Immunodeficiency-Associated Lymphoproliferative Disorder

Juehua Gao and Yi-Hua Chen

Immunodeficiency-associated lymphoproliferative disorders (LPDs) can occur in the setting of HIV infection, after transplantation (posttransplant lymphoproliferative disorder, PTLD), or in other clinical conditions including primary immunodeficiency or the use of immunosuppressive drugs (iatrogenic immunodeficiency-associated LPD). LPDs in the setting of immunodeficiency share similar morphologic features, with a broad spectrum of findings from polymorphous lymphoplasmacytic proliferations to aggressive lymphoma. In patients diagnosed with an immunodeficiency-associated LPD, a staging bone marrow is recommended as part of the initial workup.

## Lymphoproliferative Disorders in HIV Patients

LPDs in HIV patients are heterogeneous and range from polyclonal hyperplastic lesions to aggressive lymphomas. At one end of the spectrum are the early and polymorphic lesions that typically show a heterogeneous cellular proliferation composed of small lymphocytes, plasma cells, and immunoblasts resembling polymorphic PTLD (Fig. 8.1). Bone marrow involvement by early and polymorphic LPDs may show features overlapping with reactive changes commonly seen in HIV-infected patients. The frequency of early and polymorphic LPDs in HIV patients is unknown, but they seem much less common than in the PTLD setting. At the other end of the spectrum is HIV-associated lymphoma, which includes lymphomas also occurring in immunocompetent patients, such as diffuse large B-cell lymphoma, Burkitt lymphoma, and Hodgkin lymphoma, as well as lymphomas occurring much more commonly in HIV patients, such as primary effusion lymphoma and plasmablastic

lymphoma. HIV-associated lymphomas are usually aggressive and often spread to the bone marrow; in some cases, the bone marrow may be the primary or initial diagnostic site (Figs. 8.2, and 8.3) [1, 2]. The morphologic features of HIV-associated lymphomas are similar to their counterparts in the immunocompetent population, but Epstein-Barr virus (EBV) is more often positive. HIV-related Hodgkin lymphoma, for example, is almost always associated with EBV [3]. The reported frequency of bone marrow involvement by HIV-related lymphoma varies. In one of the largest series, the German HIV Lymphoma Cohort reported bone marrow involvement in 25 (16%) of 154 diffuse large B-cell lymphomas, 32 (31%) of 103 Burkitt lymphomas, and 6 (18%) of 34 plasmablastic lymphomas [4]. Primary effusion lymphoma almost always occurs in immunodeficient patients, with universal association with human herpesvirus 8 (HHV8) infection and common EBV coinfection, but bone marrow involvement is uncommon (11%) [5]. The features of bone marrow involvement by HIV-associated LPD are summarized in Table 8.1.

## Posttransplant Lymphoproliferative Disorders

PTLD comprises another major group of immunodeficiency-associated LPDs and includes four categories based on the current WHO classification: early lesions, polymorphic PTLD, monomorphic PTLD (B- and T-cell lymphomas), and classical Hodgkin lymphoma (Table 8.2). The frequency of bone marrow involvement by PTLDs after solid organ transplant varies from 14% to 40% [6–13]; monomorphic (23.5%) and polymorphic (15.7%) types predominate [13]. The bone marrow involvement by monomorphic PTLD can be either B-cell or T-cell type (Fig. 8.4) [13]. Among all types of monomorphic PTLDs involving the bone marrow, diffuse large B-cell lymphoma is the most common, but other types such as Burkitt lymphoma, plasmacytoma-like lesions,

