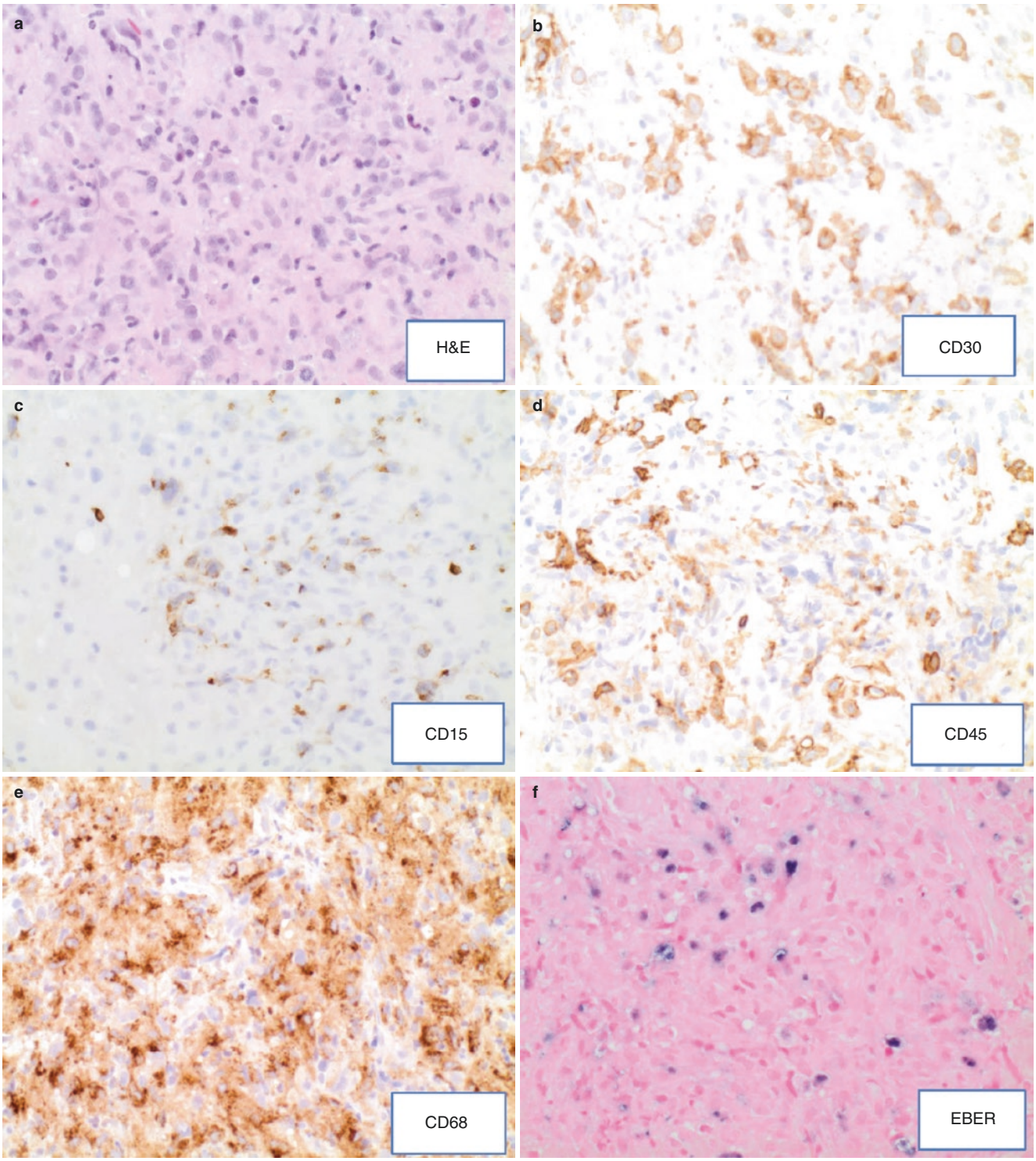

Fig. 11.4 Iatrogenic immunodeficiency-related B-cell lymphoproliferative disorder associated with CLL/SLL (Case 2). (**a**) H&E section of liver biopsy showed mixed inflammatory cell infiltrate with scattered large lymphoid cells. The large cells are positive for CD30 (**b**) and CD15 (**c**) and negative for CD45 (**d**). (**e**) CD68 stain. Note many positive cells consistent with histiocytes in the background. (**f**) EBER ISH is positive in scattered large cells

