Chapter 11
Lymphomatoid Granulomatosis

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11.1 Introduction

Lymphomatoid granulomatosis (LG) is a rare, Epstein-Barr virus (EBV)-positive, B-cell lymphoproliferative disorder often accompanied by an exuberant reactive but cytotoxic T-cell infiltrate. The density of the T-cell infiltrate led to the initial impression that LG was a T-cell malignancy. Also, LG used to be included under the rubric of angiocentric lymphomas and shares many features with nasal-type, extranodal, natural killer (NK)/T-cell lymphoma (NKL). Both LG and NKL can present in the airways/nasal cavity, both are associated with an angiocentric, angiodestructive, and cytotoxic lymphoid infiltrate, and both are associated with EBV infection. However, the neoplastic, EBV-infected lymphoid cells of LG are of B-cell lineage and NK cell lineage in NKL. A broad clinical and pathologic spectrum is observed for LG, ranging from indolent and regressive disease to an aggressive large B-cell lymphoma. Consequently, controversy still surrounds the precise nosologic designation of LG as a reactive, inflammatory versus a neoplastic lymphoid process. Some cases of LG would be well characterized as immunosupression-related or posttransplant lymphoproliferative disorders and reduction of immunosuppression in many of these cases has been associated with resolution of disease. Other cases require aggressive chemotherapeutic agents to halt disease progression.

11.2 Pathogenesis

Lymphomatoid granulomatosis represents an EBV-driven B-cell lymphoma resulting in recruitment and activation of cytotoxic, CD8-positive T-lymphocytes. A remarkably low number of neoplastic B-cells might be observed in a given LG infiltrate and it is the non-neoplastic, cytotoxic T-lymphocytes that mediate vascular destruction and tissue necrosis.

S.M. Ansell (ed.), *Rare Hematological Malignancies.*

11.3 Clinical Features

Nodular mass lesions predominate and are characteristically angiocentric and angiodestructive, which frequently results in necrosis of affected tissue. The most common sites of involvement are the lungs (great majority of patients affected during the course of the disease). Other commonly involved sites include the skin (25–50%), kidney (30–40%), liver (29%), central nervous system (CNS) (26%), upper respiratory system, and peripheral nervous system (PNS) (1–4). Spleen, lymph node, and gastrointestinal involvement are less common (<20% of cases) (1).

Disease onset is in the fifth to sixth decade of life for the majority of patients; however, it rarely presents in childhood immunodeficiency states (5, 6). Males are more commonly affected than females (ratio 2:1). The clinical course of LG varies widely from a "benign" or regressing indolent process to an aggressive, rapidly progressive disease. Approximately 15–25% of patients might have the disease resolve spontaneously; however, mortality rates approach 65% in previously published series. Common causes of death include extensive destruction of pulmonary parenchyma, infection, development of an aggressive large B-cell lymphoma, and CNS disease (1, 2).

Patients might present with lung involvement (cough, dyspnea, and chest pain), and constitutional symptoms occur in 35–58% of patients (fever, weight loss, myalgias, and neurological symptoms) (1, 7). Varying sized pulmonary nodules are typical and most often involve the mid and lower lung fields. Larger nodules might demonstrate central necrosis. Signs and symptoms of mass lesions might also occur elsewhere depending on the extent of involvement. Ataxia, hemiparesis, and

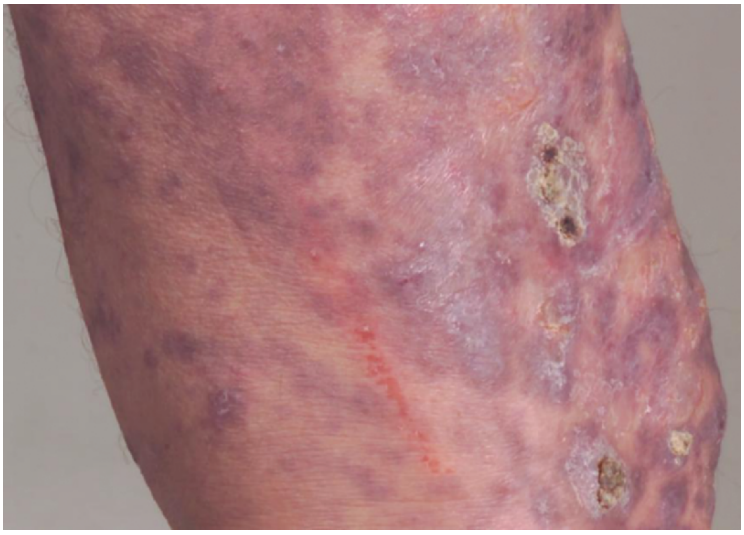

Figure 11.1 Cutaneous LG involving skin of lateral thigh and knee. Note indurated violaceous to focally necrotic plaques and nodules

seizures might accompany CNS involvement. Although hepatic and renal lesions are fairly frequent, the lesions themselves are usually asymptomatic and are only identified on radiographic imaging (4). Skin involvement by LG usually manifests as indurated, red nodules or plaques (Figure 11.1). Necrotic skin ulceration might also be observed and results from the attendant vascular destruction.