J. Gao (✉) • Y.-H. Chen
Department of Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
e-mail: j-gao@northwestern.edu; y-chen5@northwestern.edu
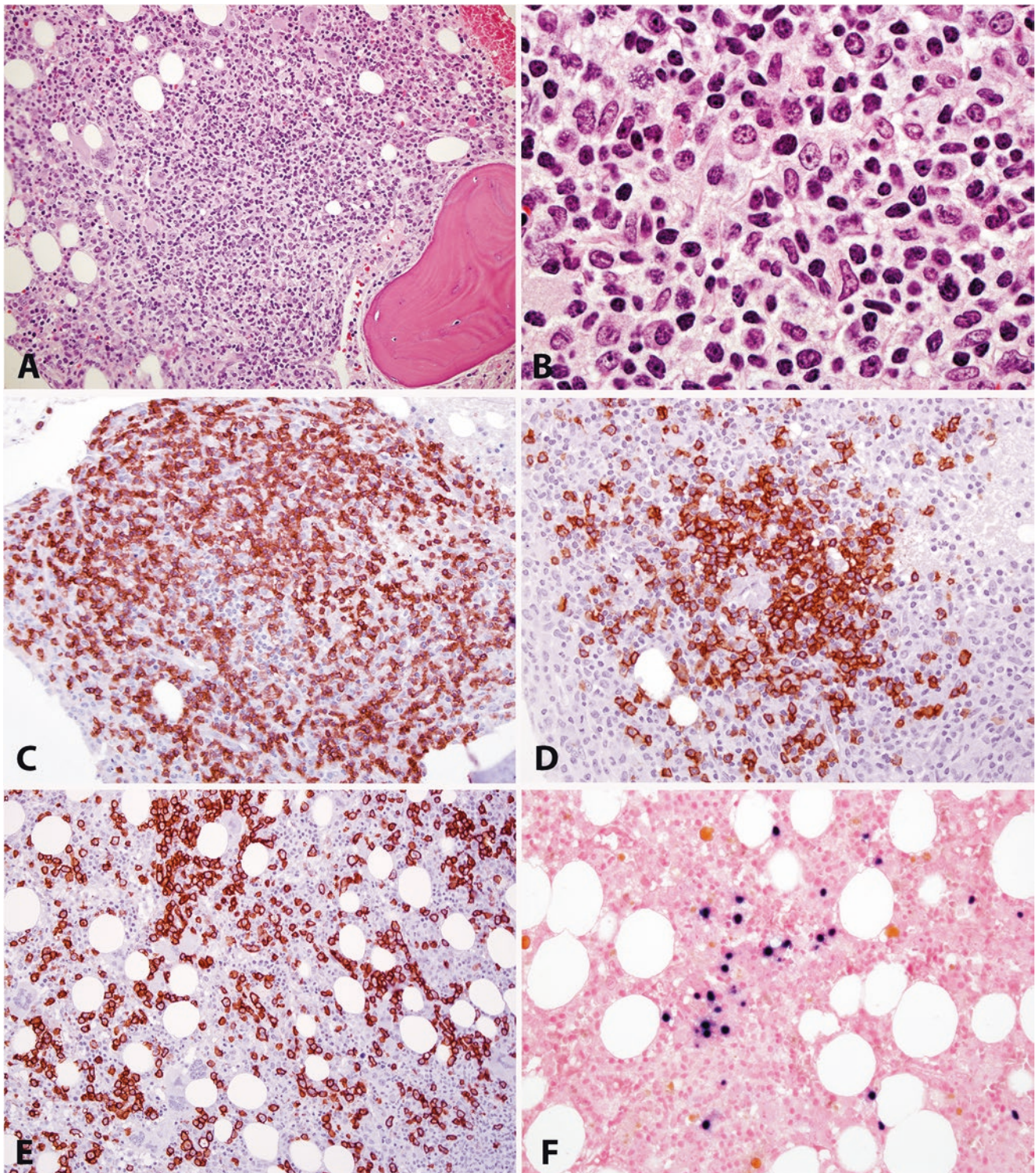
Fig. 8.1 Polymorphic lymphoid proliferation involving the bone marrow in a 43-year-old woman with HIV infection. (**a**) The bone marrow core biopsy shows multiple lymphoid aggregates and interstitial lymphoplasmacytic infiltrates. (**b**) The infiltrate is composed of a mixture of lymphocytes, plasma cells, and histiocytes. The lymphocytes are predominantly small to intermediate in size, but occasional large immunoblasts are also present. (**c**) The majority of lymphocytes are CD3+ T cells. (**d**) CD20+ B cells are present but are much less numerous than T cells. (**e**) Frequent plasma cells are seen and highlighted by CD138 staining. These plasma cells show a polytypic staining pattern for cytoplasmic kappa and lambda light chains (not shown). (**f**) In situ hybridization for EBV-encoded RNA (EBER) shows scattered positive cells. Flow cytometric analysis revealed a predominant T-cell population without immunophenotypic abnormality except for an inverted CD4-to-CD8 cell ratio. The B-cell population showed a polyclonal staining pattern for surface kappa and lambda light chains