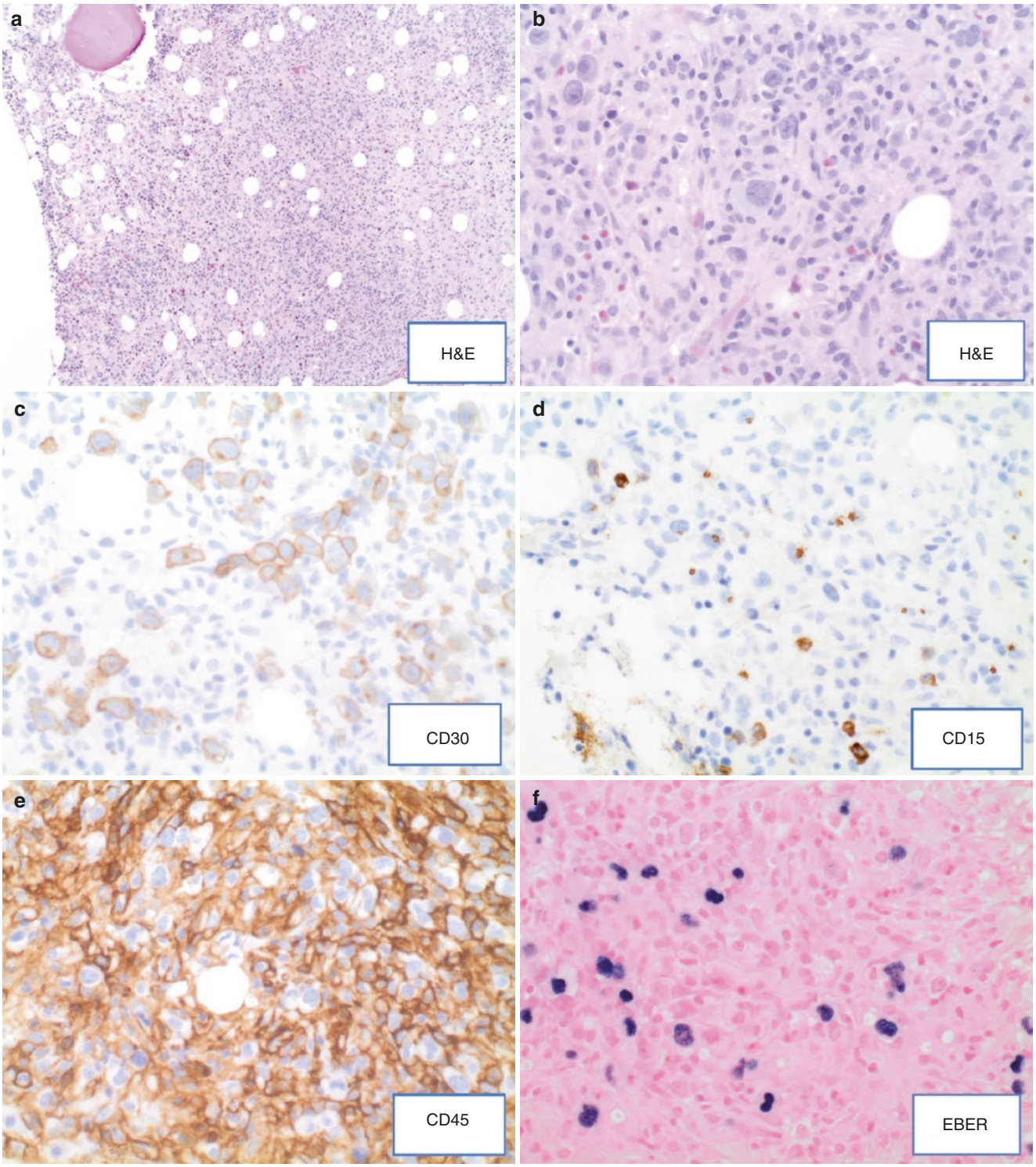

Fig. 11.5 Iatrogenic immunodeficiency-related B-cell lymphoproliferative disorder associated with CLL/SLL (Case 2). (**a**) H&E section of bone marrow biopsy shows extensive lymphomatous involvement. (**b**) A high magnification image shows scattered large lymphoid cells in a background of mixed inflammatory cell infiltrate with fibrosis. The large cells are positive for CD30 (**c**), partial weak for CD15 (**d**), and negative for CD45 (**e**). (**f**) EBER ISH is positive in scattered large cells

3. Iatrogenic immunodeficiency is the underlying pathogenesis, and the cases are often positive for *EBV*.
4. The vast majority of the cases have been demonstrated the clonal rearrangement of B-cell receptor genes that are unrelated to those seen in primary CLL.
5. Similar to posttransplant lymphoproliferative disorders (PTLD), iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorders demonstrate variable clinical outcome, depending upon the histologic classification.

Case 3

Learning Objectives

1. To become familiar with the clinical presentation and pathologic diagnosis of HIV-associated lymphoproliferative disorder
2. To become familiar with the morphologic spectrum of lymphoproliferative disorders associated with HIV infection
3. To become familiar with the diagnosis of high-grade B-cell lymphoma associated with HIV infection
4. To be familiar with other types of benign and neoplastic lymphoid proliferations associated with HIV infection

Case History

A 39-year-old male with a history of HIV infection presented with fever, fatigue, and weight loss as well as abdominal pain. Physical examination and radiologic evaluation revealed generalized lymphadenopathy. Laboratory data showed pancytopenia, including lymphopenia with CD4 cell count of 258/μl. CT scan revealed intestinal mass, in addition to generalized lymphadenopathy.

Histologic Findings

- H&E sections of upper GI endoscopic biopsy demonstrated intestinal mucosa architecture effaced by diffuse proliferation of homogeneous medium-sized lymphoid cells with increased apoptosis and tingible body macrophages, giving a starry-sky-like appearance (Fig. 11.6a).
- Immunohistochemical analysis showed the findings as follows: the lymphoid cells were positive for CD20 (Fig. 11.6b) and CD10 (Fig. 11.6c) and had very high proliferation index (Fig. 11.6d); they were negative for BCL2 (Fig. 11.6e).

Differential Diagnosis

- Burkitt lymphoma
- Burkitt lymphoma associated with HIV infection
- High-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements
- High-grade B-cell lymphoma, NOS

Ancillary Studies

- EBER ISH was positive in >90% of the total abnormal lymphoid cells (Fig. 11.6f).
- Flow cytometric analysis detected a monoclonal B-cell population with bright CD45 and CD10 and bright surface light chain restriction. The events were medium-sized to large based on forward scatter features.
- FISH analysis demonstrated isolated *IGH/MYC* fusion without rearrangement of either *BCL2* or *BCL6* gene.

Final Diagnosis

Burkitt lymphoma associated with HIV infection

Take-Home Messages

1. Patients with HIV infection could develop B-cell lymphoproliferative disorders.
2. This category of lymphoproliferative disorder could demonstrate a spectrum of histologic features, as seen in PTLD, including Burkitt lymphoma.
3. Immunodeficiency is the underlying pathogenesis, and more than one third of Burkitt lymphoma in HIV patients are positive for *EBV*.
4. Diagnosis of Burkitt lymphoma associated with HIV infection relied on histologic examination, immunophenotypic profiling, and cytogenetic studies, as does the Burkitt lymphoma without HIV infection.
5. Similar to PTLD, B-cell lymphoproliferative disorders associated with HIV infection demonstrate variable clinical outcome, depending upon the histologic classification.

