

# Lymphomatoid Granulomatosis

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**Abstract:** Lymphomatoid granulomatosis (LYG) is a very rare Epstein-Barr virus (EBV)-driven lymphoproliferative disease. The atypical lymphoid cells directly accumulate within affected tissues and clinically present in the form of infiltrative lesions. It is usually a progressive disorder that virtually always involves the lung and characteristically presents as bilateral pulmonary nodules. Other commonly affected organ systems include the skin, central nervous system, and kidneys. The rareness of LYG in conjunction with its nonspecific presentation contributes to delays in diagnosis in many situations. Pathologically, it is characterized by the presence of an angiocentric and angiodestructive accumulation of varying numbers of T cells with varying numbers of atypical clonal EBV-positive B cells in a polymorphous inflammatory background. It can be subclassified using a grading system based on the number of EBV-positive large B-cell malignant cells, which is critical in selecting appropriate management strategies. Lower-grade LYG occasionally undergoes spontaneous remission and is best managed with strategies designed to enhance the host's underlying immune system, whereas high-grade LYG is best managed by combination chemioimmunotherapy but has inferior outcomes. Lymphomatoid granulomatosis can lead to progressive pulmonary failure, central nervous system disease, or progression to overt EBV-positive lymphoma without appropriate recognition and management. Improvements in the modern understanding of the biology of LYG, particularly the precise role of EBV in its pathogenesis, offer promise in the development of improved management strategies.

**Key Words:** Lymphomatoid granulomatosis, LYG, Epstein-Barr virus, EBV

(*Cancer J* 2012;18: 469–474)

Lymphomatoid granulomatosis (LYG) is a progressive Epstein-Barr virus (EBV)-driven lymphoproliferative disease in which the abnormal cells directly accumulate within affected tissues, usually in the form of infiltrative nodular lesions and with T-cell

invasion and destruction of blood vessels. Its low incidence combined with its overlapping clinical features with more common pulmonary disorders contribute to frequent delays in diagnosis as well as uncertainties regarding its appropriate management. Lymphomatoid granulomatosis is diagnosed more commonly in men than in women, typically between the fourth and sixth decades of life. An increasing number of young adults and children are recognized as having LYG; however, and it has been reported in patients as young as 4 years old.<sup>1,2</sup>

Lymphomatoid granulomatosis was first described in the medical literature in 1972 based on 40 cases of patients with nodular and granulomatous lesions predominantly involving the lungs.<sup>3</sup> It is probable, though, that many of these cases would not meet current criteria for the diagnosis of LYG. Its etiology was initially enigmatic, and it was postulated to be a limited form of pulmonary vasculitis owing to pathologic and clinical features reminiscent of Wegener granulomatosis and the marked predilection for destruction of blood vessels.<sup>3</sup> Features suggestive of an atypical lymphoma were recognized from the beginning, and some authors considered it an “overlap syndrome” between angiitis and lymphoma, but the concept of extranodal lymphoma was not widely accepted at the time of original description.<sup>4</sup> Owing to the abundance of surrounding T cells in the biopsy specimens, LYG was considered a form of T-cell lymphoma. However, attempts to demonstrate clonal T-cell receptor rearrangements by Southern blotting were unsuccessful, and it was eventually noted using modern techniques such as polymerase chain reaction and in situ hybridization (ISH) that the large atypical cells were EBV-infected B cells.<sup>5,6</sup> Although LYG is currently described as a “lymphoproliferative disease” instead of a frank lymphoma, the cells are often monoclonal and driven by EBV. In this way, it shares many clinical features with related lymphoproliferative disorders such as post-transplantation lymphoproliferative disease (PTLD).<sup>7,8</sup> Clinicians must be aware that even lower-grade cases of LYG can evolve into an aggressive lymphoma in up to 15% of cases<sup>9</sup> and the distinction between high-grade LYG and diffuse large B-cell lymphoma (DLBCL) can be subtle and are treated with similar strategies.