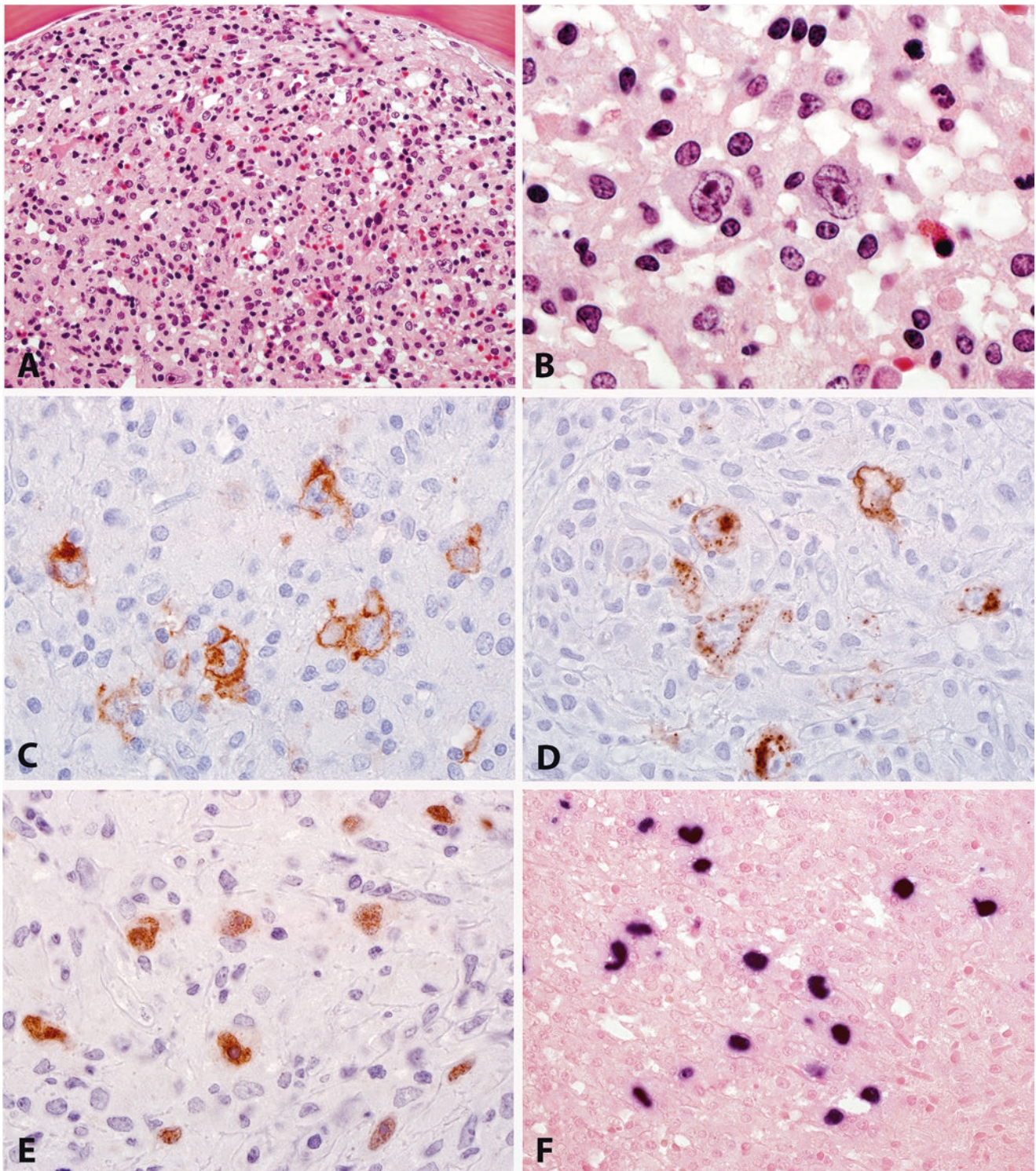
Fig. 8.2 Classical Hodgkin lymphoma identified initially in a bone marrow biopsy of a 40-year-old man with HIV infection. (**a**) The bone marrow is focally effaced by fibrosis and a polymorphous infiltrate composed of small lymphocytes, histiocytes, plasma cells, eosinophils, and scattered large, atypical cells. (**b**) The large cells contain large nuclei and prominent eosinophilic nucleoli, consistent with Hodgkin cells. The large cells are positive for CD30 (**c**), CD15 (**d**), PAX-5 (**e**), and EBER (**f**) and negative for CD45, CD20, and CD3 (not shown)
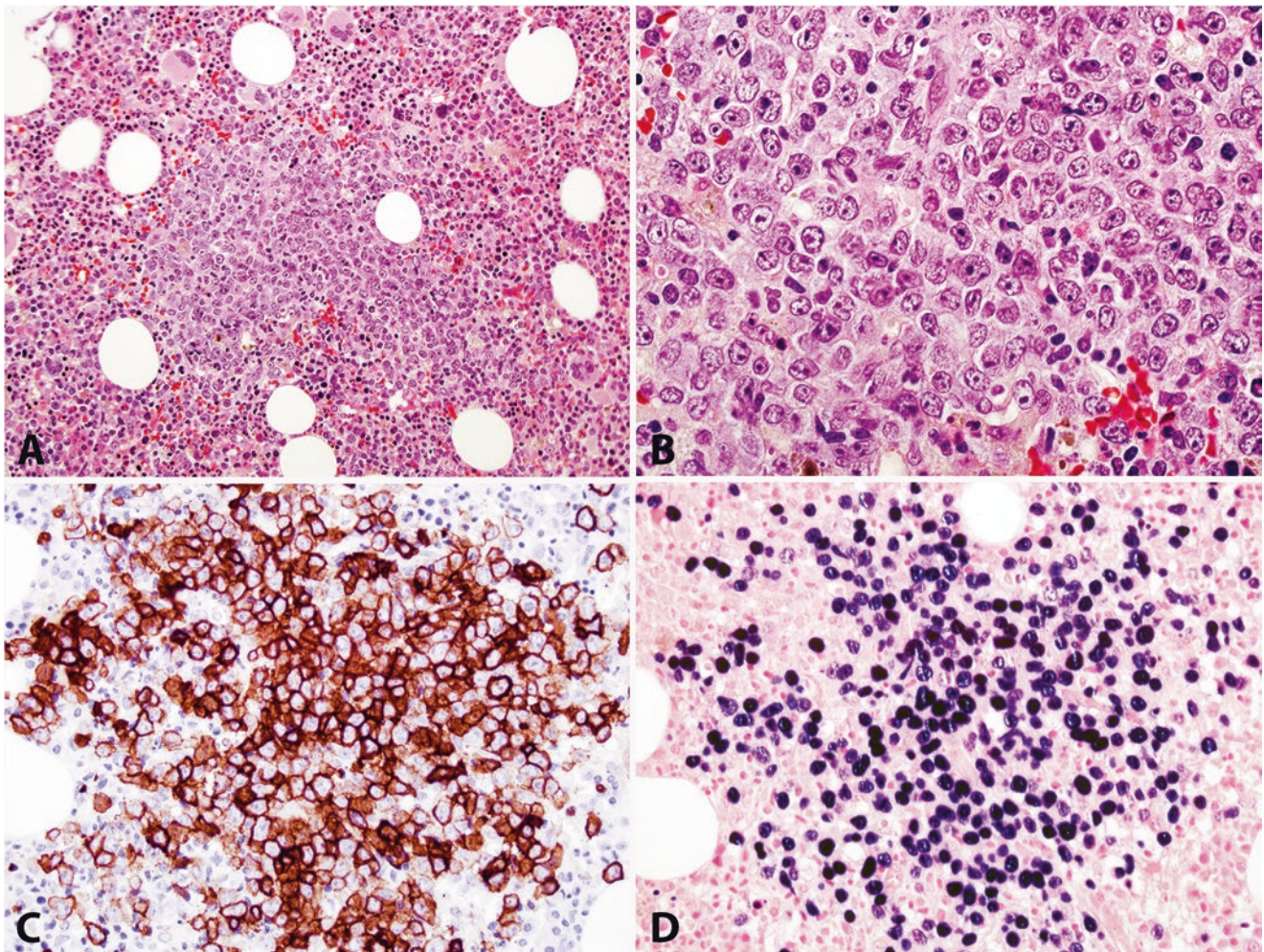
Fig. 8.3 High-grade B-cell lymphoma involving the bone marrow in a 50-year-old woman with HIV infection and a newly diagnosed high-grade B-cell lymphoma with *MYC* gene rearrangement. (a) The bone marrow core biopsy shows lymphoid aggregates composed of large lymphoid cells. (b) The large cells have distinct to prominent nucleoli and ample amphophilic cytoplasm. The large cells are positive for CD20 (**c**) and EBER (**d**). Cytogenetic studies revealed a complex karyotype with three separate clones, and each clone had t(8;14) (q24,1;q32)