Case 4

Learning Objectives

1. To become familiar with the clinical presentation and pathologic diagnosis of HIV-associated benign lymphoid hyperplasia
2. To become familiar with the morphologic spectrum of lymphoid hyperplasia associated with HIV infection
3. To be familiar with other types of benign and neoplastic lymphoid proliferations associated with HIV infection

Case History

A 34-year-old male with a history of HIV infection presented with bilateral enlargement of parotid glands associated with submandibular lymphadenopathy. Physical examination and radiologic evaluation revealed enlarged

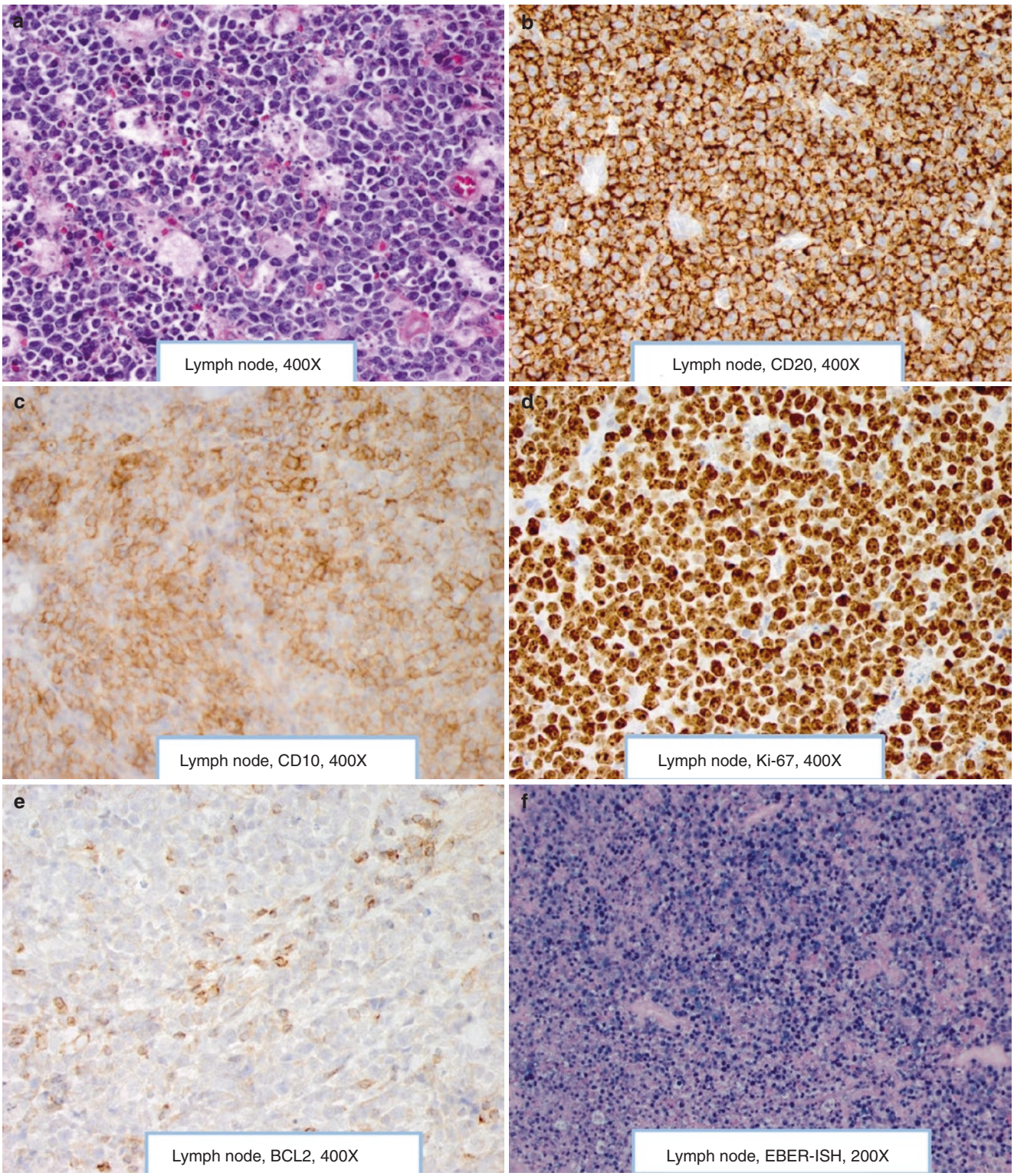

Fig. 11.6 Burkitt lymphoma associated with HIV infection (Case 3). (**a**) H&E section of upper GI endoscopic biopsy demonstrates diffuse proliferation of homogeneous medium-sized lymphoid cells with increased apoptosis and tingible body macrophages. Note the starry-sky pattern of the neoplastic proliferation. The lymphoid cells are positive for CD20 (**b**) and CD10 (**c**) and had very high proliferation index (**d**); they are essentially negative for BCL2 (**e**). (**f**) EBER ISH is positive in the majority of lymphoid cells

