

# Current histological diagnosis of lymphomatoid granulomatosis

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**The current histological criteria for the diagnosis of lymphomatoid granulomatosis (LYG) are reviewed and summarized. The majority of patients present with multiple bilateral nodules involving the lung. Key histologic features necessary for the diagnosis include a mixed mononuclear cell infiltrate that shows vascular infiltration, appreciable numbers of T-cells, and variable numbers of CD20-positive B cells that show positivity for EBV by *in situ* hybridization.**

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## Overview

Lymphomatoid granulomatosis is an iconic lesion that dates to the 1960's, when it was first described among the five categories of 'angiitis and granulomatoses'.<sup>1</sup> It has weathered redefinition and reclassification, and has maintained itself as a clinicopathological entity,<sup>2</sup> whereas many contemporary lesions such as histiocytic lymphoma, reticulum cell sarcoma, malignant histiocytosis, and many others<sup>3</sup> have fallen by the wayside.

Lymphomatoid granulomatosis is an angiocentric and angiodestructive process that most commonly affects the lung as bilateral nodular infiltrates composed of a mixed population of lymphoreticular cells lacking true granulomatous features.<sup>1,2,4–6</sup> The infiltrating cells show a distinct predilection for vascular invasion and are associated with necrosis, albeit central ('tumor') necrosis in the nodules rather than classic wedge-shaped infarct-like necrosis. There are varying numbers of large transformed lymphocytes, which, at the high-grade end of the spectrum, occur in sheets, which, field for field, are indistinguishable from diffuse large (B) cell lymphoma. LYG more frequently affects males and typically presents in the fifth decade; affected patients most frequently show evidence of lung involvement, followed by central nervous system, skin, liver, and kidney.<sup>1,2,5,6</sup> The demographics of

LYG still derive primarily from the two largest series, which predate the current definition of LYG.<sup>1,5</sup>

Although LYG has persisted in the lexicon of hematopathology and pulmonary pathology, it has not escaped redefinition. As originally described, it was thought to be in a gray zone between vasculitis and lymphoma,<sup>1</sup> although over time, it has been suggested that it is primarily a lymphoproliferative process, which at one time was thought to be an angiocentric T-cell immunoproliferation,<sup>7</sup> although now it is considered a distinct form of T cell-rich large B-cell lymphoma.<sup>2,4,6,8–10</sup>

## Current criteria for the diagnosis of LYG

Although Liebow *et al.*,<sup>1</sup> in the original description, considered the possibility of a viral pathogenesis for LYG, it was not until 1990, when Katzenstein and Peiper<sup>11</sup> identified Epstein-Barr virus (EBV) DNA in 21 of 29 cases studied (72%). Subsequently Guinee *et al.*<sup>8</sup> in 1994 and Myers *et al.*<sup>9</sup> in 1995 showed the presence of EBV RNA by *in situ* hybridization in the large B cells in LYG, and this finding has been confirmed in numerous studies subsequently.

The presence of large B cells showing the presence of EBV-positive cells by *in situ* hybridization with the EBER probe is now definitional for LYG, '... an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of Epstein-Barr virus (EBV)-positive B cells admixed with reactive T cells, which usually predominate.'<sup>2</sup> To further quote the 2008 WHO

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description of LYG, 'In some cases, EBV-positive cells may be absent, but in this setting, the diagnosis should be made with caution ....'<sup>12</sup> Thus EBV+ large B-cells are a key feature.

The current definition of LYG is more restrictive than that originally applied by Liebow *et al*<sup>1</sup> in the first large series, and also more restrictive than that used by Katzenstein *et al*<sup>5</sup> in a subsequent much larger series. Even with a current more restrictive definition, the majority of cases reported in these two large series would likely meet current criteria for LYG (E Jaffe, MD; personal communication, 2010). The possibility that a small number of cases of LYG might have a T-cell lineage, as suggested in the series of Myers *et al*<sup>9</sup> has not been generally accepted.

Although the criteria of the 2008 WHO are clear, there are clearly cases that fulfill some, but not all, of the criteria. For practical purposes, Katzenstein *et al*<sup>6</sup> have proposed the following criteria for LYG in a recent review:

Findings necessary for diagnosis, always present

- (1) Mixed mononuclear cell infiltrate containing large and small lymphoid cells, often along with plasma cells and histiocytes, which replaces the lung parenchyma and shows vascular infiltration.
- (2) Variable numbers of CD20-positive large B cells, often with atypia, present in a background of CD3-positive small lymphocytes.

Supportive findings, usually but not always present

- (1) Necrosis of the cellular infiltrate.
- (2) Positive ISH for EBER.
- (3) Multiple lung nodules radiologically, or skin or nervous system involvement.

As stated in that review, 'Probably the most controversial point is whether identification of EBER is necessary for the diagnosis of LYG. In our opinion, as sampling can be a problem in identifying EBER, negative ISH for EBER in a single biopsy specimen does not exclude LYG, provided that criteria 1 and 2 are present in the appropriate clinical setting (criterion 5).'<sup>16</sup>

In this author's opinion, the criteria for the diagnosis of LYG will remain an area of contention between the worlds of pulmonary pathology and hematopathology.