Patients with underlying immunodeficiency are at increased risk of developing LG. Predisposing immunodeficient states include history of organ transplant, HIV, Wiskott-Aldrich syndrome, other preceding lymphoproliferative disorders, and immunosuppressive medications. Upon close examination, most patients without an underlying specific immunodeficiency will manifest decreased immune function. Defects in cytotoxic T-cell function or reduced numbers of CD8+ T-cells have been implied. Decreased cellular immunity is important in propagating the disease by incomplete eradication of EBV and the EBV-infected B-cell clone (4).

The differential diagnosis of LG includes Wegener's granulomatosis (WG), angiocentric NK/T-cell lymphoma, posttransplant lymphoproliferative disease (LPD), as well as other Hodgkin's and non-Hodgkin's lymphomas. Table 11.1 lists the distinctive clinical and histologic differences among these entities (4, 11).

Table 11.1 Differential Diagnosis and Distinguishing features of lymphomatic granulomatosis

	Lymphomatoid granulomatosis	Wegener's granulomatosis	NK/T-cell lymphoma	Posttransplant LPD	Hodgkin's lymphoma
Primary involvement	Lungs	Upper respiratory tract; lungs	Nasal cavity	Variable	Cervical Lymph Nodes, Mediastinum
Renal findings	Nodular mass lesions	Segmental glomerulonephritis	Rare	Might involve allograft	Rare
EBV association	Yes	No	Yes	Yes	Variable
Typical histology	Variable number of EBV-positive atypical B-cells	Necrotizing granuloma formation	Sheets of atypical cells	Variable (early, pleomorphic, monomorphic)	Occasional multinucleate; Hodgkin and Reed-Sternberg cells
Angiocentric, angiodestructive	Yes	Yes	Yes	No	No
Background inflammatory infiltrate	Predominantly T-cells; eosinophils and neutrophils rare	Prominent multinucleate giant cells and neutrophils	Usually mixed	Predominantly plasmacytoid B-cells	Usually mixed with numerous eosinophils
Neoplastic cell phenotype	CD20+	N/A	CD2+ CD56+	Usually CD20+	CD15+ CD30+

11.4 Diagnosis

Definitive diagnosis of LG requires careful clinical workup and tissue biopsy. Open lung biopsies are recommended, as only approximately 30% of transbronchial biopsies are diagnostic [8]. Histologically, LG is characterized by varying numbers of large atypical CD20-positive B-cells set within a nodular polymorphous inflammatory cell background (Figure 11.2). The inflammatory milieu includes small lymphocytes, plasma cells, histiocytes (some might contain karyorrhectic debris), and larger reactive lymphocytes. Numerous CD3-positive T-cells are usual, and consist of an admixture of CD4 and CD8-positive cells (Figure 11.3). The inflammatory infiltrate is generally centered around bronchovascular structures in the lung and perivascularly in other sites. EBV is demonstrated within the large atypical B-cells by *in situ* hybridization studies, and these cells might resemble immunoblasts or Hodgkin cells. Occasional multinulcleate cells might also be seen. Vascular damage by neoplastic and non-neoplastic lymphoid cells is remarkable and includes transmural lymphocytic infiltration and necrosis of vessel walls. Associated coagulative tissue necrosis is common and was observed in 93% of cases in one study (7). Well-formed granulomas are not present (1, 4, 7–9). Biopsies of involved skin usually demonstrate a dense perivascular, often angiodestructive lymphohistiocytic infiltrate within the mid to deep dermis (Figure 11.4). Neoplastic EBV-positive B-lymphocytes might be rare or absent in LG skin lesions. Therefore,