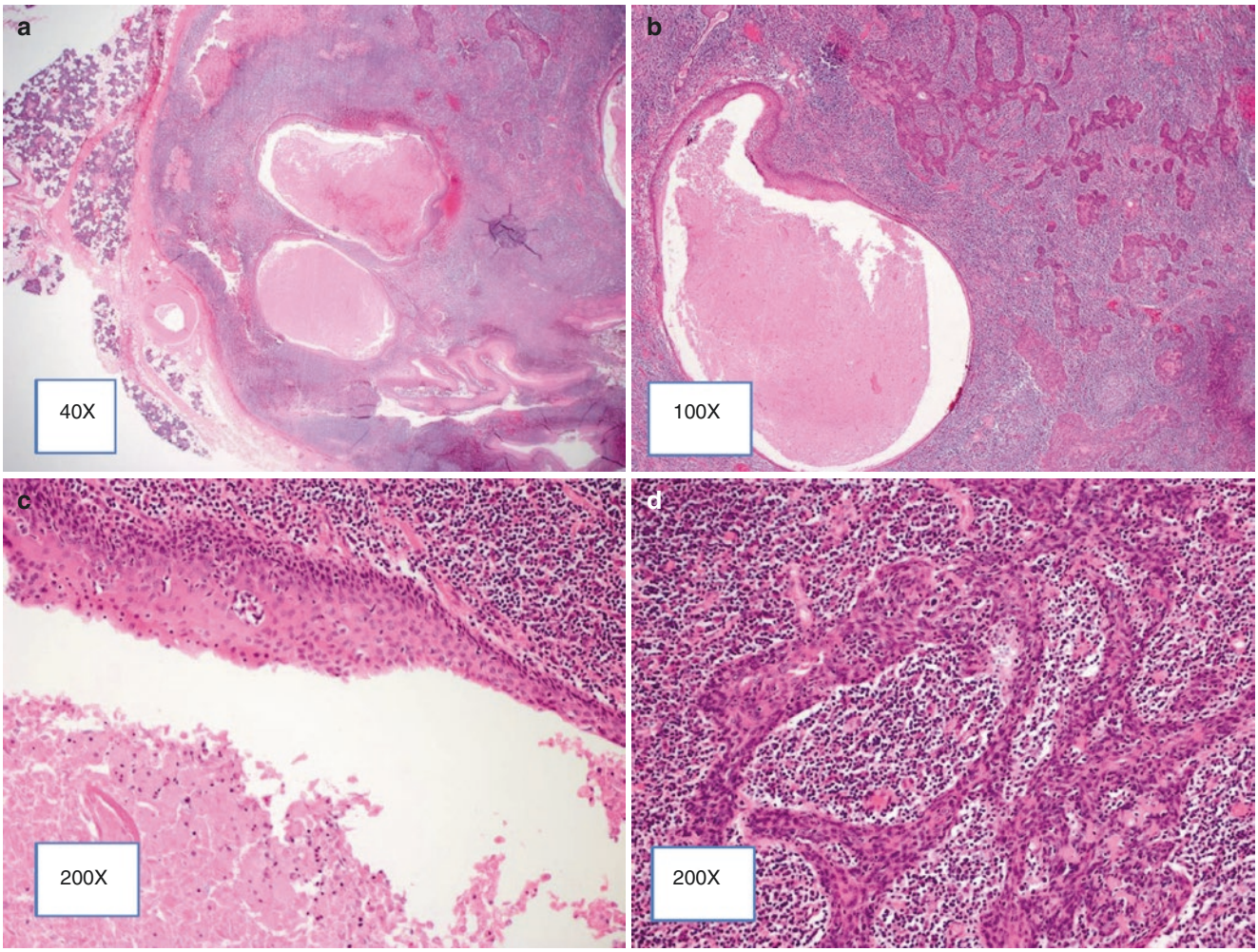

Fig. 11.7 Benign lymphoepithelial cyst associated with HIV infection (Case 4). (**a**, **b**) H&E sections of excisional biopsies demonstrate lymphoid proliferation with squamous epithelium-lined cysts. Note tissue of salivary glands in the left of image a and lymphoid follicles with germinal centers in the lower right in image **b**. Cystic content contained desquamous epithelial cells (**c**). Epithelial islets were present in the background of lymphoid hyperplasia (**d**)

bilateral parotid glands and regional lymphadenopathy. Laboratory data showed lymphopenia with CD4 cell count of 169/μl.

Histologic Findings

- Fine-needle aspiration collected clear to pink fluid with scattered lymphoid cells.
- H&E sections of excisional biopsies demonstrated lymphoid proliferation with squamous epithelium-lined cysts (Fig. 11.7a, b). A few lymphoid follicles with germinal centers were seen.
- Cystic content contained desquamous epithelial cells (Fig. 11.7c).
- Epithelial islets were present in the background of lymphoid hyperplasia (Fig. 11.7d).

Differential Diagnosis

- Epithelial inclusion cyst
- Benign lymphoepithelial cyst (BLC) associated with HIV infection
- Autoimmune sialadenitis
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Ancillary Studies

- Immunohistochemical analysis demonstrated lymphoid follicular hyperplasia and interfollicular hyperplasia (data not shown).
- Flow cytometric analysis showed polytypic B-cell population and unremarkable T-cell population except for an inverted CD4:CD8 ratio.

- *IGH/K* gene rearrangement analysis detected no clonal rearrangement of the genes

Final Diagnosis

Benign lymphoepithelial cyst associated with HIV infection

Take-Home Messages

1. Patients with HIV infection could develop enlargement of bilateral parotid glands that is often confirmed to be benign lymphoepithelial cyst.
2. The diagnosis relies on morphologic examination, flow cytometric analysis, and molecular diagnostic tests as well as clinical correlation.
3. Surgical excision carries diagnostic and therapeutic implications.

Case 5

Learning Objectives

1. To become familiar with the clinical presentation and pathologic diagnosis of *EBV*-positive lymphoproliferative disorder associated with treatment for underlying autoimmune diseases
2. To become familiar with the morphologic spectrum of *EBV*-positive lymphoproliferative disorders associated with iatrogenic immunodeficiency other than organ transplant
3. To be familiar with the clinical outcome of *EBV*-positive lymphoproliferative disorder associated with iatrogenic immunodeficiency other than organ transplant.

Case History

A 22-year-old female patient with a history of Sjögren's syndrome, systemic lupus erythematosus (SLE), and transverse myelitis developed cervical and axillary lymphadenopathy. Pertinent drug history included mycophenolate mofetil and prednisone. She also received pulse high-dose steroids for SLE flare. Excisional biopsy of axillary lymph node was performed for a diagnosis.

