Lymphomatomoid granulomatosis: a poorly-recognized lymphoproliferative disorder of the lung

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Summary
Lymphomatomoid granulomatosis (LYG) is a rare B-cell lymphoproliferative disorder predominantly involving the lungs, but poorly-recognized among clinicians and pathologists. It is an Epstein-Barr virus (EBV)-driven disease mimicking several other diseases on clinical and radiological grounds, generally showing multiple, bilateral nodular, ill-defined infiltrates of the lungs tending to coalescence and/or cavitation. LYG often affects middle-aged males with an underlying immunodeficiency and commonly involves skin and central nervous system during disease progression. Diagnosis requires a generous biopsy and a careful histologic examination with immunohistochemical stains and molecular demonstration of EBV genome in large atypical B-cells. LYG is graded from I to III based on the number of EBV-positive B-cells and grade II/III are now considered as a peculiar variant of T-cell rich diffuse large B-cell lymphoma. In this brief review, the main clinical-radiologic and pathologic findings of LYG are reviewed in order to highlight the most helpful diagnostic features to be kept in mind in routine practice when dealing with this controversial and difficult entity.

KEY WORDS: lung; lymphoma; EBV; immunohistochemistry; immunodeficiency.

Introduction
Lymphomatomoid granulomatosis (LYG) is a misnomer coined by Liebow in 1972 (1) actually designating a rare Epstein-Barr virus (EBV)-driven lymphoproliferative disorder with different aggressiveness, ranging from low-grade to high-grade angiocentric and angiodestructive lymphoma (2-8). The lungs are the most commonly involved organ, but the skin and nervous system are also frequently affected (7, 8). The disease mainly affects middle-aged patient with a male prevalence, clinical outcome is generally poor and an effective therapy is lacking (7-14). Imaging work-up generally reveal multiple, bilateral nodules tending to central cavitation (15-21). At histology, LYG appears as a polymorphic lymphoproliferative, angiocentric and necrotic process with a predominant T-cell rich infiltrate obscuring large lymphomatous B-cells (1-8, 22, 23). Diagnosis is almost impossible on cytology and rarely feasible on small biopsies, most often requiring a generous amount of pathologic tissue as a surgical specimen (22, 23). Demonstration of EBV RNA genome is the crucial point for the correct diagnosis and LYG is graded from I to III based on the rate of EBV-positive large B-cells (3-8, 22, 23). From practical purposes, LYG is suggested to represent a EBV-driven T-cell rich diffuse large B-cell lymphoma (22, 23).

In this brief report, the main clinical-radiologic and pathologic findings of LYG are reviewed in order to highlight the most helpful diagnostic features to be kept in mind in routine practice when dealing with this controversial and difficult entity.

Methods
Clinical features
LYG has a predilection for men in a 2:1 ratio and may affect children and elderly, with a prevalence in the forth and fifth decades of life (2, 3, 7, 8, 10-14). The disease more commonly occurs in patients with immunodeficiency or predisposing conditions, as Wiskott-Aldrich syndrome, human immunodeficiency virus infection (HIV), allogenic organ transplantation, common variable immunodeficiency, X-linked hypo- or agammaglobulinemia, rheumatoid arthritis, previous history of solid or hematologic neoplasms, and chronic treatment with methotrexate (Table 1) (2, 3, 7-14, 22-27). The mean time from onset of symptoms to diagnosis is about 8 months (2, 3, 7-14).

It is a common view that LYG may derive from a deficit of CD8 T lymphocytes that cannot control EBV-specific immunity (3, 7, 8, 10-14, 22, 23). LYG may be localized to the lungs or rather presents as a systemic disease involving skin (50%), central nervous system (25%) and less commonly kidneys (3, 7-14). Of note, lymph nodes, bone marrow and spleen are rarely involved (3, 7-14). Cough, chest pain and dyspnea are the main pulmonary symptoms, while haemoptysis usually indicates cavitation of the parenchymal nodules (3, 7-14-16, 28-30). However, pa-
Patients with LYG often suffer from systemic symptoms including fever, asthenia, night sweats and weight loss (11-16, 28-30). Cutaneous involvement often occur in the arms and legs with a very heterogeneous manifestation, ranging from an erythematous maculopapular eruption to subcutaneous nodules with non confluent rash (11-16, 28-30). Neurologic presentation may present as an isolated peripheral or cranial neuropathy, as a central mass lesion, or with seizures (11-16, 28-30).

Predictors of poor prognosis are central nervous system involvement, high grade, young age at diagnosis (less than 25 years), leukocytosis and hepatomegaly (11-16, 28-30).

**Imaging studies**

The most common radiographic feature is multiple lung nodules, occurring in approximately 80% of the cases, predominantly involving the lung bases (15-21). The lesions can progress rapidly, coalesce and commonly cavitate, therefore mimicking Wegener’s granulomatosis or metastases (Figure 1) (15-21, 26). Dee et al. (18) described two distinct radiographic manifestations of LYG. In their series of five patients, diffuse reticulonodular opacities correlated microscopically with angiocentric granulomatous infiltration without pulmonary infarction, whereas larger mass-like opacities corresponded to biopsy-proven pulmonary infarcts (18). There is a wide range in the number (5-60) and diameter of the nodules (up to 6.5 cm) but generally they measure 1 cm and tend to be located along the bronchovascular bundles and interlobular septa (15, 18). Nodules can disappear or migrate spontaneously, and may display central ground-glass opacity surrounded by denser consolidation at least 2 mm thick – the so called “reversed halo sign” (20). However, this is a non-specific sign, most commonly seen in organizing pneumonia. Differential diagnosis at imaging presentation may be very challenging and includes several other, more common diseases, including metastases, lymphocytic interstitial pneumonia (LIP), sarcoidosis, Wegener’s granulomatosis, and cryptogenic organizing pneumonia (Table 2) (15-21). In contrast with other lymphomas involving the thoracic region, mediastinal lymphadenopathy is very uncommon in LYG (15-21).