## CLINICAL MANIFESTATIONS AND DIFFERENTIAL DIAGNOSIS OF LYG

Lymphomatoid granulomatosis has a complex relationship with the function of the host's underlying immune system. It is most commonly diagnosed in patients who do not carry a preexisting diagnosis of an overt immunodeficiency, but evidence of immune dysregulation can be found in almost all patients. With the contemporary recognition that EBV is central to all aspects of the disease process, it is probable that most, if not all, patients have an intrinsic level of immunologic defect that is unable to adequately control EBV-infected B-cells.<sup>7,10</sup> Patients may have a history of recurrent or persistent infections, including EBV, and most have abnormal T-cell subsets such as CD4 and CD8.<sup>1,7</sup> Lymphomatoid granulomatosis has also been reported in conjunction with autoimmune illnesses such as Sjogren syndrome and rheumatoid arthritis, sarcoidosis, ulcerative colitis, as well as chronic persistent hepatitis infections<sup>9</sup> and in persons with congenital immunodeficiencies such

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**Conflicts of Interest and Sources of Funding:** All research support comes from the intramural research program of the NIH.

The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article. Reprints: Wyndham H. Wilson, MD, PhD, Lymphoma Therapeutics Section, Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892. E-mail: wilsonw@mail.nih.gov.

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ISSN: 1528-9117

**TABLE 1.** Organs Affected by LYG at Presentation

Organ System	Involvement at Diagnosis
Pulmonary	>90%
Constitutional (fever and malaise)	50%–60%
Kidneys	40%–50%
Skin	25%–50%
Central nervous system	25%–50%
Peripheral nervous system	15%–20%
Liver	10%
Spleen	10%
Lymph nodes	<10%
Bone marrow	Rare
Adrenal glands	Unknown—autopsy only
Heart	Unknown—autopsy only

as Wiscott-Aldrich syndrome and common variable immunodeficiency. Additional evidence for the role of immune dysfunction in its pathogenesis includes reports of LYG occurring after intensive therapy for leukemia<sup>11</sup> and organ transplantation.<sup>12</sup>

The anatomic sites of involvement at diagnosis of LYG are extremely variable between cases, but the lung is virtually always involved in bilateral fashion.<sup>9</sup> Despite the fact that the abnormal cells are currently recognized to be of B-cell origin, it is virtually always limited to extranodal sites. In fact, a particular striking feature of LYG is that lymph nodes and spleen are almost always spared at initial diagnosis but may become involved upon progression to DLBCL (Table 1).<sup>3,9</sup> The symptoms that most commonly prompt patients to seek medical attention include fever, persistent productive cough, dyspnea, and chest tightness. The presentation is typically insidious, and lung lesions may wax and wane, but occasionally, patients present with the rapid onset of life-threatening symptoms such as pulmonary failure. Other constitutional symptoms such as weight loss, malaise, and fatigue may be present leading to the presumption of

**FIGURE 1.** Chest x-ray of extensive bilateral nodular involvement with LYG.

an infectious process.<sup>13</sup> Routine laboratory data, however, are usually normal in cases of LYG to include normal leukocyte counts and inflammatory markers.

Although pulmonary symptoms are present in most patients, LYG is occasionally diagnosed incidentally from abnormalities seen on chest x-ray performed for other reasons (Fig. 1). Radiographic imaging at first presentation characteristically demonstrates multiple bilateral pulmonary nodules of variable size involving mainly the mid and lower lung fields (Fig. 2), occasionally with evidence of central necrosis and/or cavitation and without hilar lymphadenopathy. The distinction between LYG and other pulmonary processes, which have similar presentations, can be difficult if LYG is not considered early in the differential diagnosis and EBV-encoded RNA ISH is not ordered on biopsy specimens; but characteristic patterns do exist (Table 2).

Other common sites of extranodal involvement include the skin, central nervous system (CNS), and kidneys; typically, these areas are affected in conjunction with pulmonary involvement but, on rare occasion, may be isolated. Involvement of the adrenal glands and heart usually do not result in clinical symptoms, but can be demonstrated on autopsy specimens.<sup>9</sup> Skin manifestations of LYG are quite heterogeneous but typically appear as scattered subcutaneous or dermal nodules that vary in size similar to the lesions seen in the lung and seen predominantly on the extremities (Fig. 3). Erythematous or purplish maculopapular eruptions are the most common skin lesions observed (Fig. 4), but some patients will have indurated plaques. Varying degrees of ulceration accompany the skin lesions and may become necrotic when the disease is not well controlled (Fig. 5). In up to 10% of patients, the skin lesions will antedate the lung lesions and, in these cases, dermal biopsy may lead to the diagnosis.