Histologic Findings

- Nodal architecture was effaced by heterogeneous lymphoid proliferation. There was a vague nodularity, but otherwise a diffuse process (Fig. 11.8a) with scattered large cells that were mostly consistent with immunoblast-like cells; rare large cells resembled Hodgkin cell variants; however, classic Reed-Sternberg cells or "popcorn" cells were not identified (Fig. 11.8b).
- Background cells included mixture of lymphocytes, plasma cells, and some histiocytes without apparent neutrophils or eosinophils.
- Summary of immunohistochemical stains: the large cells were positive for CD30 (Fig. 11.8c), CD20 (variably) (Fig. 11.8d), CD45 (variably) (Fig. 11.8e), PAX5 (strong), and MUM1, but negative for CD15.
- EBER ISH was positive in scattered small lymphocytes and some large cells (Fig. 11.8f).

Differential Diagnosis

- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive DLBCL type
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive CHL type
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive CHL-like
- Iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorder, *EBV*-positive polymorphic type
- Infectious mononucleosis lymphadenopathy

Ancillary Studies

- Flow cytometric analysis of lymph node biopsy demonstrated polytypic B-cell population and unremarkable T-cell population.
- *IGH* gene rearrangement analyses were positive for clonal rearrangement.
- Laboratory evaluation demonstrated a high copy number of *EBV* genome in the blood sample.

Final Diagnosis

***EBV*-positive B-cell lymphoproliferative disorder, polymorphic variant, associated with iatrogenic immunodeficiency related to the treatment for underlying autoimmune diseases**

Take-Home Messages

1. Patients with autoimmune disorder such as Sjögren's syndrome and SLE could develop B-cell lymphoproliferative disorders due to immunosuppressive therapy.
2. This category of LPD could demonstrate a spectrum of histologic features, as seen in PTLD.
3. Iatrogenic immunodeficiency is the underlying pathogenesis, and the cases are often positive for *EBV*.
4. The vast majority of the cases have clonal rearrangement of B-cell receptor genes.
5. Similar to PTLD, iatrogenic immunodeficiency-associated B-cell lymphoproliferative disorders demonstrate variable clinical outcome, depending upon the histologic classification.

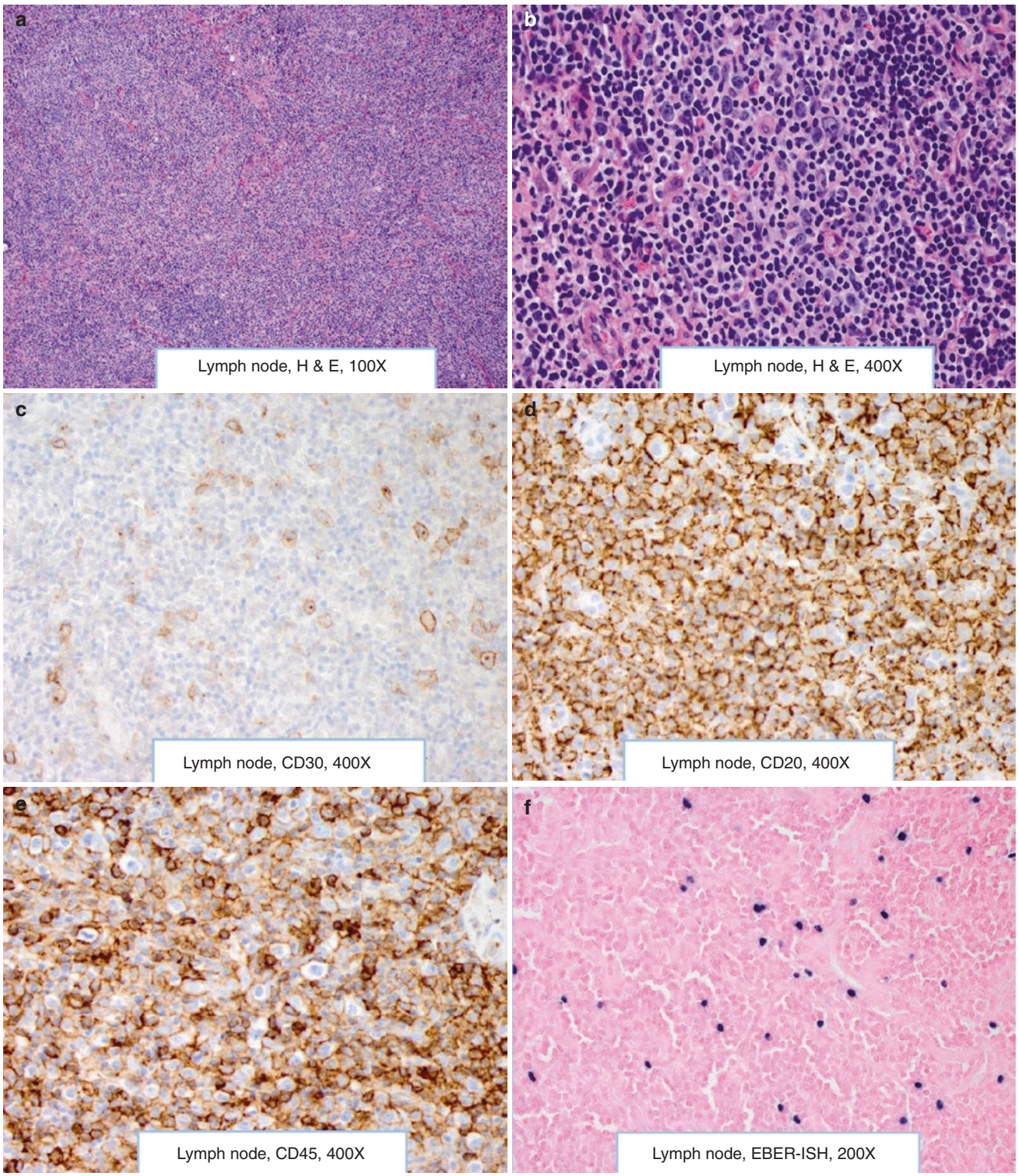

Fig. 11.8 B-cell lymphoproliferative disorder associated with iatrogenic immunodeficiency related to immunosuppressive therapy for autoimmune diseases (Case 5). (**a**) Section of axillary lymph node biopsy shows nodal architecture effaced by heterogeneous lymphoid proliferation. Note a vague nodular appearance. High magnification demonstrates scattered large cells admixed with otherwise heterogeneous lymphoid cells (**b**). The large cells are positive for CD30 (**c**), CD20 (**d**), and CD45 (**e**). Note many small and intermediate lymphoid cells are positive for CD20 and CD45 with weak staining, in addition to some positive large cells. (**f**) EBER ISH is positive in scattered cells including small cells and some large cells