## LYG as a large B-cell lymphoma

Although LYG has persisted among lymphoproliferative disorders, it remains an unusual lesion, histologically and clinicopathologically distinct from most diffuse large B-cell lymphomas. LYG is included by the 2008 WHO classification among the diffuse large B-cell lymphomas in the category of 'other lymphomas of large B cells,'

which also includes primary mediastinal large B-cell lymphoma, intravascular large B-cell lymphoma, diffuse large B-cell lymphoma associated with chronic inflammation, ALK-positive large B-cell lymphoma, plasmablastic lymphoma, large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, and primary effusion lymphoma.<sup>12</sup>

LYG is considered distinct from the common variety of diffuse large B-cell lymphoma, diffuse large B-cell lymphoma not otherwise specified.<sup>12</sup> In addition, regarding EBV positivity, the WHO states as follows: a lymphoma composed of 'a uniform population of atypical EBV-positive B cells without a polymorphous background should be classified as diffuse large B-cell lymphoma and is beyond the spectrum of LYG.'<sup>12</sup> Thus, it is important to recognize that the polymorphous background cellular infiltrate and EBV positivity are necessary for the diagnosis of LYG, and to distinguish it from other large B-cell lymphomas.

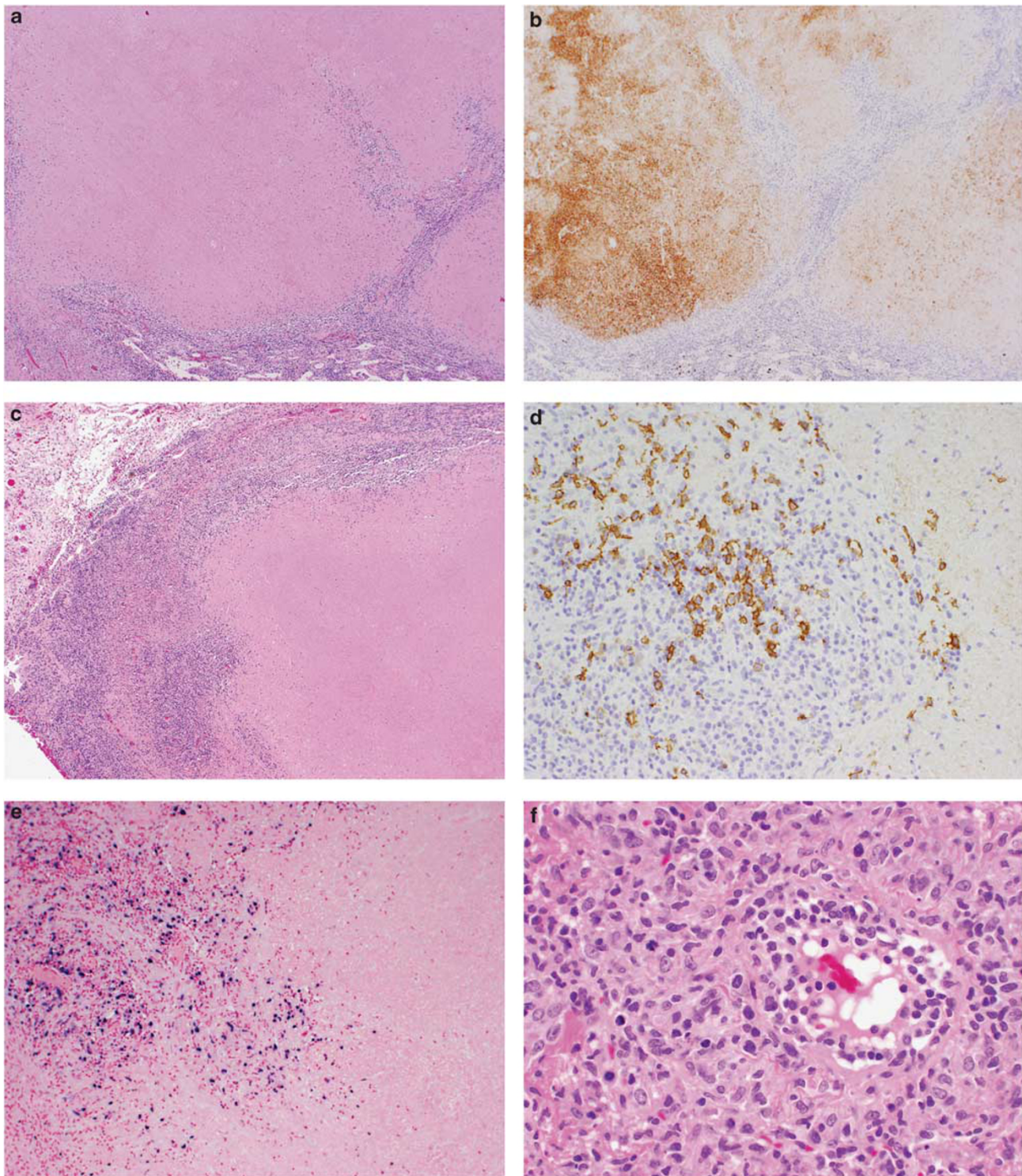
A spectrum in the numbers of large 'atypical' lymphoid cells in cases of LYG has been recognized since the initial descriptions. Despite relatively little evidence-based data, the WHO recommends that LYG be graded as grade 1, grade 2, or grade 3, according to the number of EBV-positive large B cells,<sup>2</sup> grade 1 having less than five EBV-positive cells in a single high-power field, grade 3 having greater than 50 EBV-positive cells in a high power field, and grade 2 encompassing the remainder. Grading may be conceptually reasonable, but practically speaking, there is considerable diversity in sampling from one LYG nodule to the next in the same biopsy, and from one biopsy to another in the same patient, with some regions showing grade 1 LYG and others showing grade 3 LYG. Thus, sampling is an issue in grading (Figure 1).