Neurologic disturbances are alternative patterns of presentation. Involvement of the peripheral nervous system is uncommon with paresthesias involving the extremities in some patients. Central nervous system involvement occurs in up to one third of patients and may be a poor prognostic factor.<sup>9</sup> Patients may present with symptoms such as mental status changes, ataxia, cranial nerve palsies, hemiparesis, or even seizures.<sup>3,9</sup> If, however, magnetic resonance imaging is performed in all patients, the presence of multiple focal asymptomatic lesions that involve the white matter, deep gray matter, or brainstem may be found in even more patients.<sup>14</sup> These lesions are characterized by punctate linear enhancement seen best on T2-weighted images consistent with their perivascular nature. Additionally, enhancement of the leptomeninges can be found in a significant number of these patients, suggesting subclinical involvement.<sup>14</sup> Similarly, involvement of abdominal

**FIGURE 2.** Chest computed tomography of bilateral nodules of varying size in lung base.

**TABLE 2.** Differential Diagnosis of Multisystem Diseases Affecting the Lungs

Organ System	Clinical Features Shared With LYG	Clinical Features Distinct From LYG
Wegener granulomatosis	Fever and bilateral lung and kidney lesions	Upper respiratory tract; granulomatous inflammation; Renal dysfunction; CNS lesions rare
Churg-Strauss syndrome	Lung, kidney, and peripheral nerve involvement	Eosinophilia and asthma
Tuberculosis	Lung and skin lesions	Upper airways more involved; systemic symptoms more pronounced; exposure to TB required
Sarcoidosis	Lung and skin lesions; occasionally peripheral nerves	Hilar lymphadenopathy common; more commonly females and African Americans; commonly involves eyes and spleen
Histoplasmosis	Bilateral nodular lesions in lungs	Travel history distinguishes; spleen commonly involved
Coccidioidomycosis	Lung and CNS lesions common	Ethnicities (African Americans, Native Americans) with increased risk; travel history distinguishes
Lymphoma, non-Hodgkin	EBV-associated; increased in immunocompromised patients	Usually involves lymph nodes and, commonly, spleen

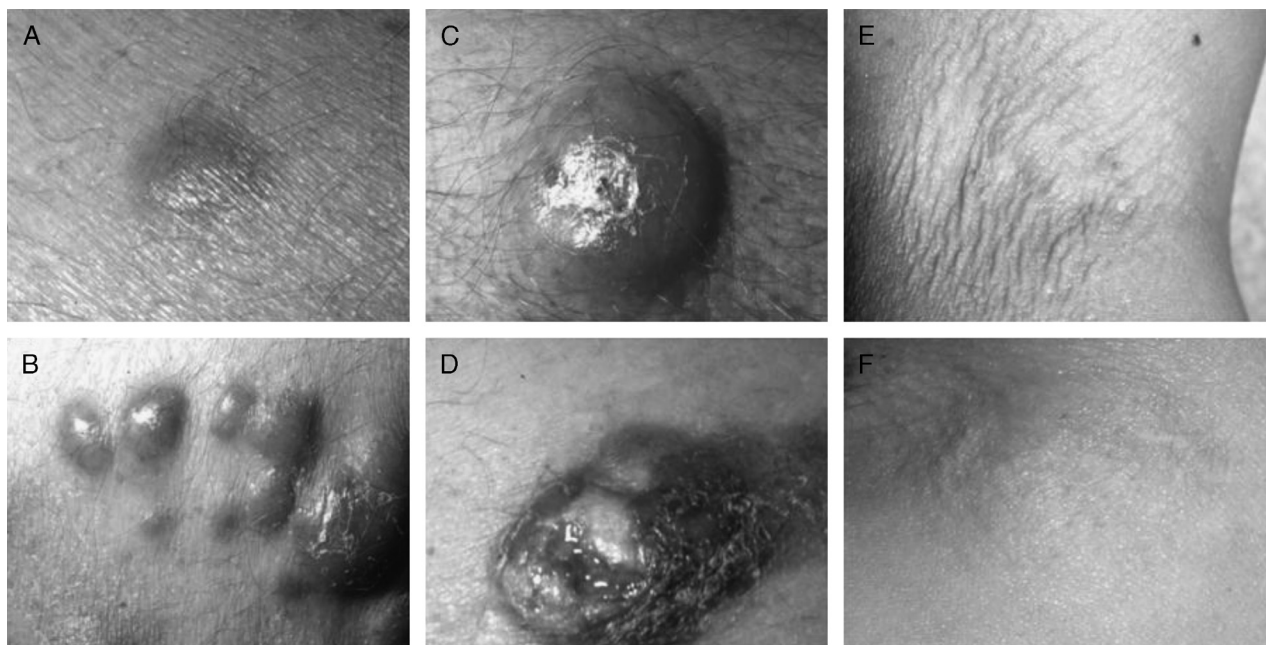
viscera such as focal nodular lesions within the kidneys or hepatomegaly are commonly seen on radiographic imaging, but uncommonly associated with clinical symptoms or organ dysfunction (Fig. 6). In contradistinction to Wegener granulomatosis and Churg-Strauss syndrome, there is no evidence of focal glomerulonephritis in LYG.<sup>3,9</sup>