plasma cell myeloma, and rare NK/T-cell lymphoma have also been reported) (Figs. 8.5, 8.6, 8.7, and 8.8) [13]. Neither EBV status, based on in situ hybridization for EBV-encoded RNA (EBER), nor the type of organ transplanted is statistically significant in predicting the presence or absence of bone marrow involvement [13]. The morphologic findings of bone marrow involvement by PTLD vary from lymphoid aggregates, interstitial infiltration, and increased plasma cells to architectural, destructive lesions consisting of sheets of atypical lymphocytes [13–15]. The bone marrow involvement by early lesions or polymorphic PTLD can be subtle and may overlap with reactive or infectious conditions. The positive EBER is seen in scattered hematopoietic cells or in aggregates, co-localized with lymphocytes, plasmacytoid lymphocytes, or plasma cells [14]. In cases with subtle morphologic findings such as small lymphoid aggregates and mild plasmacytosis, the presence of rare EBER-positive cells could be expected in posttransplant immunodeficiency; this is not considered definitive evidence of bone marrow involvement by PTLD [14]. However, the presence of cytologic atypia, extensive necrosis or increased large transformed cells, and detection of clonality or chromosomal aberrancies favor a lymphoproliferative process [14, 16]. The morphologic findings of monomorphic PTLD are similar to the corresponding lymphoma occurring in immunocompetent patients; the bone marrow involvement ranges from subtle interstitial infiltrates highlighted by immunohistochemistry to overt nodular or diffuse infiltrates [13, 15].