Early descriptions of LYG likely included entities which no longer meet the current criteria, such as Hodgkin lymphoma, other non-Hodgkin lymphomas, anaplastic large-cell lymphoma, angioimmunoblastic T-cell lymphoma, post-transplant lymphoproliferative disorders, iatrogenic lymphoproliferative disorders, and IgG4-related disease, most of which have been recognized since the original descriptions of LYG.

## Is LYG a specific entity?

Given a more restrictive definition for LYG, one would expect that would result in a fairly homogeneous entity. Diversity remains, however, from several points of view, as illustrated by grade 1 LYG containing less than 5 EBV-positive cells in a high-power field vs grade-3 LYG that contains greater than 50.<sup>1,2</sup> One could use the histological heterogeneity of LYG to support the claim that it is not a specific entity. However, as multiple lesions in a





**Figure 1** Photomicrographs from wedge biopsies taken from a 40-year-old woman who presented with fever, weight loss, and multiple bilateral pulmonary nodules suspected to be metastatic disease. Some of the nodules (a) were entirely necrotic with a rim of histiocytes and T cells, but no viable B cells and negative ISH for EBER; in the necrotic regions, CD20 staining showed extensive positivity (b). Other nodules (c) showed extensive necrosis, but also regions of more viable peripheral mixed cellular infiltrate, including CD3-positive T-cells and scattered transformed cells that were CD20-positive (d), and which also showed EBER positivity by *in situ* hybridization (e). There were also separate cellular nodules showing vascular infiltration exclusively by T cells and histiocytes (f).

given patient and multiple biopsy sites in a given patient may show variation from grade 1 to grade-3 histology, different morphological faces of a similar

entity are more appealing. Further support for this conclusion comes from the fact that patients with grade-1 LYG initial biopsies may show subsequent

biopsies with a grade-3 histology and *vice versa* (E Jaffe, MD; personal communication, 2010).

Treatment for LYG has varied according to grade; grade 3 is treated as diffuse large B-cell lymphoma, and shows a prognosis roughly similar to that of diffuse large B-cell lymphoma.<sup>2,13,14</sup> Grade 1 and grade 2 lesions, although rare, have shown response to interferon alpha-2B therapy.<sup>2,15</sup> Though the evidence is anecdotal and uncontrolled, one could use the differences in treatment to suggest that LYG not be considered a specific entity.

Finally, it is known that a number of different lesions may show similar histology (and immunohistochemistry, and EBER positivity), if not identical to that of LYG. These include the following: iatrogenic lymphoproliferations, HIV infection, lymphoproliferative disease in the setting of immune deficiency, and post-transplant lymphoproliferative disorders.<sup>2,6</sup> Does LYG then represent a nonspecific reaction pattern rather than a specific entity? When one puts aside the distinct clinical situations in which these other lesions are encountered, the vast majority of cases of LYG fit into a relatively distinct clinicopathological syndrome: primary presentation in the lung with multiple bilateral nodules showing the presence of EBV in large B cells, with variable involvement of other organ systems including CNS, skin, etc.

## Practical considerations

As previously mentioned, as the criteria of LYG have become more refined/narrow, there remain a minority of cases that are left 'out in the cold,' by not fulfilling all the criteria for LYG. Examples include cases with typical clinical and radiological findings, but which lack large B cells (or the large B cells are all necrotic), or cases that have B cells, but no evidence of EBV infection. As noted in the practical criteria of Katzenstein *et al* (2010)<sup>6</sup> discussed above, sampling error should always be remembered in such problem cases (Figure 1). In problem cases, one should be sure that all the tissue has been evaluated, both histologically and immunohistochemically.

Criteria are only as good as our clinicians' acceptance of them, and a diagnosis by pulmonary pathology criteria may not suffice for an oncologist who requires the hematopathological criteria to be fulfilled. This problem remains one that we should continue to address as we learn more about this extremely interesting disease.

## Disclosure/conflict of interest

The author declares no conflict of interest.

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