References

1. Yong PF, Tarzi M, Chua I, Grimbacher B, Chee R. Common variable immunodeficiency: an update on etiology and management. Immunol Allergy Clin North Am. 2008;28:367–86.
2. Park MA, Li JT, Hagan JB, Maddox DE, Abraham RS. Common variable immunodeficiency: a new look at an old disease. Lancet. 2008;372:489–502.
3. Kalman L, Lindegren ML, Kobrynski L, Vogt R, Hannon H, Howard JT, et al. Mutations in genes required for T-cell development: IL7R, CD45, IL2RG, JAK3, RAG1, RAG2, ARTEMIS, and ADA and severe combined immunodeficiency: HuGE review. Genet Med. 2004;6:16–26.
4. Schuetz C, Huck K, Gudowius S, Megahed M, Feyen O, Hubner B, et al. An immunodeficiency disease with RAG mutations and granulomas. N Engl J Med. 2008;358:2030–8.
5. Qamar N, Fuleihan RL. The hyper IgM syndromes. Clin Rev Allergy Immunol. 2014;46:120–30.
6. Taylor AM, Harnden DG, Arlett CF, Harcourt SA, Lehmann AR, Stevens S, et al. Ataxia telangiectasia: a human mutation with abnormal radiation sensitivity. Nature. 1975;258:427–9.
7. Savitsky K, Sfez S, Tagle DA, Ziv Y, Sartiel A, Collins FS, Shiloh Y, et al. The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species. Hum Mol Genet. 1995;4:2025–32.
8. Derry JMJ, Ochs HD, Francke U. Pillars Article: Isolation of a Novel Gene Mutated in Wiskott-Aldrich Syndrome. Cell. 1994;78:635–44. J Immunol. 2018;200:3671–80
9. Featherstone C. How does one gene cause Wiskott-Aldrich syndrome? Lancet. 1996;348:950.
10. Rezaei N, Mahmoudi E, Aghamohammadi A, Das R, Nichols KE. X-linked lymphoproliferative syndrome: a genetic condition typified by the triad of infection, immunodeficiency and lymphoma. Br J Haematol. 2011;152:13–30.
11. Booth C, Gilmour KC, Veys P, Gennery AR, Slatter MA, Chapel H, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. Blood. 2011;117:53–62.
12. Sneller MC, Wang J, Dale JK, Strober W, Middelton LA, Choi Y, et al. Clinical, immunologic, and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. Blood. 1997;89:1341–8.
13. Shah S, Wu E, Rao VK, Tarrant TK. Autoimmune lymphoproliferative syndrome: an update and review of the literature. Curr Allergy Asthma Rep. 2014;14:462.
14. Price S, Shaw PA, Seitz A, Joshi G, Davis J, Niemela JE, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood. 2014;123:1989–99.
15. Lim MS, Straus SE, Dale JK, Fleisher TA, Stetler-Stevenson M, Strober W, et al. Pathological findings in human autoimmune lymphoproliferative syndrome. Am J Pathol. 1998;153:1541–50.
16. Bleesing JJ, Brown MR, Straus SE, Dale JK, Siegel RM, Johnson M, et al. Immunophenotypic profiles in families with autoimmune lymphoproliferative syndrome. Blood. 2001;98:2466–73.
17. Oliveira JB, Bleesing JJ, Dianzani U, Fleisher TA, Jaffe ES, Lenardo MJ, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood. 2010;116:e35–40.
18. Sander CA, Medeiros LJ, Weiss LM, Yano T, Sneller MC, Jaffe ES. Lymphoproliferative lesions in patients with common variable immunodeficiency syndrome. Am J Surg Pathol. 1992;16:1170–82.
19. Caballero FM, Brown WR, Kohler PF, Hayward AR. B cell numbers and responses in patients with common variable immunodeficiency and nodular lymphoid hyperplasia of the bowel. J Clin Lab Immunol. 1984;13:59–63.
20. Washington K, Stenzel TT, Buckley RH, Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. Am J Surg Pathol. 1996;20:1240–52.
21. Hugle B, Astigarraga I, Henter JI, Porwit-MacDonald A, Meindl A, Schuster V. Simultaneous manifestation of fulminant infectious mononucleosis with haemophagocytic syndrome and B-cell lymphoma in X-linked lymphoproliferative disease. Eur J Pediatr. 2007;166:589–93.
22. Tran H, Nourse J, Hall S, Green M, Griffiths L, Gandhi MK. Immunodeficiency-associated lymphomas. Blood Rev. 2008;22:261–81.
23. Tinguely M, Vonlanthen R, Muller E, Dommann-Scherrer CC, Schneider J, Laissue JA, et al. Hodgkin's disease-like lymphoproliferative disorders in patients with different underlying immunodeficiency states. Mod Pathol. 1998;11:307–12.
24. Cotelingam JD, Witebsky FG, Hsu SM, Blaese RM, Jaffe ES. Malignant lymphoma in patients with the Wiskott-Aldrich syndrome. Cancer Investig. 1985;3:515–22.
25. Ilowite NT, Fligner CL, Ochs HD, Brichacek B, Harada S, Haas JE, et al. Pulmonary angiitis with atypical lymphoreticular infiltrates in Wiskott-Aldrich syndrome: possible relationship of lymphomatoid granulomatosis and EBV infection. Clin Immunol Immunopathol. 1986;41:479–84.
26. Taylor AM, Metcalfe JA, Thick J, Mak YF. Leukemia and lymphoma in ataxia telangiectasia. Blood. 1996;87:423–38.
27. Miller B, Stansfield SK, Zack MM, Curran JW, Kaplan JE, Schonberger LB, et al. The syndrome of unexplained generalized lymphadenopathy in young men in New York City. Is it related to the acquired immune deficiency syndrome? JAMA. 1984;251:242–6.
28. Mathur-Wagh U, Enlow RW, Spigland I, Winchester RJ, Sacks HS, Rorat E, et al. Longitudinal study of persistent generalised lymphadenopathy in homosexual men: relation to acquired immunodeficiency syndrome. Lancet. 1984;1:1033–8.
29. O'Murchadha MT, Wolf BC, Neiman RS. The histologic features of hyperplastic lymphadenopathy in AIDS-related complex are nonspecific. Am J Surg Pathol. 1987;11:94–9.
30. Finfer MD, Schinella RA, Rothstein SG, Persky MS. Cystic parotid lesions in patients at risk for the acquired immunodeficiency syndrome. Arch Otolaryngol Head Neck Surg. 1988;114:1290–4.
31. Terry JH, Loree TR, Thomas MD, Marti JR. Major salivary gland lymphoepithelial lesions and the acquired immunodeficiency syndrome. Am J Surg. 1991;162:324–9.
32. Oksenhendler E, Duarte M, Soulier J, Cacoub P, Welker Y, Cadranel J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. AIDS. 1996;10:61–7.
33. Katchanov J, Zimmermann U, Branding G, Arasteh K, Muller M. HIV-associated multicentric Castleman's disease after initiation of antiretroviral therapy: experience of a European Centre. Infection. 2014;42:791–3.
34. Pileri S, Rivano MT, Raise E, Gualandi G, Gobbi M, Martuzzi M, et al. The value of lymph node biopsy in patients with the acquired immunodeficiency syndrome (AIDS) and the AIDS-related complex (ARC): a morphological and immunohistochemical study of 90 cases. Histopathology. 1986;10:1107–29.
35. Biberfeld P, Ost A, Porwit A, Sandstedt B, Pallesen G, Bottiger B, et al. Histopathology and immunohistology of HTLV-III/LAV related lymphadenopathy and AIDS. Acta Pathol Microbiol Immunol Scand A. 1987;95:47–65.
36. Chadburn A, Metroka C, Mouradian J. Progressive lymph node histology and its prognostic value in patients with acquired immunodeficiency syndrome and AIDS-related complex. Hum Pathol. 1989;20:579–87.