Table 8.1 Bone marrow involvement by HIV-associated lymphoproliferative disorders

Type of lesions	Histologic subtypes	Frequency of involvement	Viral status	Morphology
Polymorphic lymphoid proliferation	Polymorphous lymphoid proliferation	Less common than in PTLD setting	Often EBV+	A range of lymphoid cells from small plasmacytoid to immunoblasts
Lymphomas also occurring in immunocompetent patients	Diffuse large B-cell lymphoma	12–16% [4, 19]	30–90% EBV+ [20]	Numerous centroblasts or immunoblasts with plasmacytoid features
	Burkitt lymphoma	31% [4]	30–70% EBV+ [20]	Similar to Burkitt lymphoma in immunocompetent patients, some with more plasmacytoid features
	Classical Hodgkin lymphoma	14% [2]	Nearly all EBV+ [20]	Space-occupying lesions with polymorphous infiltrates and Reed-Sternberg cells or variants
Lymphomas occurring specifically in HIV patients	Primary effusion lymphoma	11% [5]	Universally HHV8+, commonly EBV+	Sheets of large cells with plasmablastic or immunoblastic morphology
	Plasmablastic lymphoma	6–39% [21, 22]	91% EBV+ [21]	Sheets of large cells with plasmablastic morphology

EBV, Epstein-Barr virus; HHV8, human herpesvirus 8; PTLD, posttransplant lymphoproliferative disorder

Table 8.2 Bone marrow involvement by posttransplant lymphoproliferative disorders

Type of lesions	Frequency of involvement	EBV status	Morphology	Treatment and outcome
Early lesions	Rare	Virtually all EBV+	Lymphoid aggregates; polyclonal plasma cell hyperplasia	Tend to regress spontaneously or with reduction of immunosuppressant
Polymorphic PTLD	15.7% [13]	Majority EBV+	Polymorphous proliferation with a full spectrum of B-cell differentiation admixed with immunoblasts	Tapering of immunosuppressant with or without rituximab
Monomorphic PTLD	23.5% [13]	EBV+/−	Diffuse large B-cell lymphoma, Burkitt lymphoma, plasmacytoma-like lesion, plasma cell myeloma, NK/T-cell lymphoma	Chemotherapy; bone marrow involvement is associated with worse outcomes
Classical Hodgkin lymphoma	Rare	Majority EBV+	Morphologic features similar to classical Hodgkin lymphoma in immunocompetent patients	Chemotherapy; bone marrow involvement is associated with worse outcomes

EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder

## Iatrogenic Immunodeficiency-Related Disorders

Analogous to what has been observed in PTLDs, iatrogenic immunodeficiency-associated LPDs may occur in patients with rheumatologic diseases or inflammatory conditions treated with immune modulatory drugs (Fig. 8.9).