### PATHOBIOLOGY OF LYG

As stated previously, LYG's relationship with lymphoma was uncertain until modern techniques were able to demonstrate the malignant cell to be of B-cell lineage and positive for EBV ISH in most cases.<sup>5</sup> An accurate diagnosis of LYG requires an adequate tissue biopsy of the affected organ system, with specific attention to document the presence of EBV ISH, which defines the disorder. In fact, EBV is considered essential to the

underlying biology of LYG. However, grade 1 lesions frequently do not show EBV-positive B-cells, making it necessary to rely on other pathological characteristics and the clinical presentation. Typically, the diagnostic pulmonary biopsy is achieved via video-assisted thoracic surgery. Skin biopsies usually lack the presence of the characteristic abnormal cells.<sup>10,14</sup> Serologic tests for EBV will be positive in most patients, and lymphocyte subsets are markedly abnormal. Clonality studies with immunoglobulin heavy-chain gene rearrangements may demonstrate monoclonality, oligoclonality, or polyclonality.<sup>7</sup>

Histologically, LYG lesions exhibit a small number of atypical EBV-positive B cells admixed with a prominent background of mononuclear cells comprised of T cells, plasma cells, and histiocytes. Abnormal areas frequently congregate in monomorphous nests or larger aggregates.<sup>4</sup> Neutrophils, eosinophils, or well-formed granulomas are not seen in biopsy specimens.<sup>10</sup>



**FIGURE 3.** Wide range of cutaneous manifestations of LYG: solitary papule (A), multiple nodules of variable size (B), purplish discrete nodule (C), indurated nodule with areas of both ulceration and necrosis (D), plaquelike skin changes along skin folds (E), discrete non-erythematous lichenus lesion (F). Reprinted with permission from Beatty et al. *Am J Surg Pathol.* 2001;25(9):1111-1120. All permission requests for this image should be made to the copyright holder.



**FIGURE 4.** Purplish 3-cm maculopapular lesion typical of LYG.

The malignant B cells usually are medium to large in size and express CD20, latent membrane protein 1, and EBV by ISH. They are variably positive for CD30 and usually negative for CD15 assisting in the exclusion of Hodgkin lymphoma.

The distinctive morphologic feature of LYG, however, is its angiocentric and angiodestructive nature with marked transmural infiltration of the intima of arteries and veins as well as varying degrees of necrosis. This distinctive feature is felt to be a consequence of local vascular ischemia. One mechanism is through direct invasion of T cells into blood vessels as they are recruited to defend against EBV infection. The direct invasion of inflammatory cells in this manner leads to the infarction and tissue necrosis seen in many LYG specimens. The second mechanism of angiodestruction is through the induction of chemokines such as IP-10 and M-ip by EBV itself, which thereby mediate vascular damage.<sup>10</sup> Taken together, these data are highly suggestive that EBV infection is central to the initiation and pathological progression of LYG.