37. Weiss LM, O'Malley D. Benign lymphadenopathies. Mod Pathol. 2013;26:S88–96.
38. Raphael MM, Audouin J, Lamine M, Delecluse HJ, Vuillaume M, Lenoir GM, et al. Immunophenotypic and genotypic analysis of acquired immunodeficiency syndrome-related non-Hodgkin's lymphomas. Correlation with histologic features in 36 cases. French Study Group of Pathology for HIV-Associated Tumors. Am J Clin Pathol. 1994;101:773–82.
39. Kasamon YL, Ambinder RF. AIDS-related primary central nervous system lymphoma. Hematol Oncol Clin North Am. 2005;19:665–87.
40. Raphael M, Gentilhomme O, Tulliez M, Byron PA, Diebold J. Histopathologic features of high-grade non-Hodgkin's lymphomas in acquired immunodeficiency syndrome. The French Study Group of Pathology for Human Immunodeficiency Virus-Associated Tumors. Arch Pathol Lab Med. 1991;115:15–20.
41. Davi F, Delecluse HJ, Guiet P, Gabarre J, Fayon A, Gentilhomme O, et al. Burkitt-like lymphomas in AIDS patients: characterization within a series of 103 human immunodeficiency virus-associated non-Hodgkin's lymphomas. Burkitt's Lymphoma Study Group. J Clin Oncol. 1998;16:3788–95.
42. Bibas M, Castillo JJ. Current knowledge on HIV-associated plasmablastic lymphoma. Mediterr J Hematol Infect Dis. 2014;6:e2014064.
43. Nador RG, Cesarman E, Chadburn A, Dawson DB, Ansari MQ, Sald J, et al. Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpes virus. Blood. 1996;88:645–56.
44. Guillet S, Gerard L, Meignin V, Agbalika F, Cuccini W, Denis B, et al. Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution. Am J Hematol. 2016;91:233–7.
45. Tirelli U, Errante D, Dolcetti R, Gloghini A, Serraino D, Vaccher E, et al. Hodgkin's disease and human immunodeficiency virus infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and Tumors. J Clin Oncol. 1995;13:1758–67.
46. Clifford GM, Rickenbach M, Lise M, Dal Maso L, Battegay M, Bohlius J, et al. Hodgkin lymphoma in the Swiss HIV Cohort Study. Blood. 2009;113:5737–42.
47. Nador RG, Chadburn A, Gundappa G, Cesarman E, Said JW, Knowles DM. Human immunodeficiency virus (HIV)-associated polymorphic lymphoproliferative disorders. Am J Surg Pathol. 2003;27:293–302.
48. Bellan C, De Falco G, Lazzi S, Leoncini L. Pathologic aspects of AIDS malignancies. Oncogene. 2003;22:6639–45.
49. Pelicci PG, Knowles DM 2nd, Magrath I, Dalla-Favera R. Chromosomal breakpoints and structural alterations of the c-myc locus differ in endemic and sporadic forms of Burkitt lymphoma. Proc Natl Acad Sci U S A. 1986;83:2984–8.
50. Liapis K, Clear A, Owen A, Coutinho R, Greaves P, Lee AM, et al. The microenvironment of AIDS-related diffuse large B-cell lymphoma provides insight into the pathophysiology and indicates possible therapeutic strategies. Blood. 2013;122:424–33.
51. Ballerini P, Gaidano G, Gong JZ, Tassi V, Saglio G, Knowles DM, et al. Multiple genetic lesions in acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. Blood. 1993;81:166–76.
52. Okano M, Gross TG. A review of Epstein-Barr virus infection in patients with immunodeficiency disorders. Am J Med Sci. 2000;319:392–6.
53. Gaulard P, Swerdlow SH, Harris NL, Sundstrom C, Jaffe ES. Other iatrogenic immunodeficiency-associated lymphoproliferative disorders. WHO classification of tumours of haematopoietic and lymphoid tissues. 2016:462–4.
54. Kinlen L. Cancer epidemiology and prevention. 2nd ed. New York: Oxford University Press; 1996. p. 532–45.
55. Farrell RJ, Ang Y, Kileen P, O'Briain DS, Kelleher D, Keeling PW, et al. Increased incidence of non-Hodgkin's lymphoma in inflammatory bowel disease patients on immunosuppressive therapy but overall risk is low. Gut. 2000;47:514–9.
56. Kotlyar DS, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, et al. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. Clin Gastroenterol Hepatol. 2015;13:847–58.e4; quiz e48–50