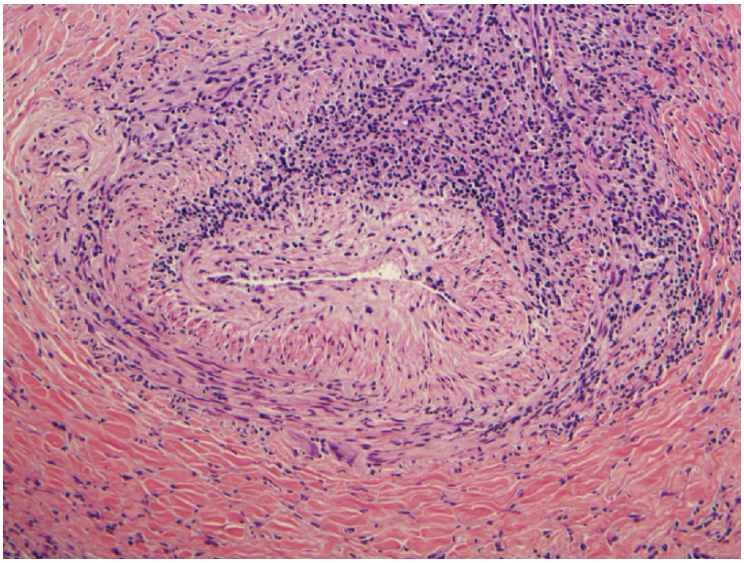

Figure 11.2 Pulmonary LG. An angioinvasive lymphocytic infiltrate composed of predominantly small cells (T-cells by immunophenotyping) is present (H&E, 20×)

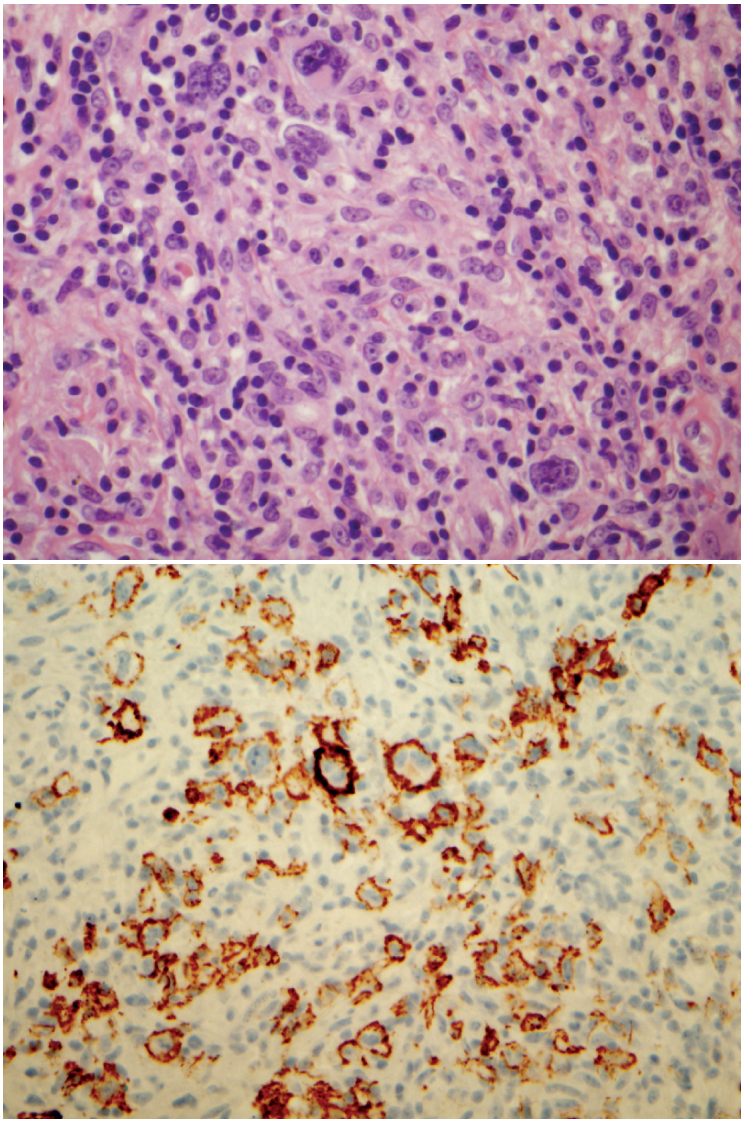

Figure 11.3 Pulmonary LG. **(A)** Grade III lesion with several large severely atypical cells (Reed-Sternberg-like appearance) admixed with background small round lymphocytes (H&E, 60×). **(B)** The large cells were B-lymphocytes that showed positive immunoreactivity with CD20 (60×).

a diagnosis of LG is precarious for patients with skin lesions that histiologically resemble LG but do not have evidence of internal organ (usually lung) involvement. These patients require close longitudinal follow-up and repeat biopsy is often needed.