Lymphomatoid granulomatosis can be divided into 3 grades based on the proportion of large atypical EBV-positive B cells and necrosis in relation to the reactive background of T lymphocytes. In grade 1 lesions, EBV-positive cells are infrequently detected; whereas in grade 2 lesions, they are readily detected—and usually number 5 to 20 high-power fields—by ISH. Grade 3 lesions consist of large atypical B cells, and EBV positive cells are very numerous and easily identified. Distinguishing grade 3 (high grade) from grades 1 and 2 (low grade) is an important distinction as grade 3 lesions are approached therapeutically like DLBCL and treated with immunochemotherapy. Histologic grading is usually based on pulmonary excisional biopsies, and it is important to recognize that the number of atypical EBV-positive B cells may vary over time or between sites. A second



**FIGURE 5.** Six-centimeter ulcerated lesion with surrounding areas of necrosis after debridement.



**FIGURE 6.** Lymphomatoid granulomatous lesions of varying size involving the liver and both kidneys. Small lesions affecting the liver (blue arrow) and right kidney (yellow arrowhead) as well as a large lesion in the upper pole of the left kidney (red arrow).

biopsy should always be considered in cases not responding as anticipated to current therapy.

### MANAGEMENT OF LYG

The optimal management of patients with LYG has recently evolved, although there is no comparative treatment data. If the etiology of immune dysfunction is iatrogenic such as in patients who are taking immunosuppressive agents such as methotrexate or tumor-necrosis factor  $\alpha$  inhibitors, these agents should be discontinued if at all possible, and patients with lower-grade lesions may be observed for regression. Even in patients who do not have reversible causes of immune dysfunction with low-grade lesions and limited amounts of disease burden, a brief period of careful observation may be justified. A small minority of these patients will actually undergo spontaneous remissions or have no progression of their disease for long periods of time.<sup>9</sup> Patients with high-grade LYG require immediate therapy, however, and should not be offered observation. The natural history of high-grade LYG may be similar to aggressive lymphomas. In general, most patients diagnosed with LYG will eventually need disease-directed therapy to prevent progressive pulmonary dysfunction, which is the most common cause of death.

Therapies that have been reported to have variable success in the management of LYG include corticosteroids, anti-CD20 monoclonal antibodies such as rituximab, interferon- $\alpha$ -2b (IFN), and combination chemotherapy. Because most patients with LYG have either subtle or overt amounts of immune dysregulation, treatments such as steroids or chemotherapy have the potential to worsen the immune defect to the detriment of the patient. Corticosteroids are the most commonly used treatment for LYG, but although the neurologic and pulmonary symptoms often transiently improve, relapse is the rule, and they are not effective for long-term disease control. In an early reported case series, the median survival time was only 14 months, and the disease was fatal in more than 60% usually within 3 years of diagnosis despite the use of antibiotics, steroids, and chemotherapy.<sup>9</sup> Given the myriad toxicities with the use of steroids, both short term and long term, they should only be used as a temporizing measure in low-grade LYG. Another temporizing measure is rituximab, but it does not mitigate the underlying immune deficiency. Rituximab might be effective in cases where other systemic therapy is not an option, but limited data exist.

The first prospective study was conducted by Fauci et al<sup>15</sup> at the National Institutes of Health (NIH) on 15 patients between

the ages of 16 and 65 years (median, 34 years) with LYG over a 10-year period. Interestingly, many of these patients had originally been referred with a diagnosis of Wegener granulomatosis, and the therapeutic program was one that consistently induces long-term disease control in Wegener granulomatosis. Other patients in this series also were later found upon reexamination to have had extranodal NK/T-cell lymphoma, nasal type. Thirteen of these patients were treated with a combination of oral cyclophosphamide at 2 mg/kg and prednisone at 1 mg/kg daily, with the prednisone reduced to every-other-day dosing after the first 2 months and gradually tapered thereafter. Overall treatment with cyclophosphamide was continued until disease progression or unacceptable toxicity ensued. They observed complete responses in 7 patients (46%) that lasted for a median of 5.2 years but still found an overall mortality rate of 53%. Fundamentally, they noted that the cause of death in the patients who failed to respond to the treatment was transformation to an aggressive lymphoma.<sup>15</sup> Importantly, many of these patients would not fulfill the current criteria for the diagnosis of LYG, so this treatment approach is unsubstantiated.