Immunodeficiency-associated LPDs arising in clinical settings other than transplantation are morphologically similar to PTLDs, though extranodal involvement is frequent and bone marrow involvement is uncommon [17, 18]. Overall, the information regarding bone marrow involvement by immunodeficiency-associated LPDs in non-transplant patients is limited.
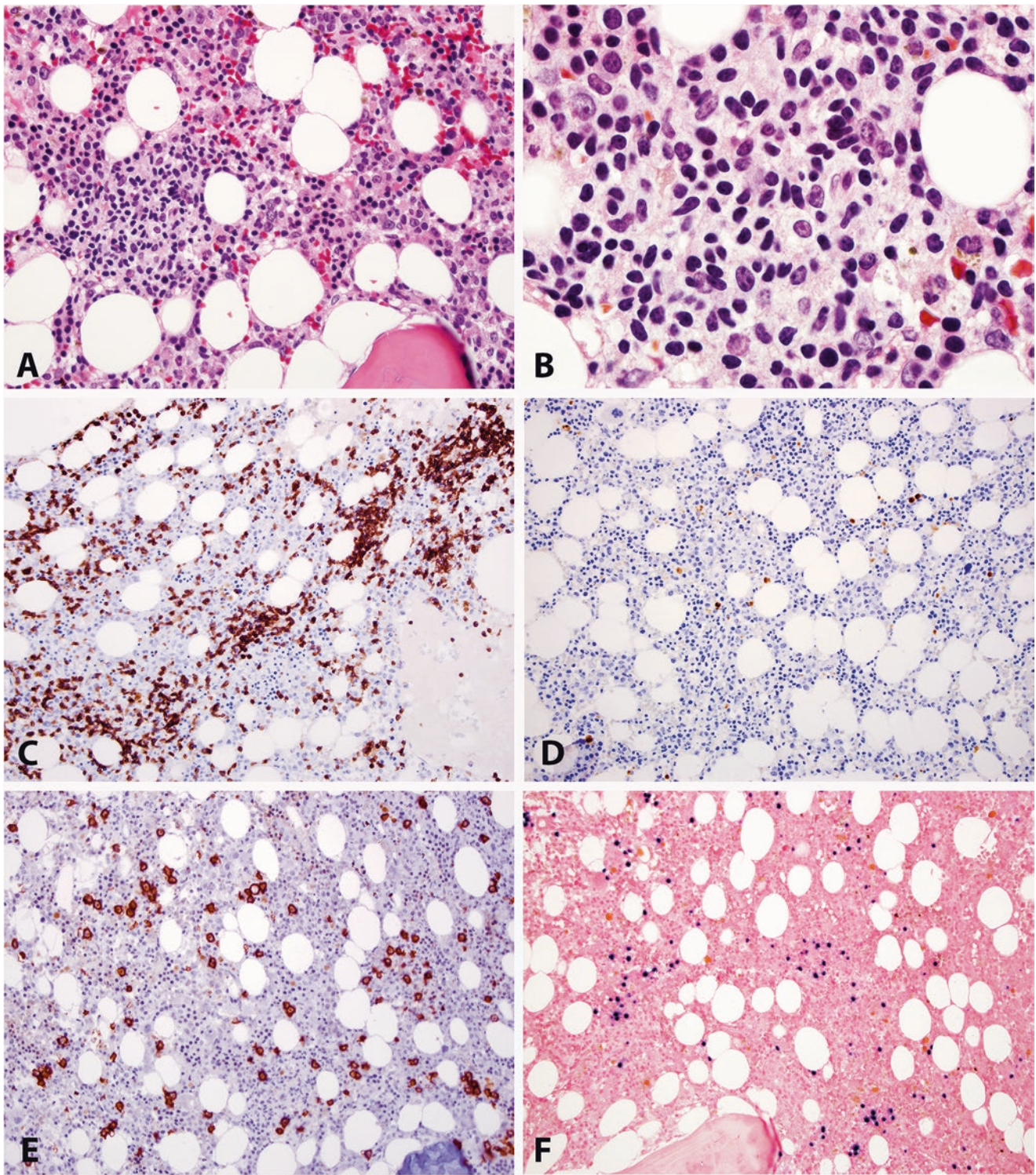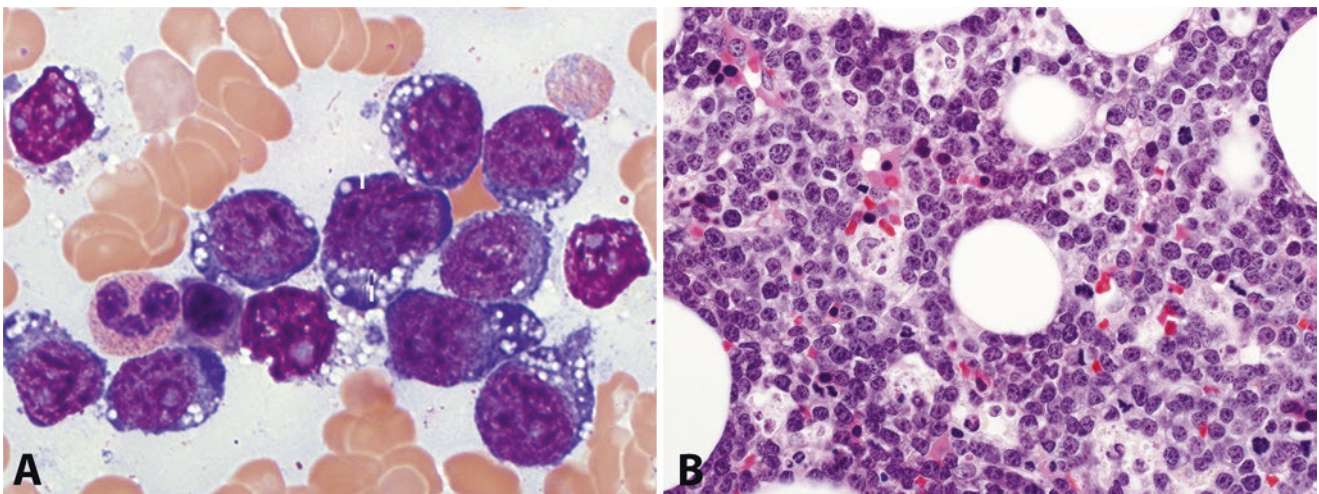
Fig. 8.4 Polymorphic posttransplant lymphoproliferative disorder (PTLD) involving the bone marrow in a 32-year-old man with history of hematopoietic stem cell transplantation for aplastic anemia 4 months ago, now with increasing lymphadenopathy and EBV titers. (**a**) The bone marrow core biopsy shows an abnormal lymphoid infiltrate in aggregates and with an interstitial infiltration pattern. (**b**) The lymphocytes are predominantly small; admixed histiocytes and occasional plasma cells are present. (**c**) Immunostaining for CD3 shows that the lymphoid infiltrate is composed predominantly of CD3+ T cells. (**d**) Very rare CD20+ B cells are seen (<1%). (**e**) Increased plasma cells (CD138+) are also present but show a polytypic staining pattern for cytoplasmic kappa and lambda light chains. (**f**) In situ hybridization for EBER shows scattered positive cells throughout the bone marrow section. Flow cytometric analysis identified a very small, monotypic B-cell population (<1% of total cells) that was negative for CD5 and CD10. The T cells showed an inverted CD4-to-CD8 cell ratio
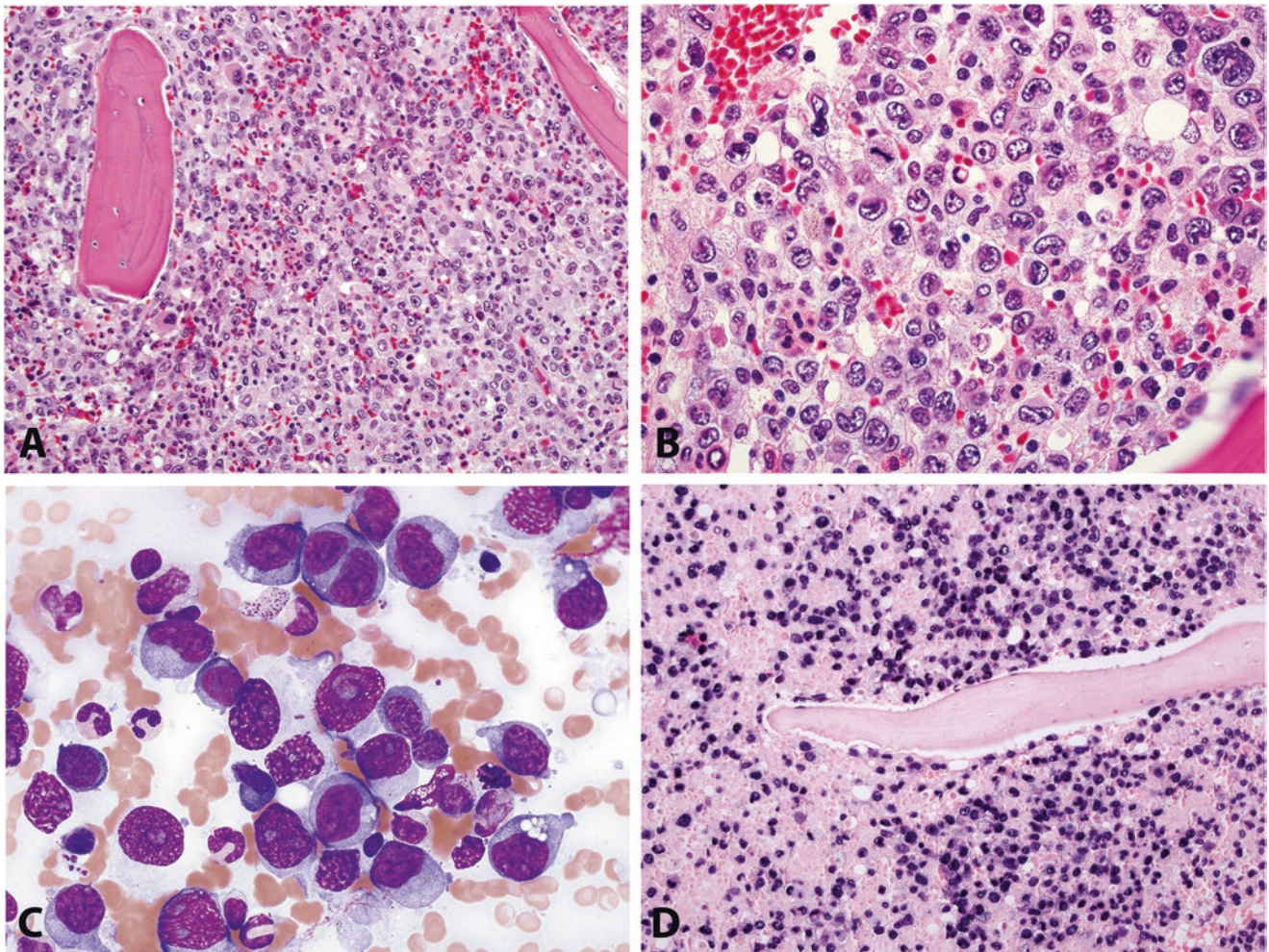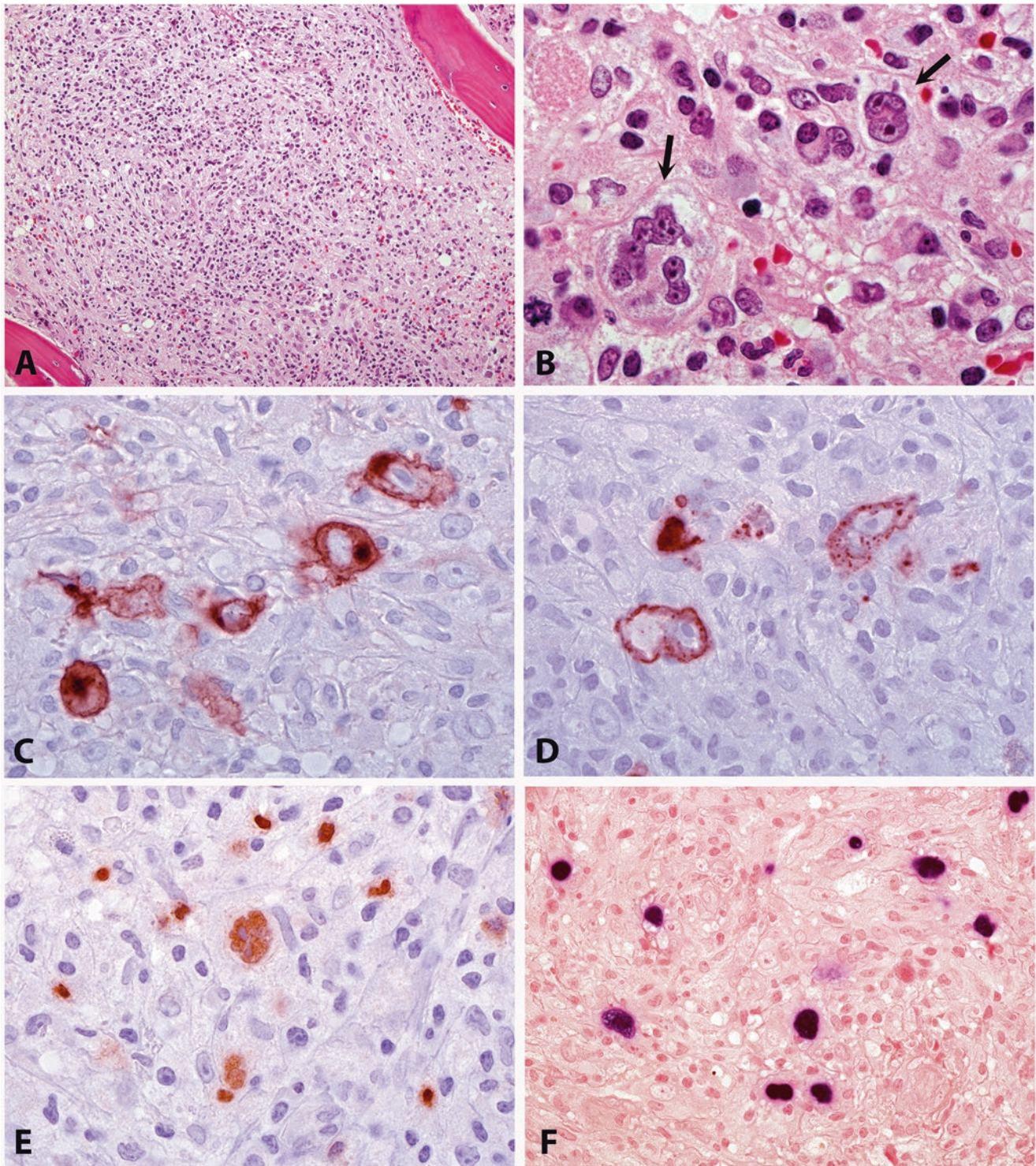
Fig. 8.5 Monomorphic posttransplant lymphoproliferative disorder (PTLD), diffuse large B-cell lymphoma (DLBCL), involving the bone marrow in a 23-year-old man with history of heart transplantation for restrictive cardiomyopathy 20 years ago. (**a**) The bone marrow core biopsy shows diffuse infiltration by large lymphoid cells. (**b**) The large cells have large nuclei, prominent nucleoli, and ample amphophilic cytoplasm. (**c**) The bone marrow aspirate smear shows large lymphoid cells with large nuclei, prominent nucleoli, and abundant basophilic cytoplasm. (**d**) The large cells are positive for EBER by in situ hybridization