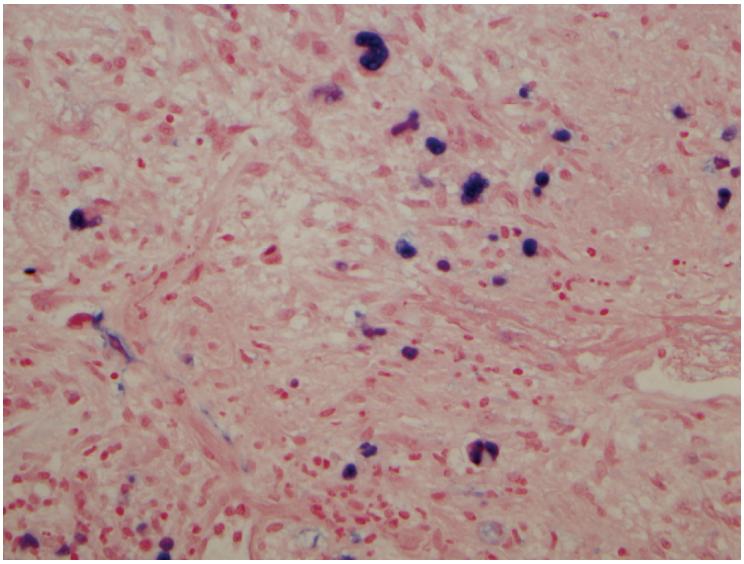

Figure 11.3 (continued) **(C)** Many of the large cells demonstrate EBV-positivity by *in-situ* hybridization (40×)

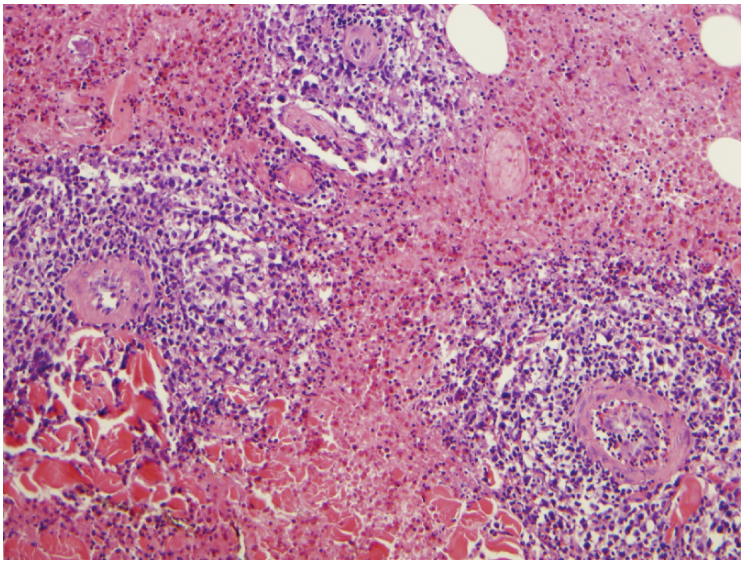

Figure 11.4 Cutaneous LG. Skin biopsy highlighting prominent angiocentric and angiodestructive nature of LG with surrounding tissue necrosis (H&E, 20×)

11.5 Prognosis

The clinical prognosis is variable in LG and poor prognostic findings include neurologic involvement and higher pathologic grade (1). Histologic grading of LG depends on the number of large atypical B-cells present in the infiltrate and on the degree of tissue necrosis. Grade I lesions contain a polymorphous angiocentric and angiodestructive lymphoid infiltrate with rare transformed EBV-positive lymphocytes (<5 per high-power field). Tissue necrosis is minimal. Grade II lesions also demonstrate a polymorphous infiltrate, including occasional transformed lymphoid cells, and EBV-positive cells are easily identified (5–20 per high-power field) by EBV *in situ* hybridization studies. Grade III disease is considered a subtype of diffuse large B-cell lymphoma with sheets of large EBV-infected pleomorphic B-cells present (>20 per high–power field). Extensive necrosis might be observed in grade III lesions (4, 8–11). Recurrent disease often demonstrates a higher histologic grade. Most cases of grade II and III lesions demonstrate monoclonal immunoglobulin gene rearrangement studies. Grade I lesions might be polyclonal, which might reflect low numbers of neoplastic B-cells or, in some cases, a truly polyclonal infiltrate.

11.6 Therapy

Due to the rarity of LG, standard treatments have not been established. Current treatment depends on histologic grade and clinical aggressiveness. Observation or corticosteroids might be reasonable in clinically indolent cases of grade I or II lesions. Reduction or discontinuation of immunosuppressive agents is prudent if clinically feasible. Interestingly, interferon=-α-2b has been used successfully in a small number of patients with grade I and II disease (12). More aggressive grade I or II cases might require single-agent or combination chemotherapy. Grade III disease should be treated as an aggressive lymphoma with combination chemotherapy such as R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). Rituximab has shown mixed results as a monotherapy (13–15). Bone marrow transplantation is a therapeutic option in patients failing chemotherapy and was associated with a prolonged remission in a recently published case (16).

11.7 Conclusions

In summary, LG is should be considered along a clinicopathologic continuum of disease ranging from a spontaneously regressing, immunosuppression-related lymphoproliferative disorder with rare neoplastic B-cells to an overtly malignant

and clinically aggressive large B-cell lymphoma. Careful clinical workup and follow-up is often required to establish a diagnosis of LG as well as to distinguish between the extremes of this disease.

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