57. Pina-Oviedo S, Miranda RN, Medeiros LJ. Cancer therapy-associated lymphoproliferative disorders: an under-recognized type of immunodeficiency-associated lymphoproliferative disorder. Am J Surg Pathol. 2018;42:116–29.
58. Hasserjian RP, Chen S, Perkins SL, de Leval L, Kinney MC, Barry TS, et al. Immunomodulator agent-related lymphoproliferative disorders. Mod Pathol. 2009;22:1532–40.
59. Bernatsky S, Clarke AE, Suissa S. Hematologic malignant neoplasms after drug exposure in rheumatoid arthritis. Arch Intern Med. 2008;168:378–81.
60. Salloum E, Cooper DL, Howe G, Lacy J, Tallini G, Crouch J, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. J Clin Oncol. 1996;14:1943–9.
61. Abruzzo LV, Rosales CM, Medeiros LJ, Vega F, Luthra R, Manning JT, et al. Epstein-Barr virus-positive B-cell lymphoproliferative disorders arising in immunodeficient patients previously treated with fludarabine for low-grade B-cell neoplasms. Am J Surg Pathol. 2002;26:630–6.
62. Mustjoki S, Ekblom M, Arstila TP, Dybedal I, Epling-Burnette PK, Guilhot F, et al. Clonal expansion of T/NK-cells during tyrosine kinase inhibitor dasatinib therapy. Leukemia. 2009;23:1398–405.
63. Ozawa MG, Ewalt MD, Gratzinger D. Dasatinib-related follicular hyperplasia: an underrecognized entity with characteristic morphology. Am J Surg Pathol. 2015;39:1363–9.
64. Giard C, Avenel-Audran M, Croue A, Verret JL, Martin L. Primary cutaneous Epstein-Barr virus-associated B-cell lymphoma arising at the site of subcutaneous injections of methotrexate. J Clin Oncol. 2010;28:e717–8.
65. Hoshida Y, Xu JX, Fujita S, Nakamichi I, Ikeda J, Tomita Y, et al. Lymphoproliferative disorders in rheumatoid arthritis: clinicopathological analysis of 76 cases in relation to methotrexate medication. J Rheumatol. 2007;34:322–31.
66. Bhamidipati PK, Jabbour E, Konoplev S, Estrov Z, Cortes J, Daver N. Epstein-Barr virus-induced CD30-positive diffuse large B-cell lymphoma in a patient with mixed-phenotypic leukemia treated with clofarabine. Clin Lymphoma Myeloma Leuk. 2013;13:342–6.
67. Loo EY, Medeiros LJ, Aladily TN, Hoehn D, Kanagal-Shamanna R, Young KH, et al. Classical Hodgkin lymphoma arising in the setting of iatrogenic immunodeficiency: a clinicopathologic study of 10 cases. Am J Surg Pathol. 2013;37:1290–7.
68. Dojcinov SD, Venkataraman G, Raffeld M, Pittaluga S, Jaffe ES. EBV positive mucocutaneous ulcer–a study of 26 cases associated with various sources of immunosuppression. Am J Surg Pathol. 2010;34:405–17.
69. Roberts TK, Chen X, Liao JJ. Diagnostic and therapeutic challenges of EBV-positive mucocutaneous ulcer: a case report and systematic review of the literature. Exp Hematol Oncol. 2015;5:13. https://doi.org/10.1186/s40164-016-0042-5.
70. Gibson SE, Swerdlow SH, Craig FE, Surti U, Cook JR, Nalesnik MA, et al. EBV-positive extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue in the posttransplant setting: a

distinct type of posttransplant lymphoproliferative disorder? Am J Surg Pathol. 2011;35:807–15.
71. Natkunam Y, Goodlad JR, Chadburn A, de Jong D, Gratzinger D, Chan JK, et al. EBV-positive B-cell proliferations of varied malignant potential: 2015 SH/EAHP workshop report-part 1. Am J Clin Pathol. 2017;147:129–52.
72. O'Neill BP, Vernino S, Dogan A, Giannini C. EBV-associated lymphoproliferative disorder of CNS associated with the use of mycophenolate mofetil. Neuro-Oncology. 2007;9:364–9.
73. Crane GM, Powell H, Kostadinov R, Rocafort PT, Rifkin DE, Burger PC, et al. Primary CNS lymphoproliferative disease, mycophenolate and calcineurin inhibitor usage. Oncotarget. 2015;6:33849–66.
74. Parakkal D, Sifuentes H, Semer R, Ehrenpreis ED. Hepatosplenic T-cell lymphoma in patients receiving TNF-alpha inhibitor therapy: expanding the groups at risk. Eur J Gastroenterol Hepatol. 2011;23:1150–6.