Fig. 8.6 Monomorphic posttransplant lymphoproliferative disorder (PTLD), Burkitt lymphoma, involving the bone marrow in a 65-year-old man with history of orthotopic renal transplantation 6 years ago and a recent diagnosis of monomorphic PTLD, Burkitt lymphoma, in a lymph node biopsy. (**a**) The bone marrow aspirate smear shows medium-sized lymphocytes with high nuclear-to-cytoplasmic ratio and deeply basophilic and vacuolated cytoplasm. (**b**) The bone marrow core biopsy shows a lymphoid infiltrate composed of a monotonous population of medium-sized lymphocytes with admixed scattered, tingible body macrophages, with a "starry sky" appearance. EBER is negative (not shown). Cytogenetic analysis is positive for t(2;8)(p11.2;q24.1), a variant *MYC* gene rearrangement involving the *IGK* gene

Fig. 8.7 Monomorphic posttransplant lymphoproliferative disorder (PTLD), classical Hodgkin lymphoma type, involving the bone marrow in a 42-year-old man with history of orthotopic liver transplantation for autoimmune hepatitis with new-onset anemia and thrombocytopenia. (**a**) The bone marrow core biopsy shows extensive polymorphous cellular infiltrates in a background of fibrosis. (**b**) There are occasional mononuclear Hodgkin cells and bilobed or multinucleated Reed-Sternberg cells (*arrows*) in a background of fibrosis and inflammatory infiltrates composed of small lymphocytes, plasma cells, histiocytes, and occasional eosinophils. The large cells are positive for CD30 (**c**), CD15 (**d**), PAX-5 (**e**), and EBER (**f**)
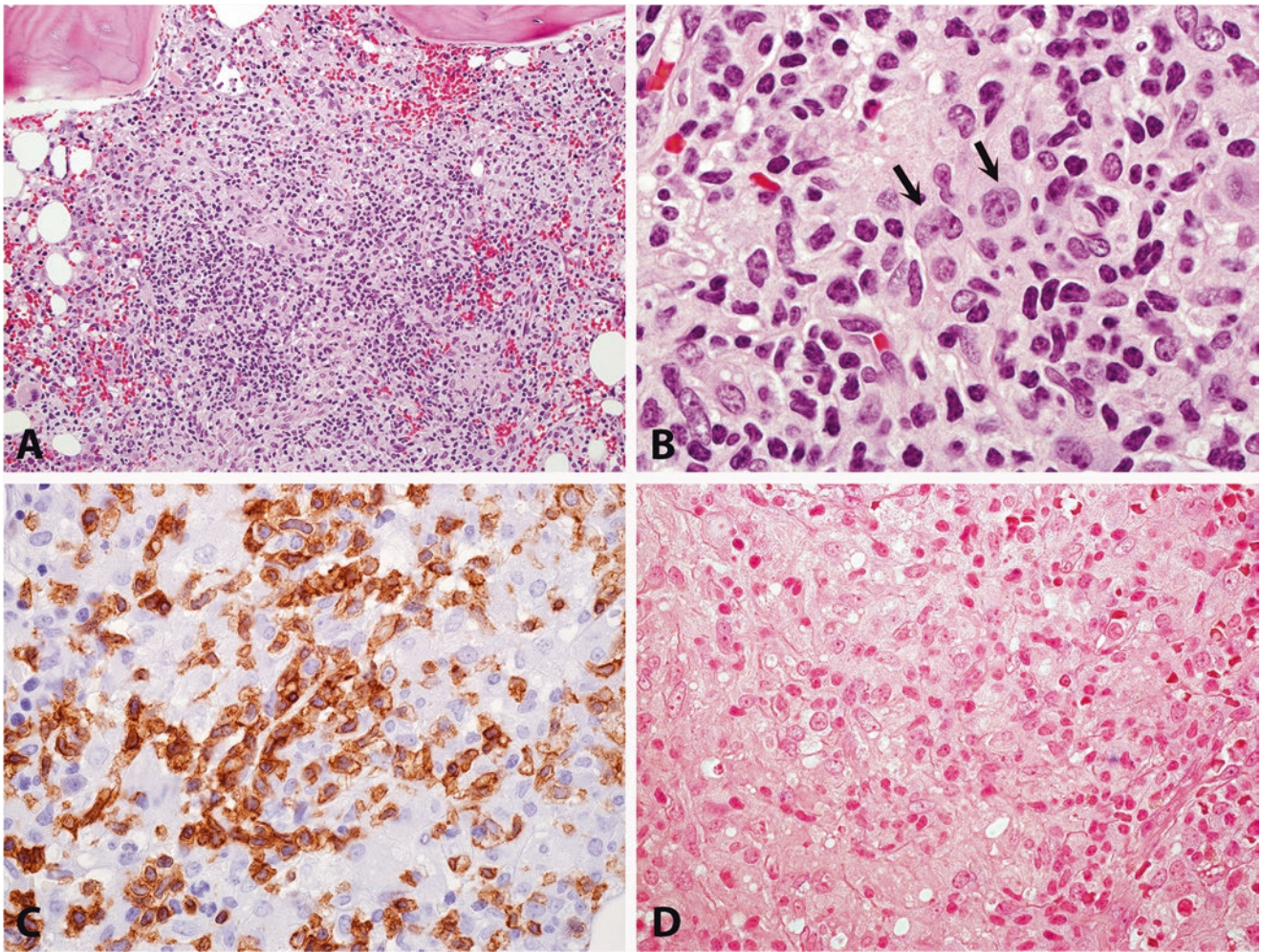
Fig. 8.8 Monomorphic posttransplant lymphoproliferative disorder (PTLD) , peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), involving the bone marrow in a 50-year-old man with a history of renal transplantation 15 months ago for end-stage renal disease secondary to hypertension and a recently diagnosed PTLD, PTCL-NOS, in a lymph node biopsy. (**a**) The bone marrow core biopsy shows multifocal lymphohistiocytic infiltrates. (**b**) The lymphocytes are predominantly small with irregular nuclei; rare Hodgkin-like cells are also present (arrows). (**c**) The vast majority of lymphocytes are CD3+ T cells. (**d**) EBER is negative. Flow cytometric analysis showed T cells with loss of CD7, similar to the lymph node biopsy
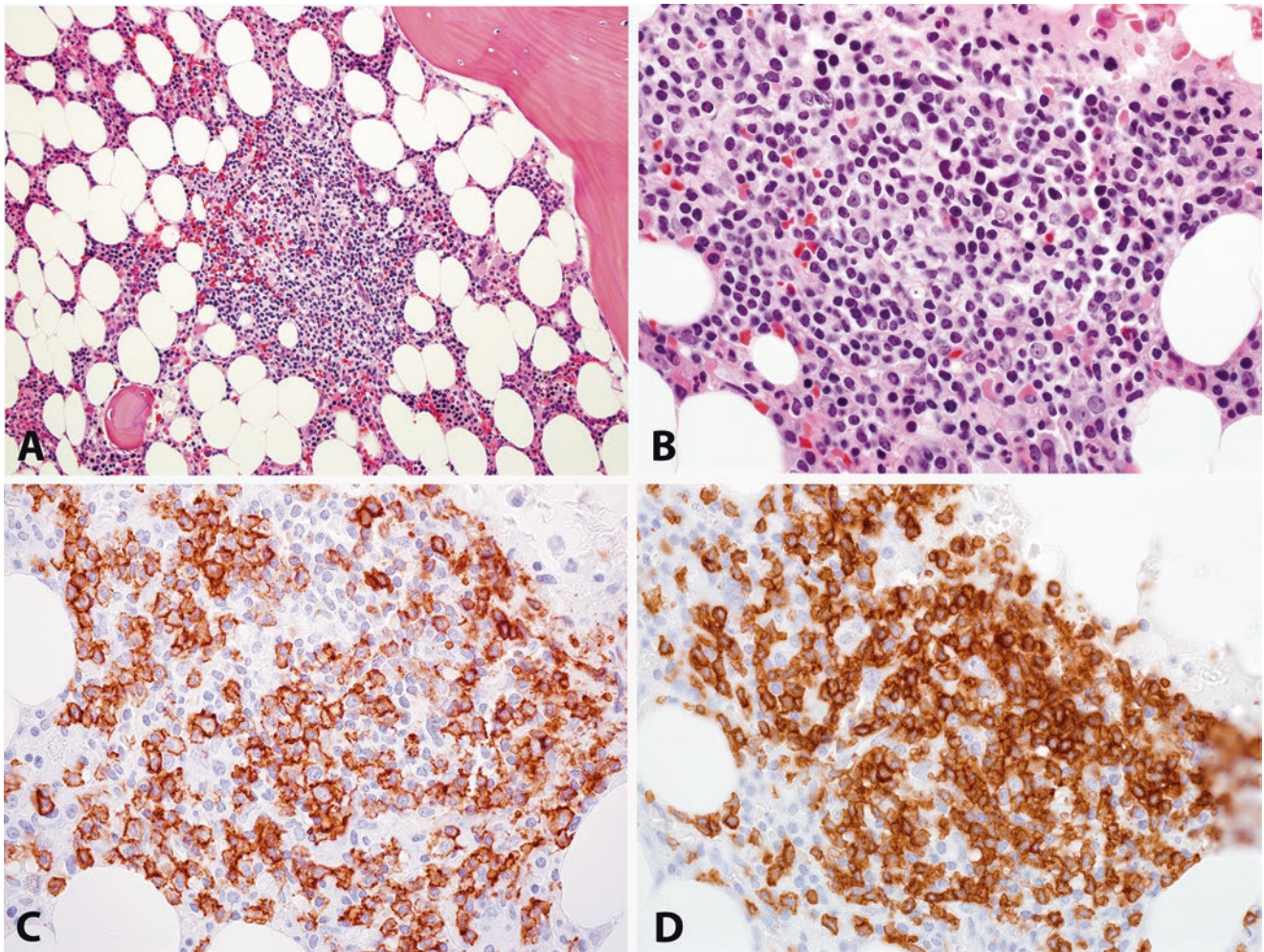
Fig. 8.9 Polymorphic-type LPD involving the bone marrow in a 47-year-old woman with a history of systemic lupus erythematosus treated with methotrexate and a recent diagnosis of polymorphic-type iatrogenic immunodeficiency-associated lymphoproliferative disorder in a lymph node biopsy. (**a**) The bone marrow core biopsy shows lymphoid aggregates and interstitial infiltration of lymphocytes with admixed histiocytes. (**b**) The lymphocytes are predominantly small, with slightly irregular nuclei and scant cytoplasm. (**c**) Immunostaining for CD20 shows many B cells ranging from small to medium in size. (**d**) Abundant CD3+ T cells are present. Occasional EBER+ cells were seen (not shown). Flow cytometric analysis did not identify monotypic B cells or immunophenotypically abnormal T cells

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