Rituximab is a chimeric anti-CD20 monoclonal antibody with reliable activity in a variety of B-cell lymphomas and lymphoproliferative disorders. Because EBV is immortalized in the B cells of the affected host, rituximab intuitively has merit in the treatment of LYG with a favorable toxicity profile. Available data, however, for the use of rituximab as a single agent in LYG are currently restricted to expert anecdotes and case reports, as there are currently no published studies on its response rate or duration of remission.<sup>16,17</sup> One case report describes a dramatic response to therapy in a patient who died of fatal pulmonary hemorrhage only a month after therapy.<sup>18</sup>

Research done at the US National Cancer Institute (NCI) uses a risk-adapted approach to the management of LYG with promising results. The premise behind the risk-adapted approach is to enhance the host's immune system with the use of IFN for cases that are grades 1 to 2 and reserve combination chemotherapy for grade 3 LYG.<sup>19</sup> The rationale for using IFN is based on its demonstrable and rapid activity against other EBV-driven B-cell lymphoproliferative disorders such as PTLD through a proposed combination of antiproliferative and immunomodulatory effects.<sup>20</sup> Interferon- $\alpha$ -2b is initiated at 7.5 million units given subcutaneously 3 times weekly and dose escalated to best response. The dose and duration of therapy with IFN is determined by response and toxicities, but patients often require treatment doses of up to 40 million units to achieve best results. The duration of therapy is typically between 1 and 2 years. Efficacy data on the first 31 patients treated at the NCI demonstrated a complete remission (CR) rate of 60%. At a median follow-up time of 5 years, the progression-free survival of low-grade LYG was 56%, with a median time to remission of 9 months.<sup>19</sup> Most of these patients had already received prior therapy. Of the patients who did not achieve CR, a significant number rapidly progressed while on IFN and were discovered to have grade 3 disease on second biopsy. This raises the possibility that the high-grade LYG was actually present before initiating treatment. Interestingly, 90% of patients with CNS disease achieved a CR with IFN, which obviates the need for the use of intrathecal chemotherapy, high-dose chemotherapy, or whole brain radiation (WBRT).

At the NCI, adult patients with high-grade LYG (grade 3) at diagnosis receive combination chemoimmunotherapy with rituximab, prednisone, etoposide, vincristine, cyclophosphamide, and adriamycin that is dose-adjusted based on neutrophil nadir counts. Patients who do not have a drop in their absolute neutrophil count of less than 500 cells/ $\mu$ L have dosage increases in

adriamycin, etoposide, and cyclophosphamide with subsequent cycles; and the regimen is given for a total of 6 cycles. A similar number of patients respond to this therapy with a CR rate of 66%, but the prognosis is more guarded with a progression-free survival of only 40% at a median follow-up of 28 months. At the time of relapse, it was observed that patients would relapse with low-grade disease and can subsequently respond to IFN. At a median of 4 years, the overall survival of all patients with LYG treated with this strategy was reported as 68%.<sup>19</sup> Other combination chemoimmunotherapy programs such as rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) have anecdotal reports of successful outcomes but have not been rigorously studied.<sup>21</sup> Thus, IFN can induce durable remissions in most patients with grade 1 or 2 disease, but there is a high rate of relapse with high-grade LYG treated with combination chemotherapy and rituximab. At the time of suspected recurrence of disease, repeat biopsy is mandatory, as patients with low-grade LYG may be reclassified as high-grade LYG and the converse has also been observed.

## SUMMARY AND CONCLUSIONS

Lymphomatoid granulomatosis is very rare multisystem angiodescriptive process affecting the lungs, the nervous system, and skin in patients who harbor overt or subtle defects in cellular immunity. Biopsy specimens demonstrate pronounced destruction of blood vessels with a prominent polymorphous inflammatory background including atypical EBV-infected B cells. The biologic driver of the angiodescriptive process is now recognized to be EBV, and the prognosis is determined chiefly by the number of EBV-infected abnormal B cells found in biopsy specimens. Although low-grade LYG may undergo spontaneous remission, the disorder is often progressive and ultimately fatal in the absence of appropriate treatment. Many patients die as a result of pulmonary hemorrhage, CNS involvement, or transformation to an aggressive lymphoma. High-grade LYG requires urgent medical treatment with combination chemoimmunotherapy similar to those used for PTLD or DLBCL, but results remain unsatisfactory as these therapies have the potential to worsen the intrinsic immunologic defect. Overall strategies to manage LYG should focus on improving immunological defects and eradicating EBV-positive B cells. Improvements in the modern understanding of the precise role of EBV in its pathogenesis and development of specific anti-EBV therapies offer promise in the future management of this frequently fatal condition. The study from the NCI has established a standard of treatment using IFN for low-grade LYG and dose-adjusted rituximab, prednisone, etoposide, vincristine, cyclophosphamide, and adriamycin for higher-grade LYG.

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