**Table 1 - Conditions associated with lymphomatoid granulomatosis.**

<table>
<thead>
<tr>
<th>Hematological disorders</th>
<th>Leukemia (acute lymphoblastic; chronic lymphocytic)</th>
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<tr>
<td>Hodgkin lymphoma</td>
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<tr>
<td>Non-Hodgkin lymphoma</td>
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<td>Myelofibrosis</td>
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<tr>
<td>Wiskott-Aldrich syndrome</td>
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<tr>
<td>Common variable immunodeficiency</td>
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<td>Acquired immune deficiency syndrome</td>
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<td>Solid tumors</td>
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<td>Renal transplantation</td>
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<td>Autologous stem-cell transplantation</td>
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<td>Rheumatoid arthritis</td>
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<td>Sarcoidosis</td>
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<td>Biliary cirrhosis</td>
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<td>Chronic hepatitis</td>
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<td>Retroperitoneal fibrosis</td>
<td></td>
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<tr>
<td>Psoriasis</td>
<td></td>
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<tr>
<td>Dermatitis herpetiformis</td>
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</table>

**Diagnosis** requires a generous amount of pathologic tissue as a surgical specimen.

The disease more commonly occurs in patients with immunodeficiency, e.g. CD8+ lymphocytopenia that cannot control EBV-specific immunity.

**Figure 1 - Chest CT showing at diagnosis several ill-defined nodular opacities along the bronchovascular bundles.**
Histology, immunohistochemistry and molecular analysis
Histology is characterized by poorly-defined pulmonary nodules (Figure 2, A) along the bronchovascular bundles and interstitial inflammatory infiltrates consisting of lymphocytes, plasma cells, histiocytes and intermediate-to-large centroblast-like lymphoid cells (Figure 2, B, C) (1-8, 22, 23). Vascular and bronchiolar involvement by lymphoid infiltrates is frequently noted. In fact, venous and arterial vessels tend to be infiltrated by a mixture of small sized and large atypical lymphocytes justifying the peculiar angiocentric involvement (Figure 2, D) (1-8, 22, 23). At the periphery of lymphoid proliferation, lung parenchyma commonly shows an acute lung injury with fibrin and alveolar membranes (Figure 2, E) (14, 27). At immunohistochemistry, there is a background of small T-lymphocytes (CD3+) predominantly with helper phenotype (CD4+) (Figure 3, A) and CD68+ histiocytes intermingled by a population of large B-cells (CD20+, PAX5+, CD79a+) (Figure 3, B, C) with high proliferative index by Ki67/MIB-1 (Figure 3, D) (3-8, 22, 23). In-situ hybridization for EBV-encoded RNA (EBER) reveals a consistent number of EBV-positive large B-cells (Figure 3, E), while molecular analyses generally demonstrate B-cell clonality by immunoglobulin heavy chain gene rearrangement (3-8, 10-13, 16, 22, 23).

Despite the misnomer, no granulomas or multinucleated giant cells are observed in LYG. According to the WHO classification criteria based on the number of EBV-positive large atypical B-cells, 3 grades are recognized in LYG. Grade I is very rare and shows a polymorphous infiltrate with minimal angiocentric lesions and fewer than 5 EBV-positive large B-cells x high-power-field (hpf) (3, 8, 22, 23). Grade II had more than 5 and fewer than 20 EBV-positive atypical B-cells x hpf, while grade III LYG contains aggregates of EBV positive large B-cells (more than 20 x hpf), prominent angiocentric lesions and necrosis (3, 8, 22, 23).

Treatment and prognosis
No standard therapy has been so far established, and treatment is controversial and problematic, basically depending on disease grade (7, 9, 10-13, 30-37). Several regimens have been considered in the past, from observation to cyclophosphamide plus prednisone or combination chemotherapy with different agents with variable success (10).

Table 2 - Main pathologic conditions mimicking LYG in the lungs.

<table>
<thead>
<tr>
<th>Neoplasms</th>
<th>Infections</th>
<th>Autoimmune diseases</th>
<th>Infectious agents</th>
<th>Sarcoidosis</th>
<th>Amyloidosis</th>
<th>LIP</th>
<th>COP</th>
<th>Pneumoconioses</th>
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<tbody>
<tr>
<td>Primary lung carcinomas</td>
<td>Fungal</td>
<td>Wegener’s granulomatosis</td>
<td>Fungal</td>
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<tr>
<td>Metastatic tumors</td>
<td>Mycobacterial</td>
<td>Churg-Strauss syndrome</td>
<td>Mycobacterial</td>
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<tr>
<td>Lymphoproliferative disease (i.e., leukaemia)</td>
<td>Nocardia</td>
<td>Microscopic polyangiitis</td>
<td>Nocardia</td>
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<tr>
<td></td>
<td>Actinomycetes</td>
<td>Rheumatoid arthritis</td>
<td>Actinomycetes</td>
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<tr>
<td></td>
<td>Paragonomiasis</td>
<td>Wegener’s granulomatosis</td>
<td>Paragonomiasis</td>
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Abbreviations: LYG, lymphomatoid granulomatosis; LIP, lymphocytic interstitial pneumonia; COP, cryptogenic organizing pneumonia.

Demonstration of EBV RNA genome is the crucial point for the correct diagnosis and LYG.

Figure 2 - Histology showing surgical lung specimens with several "blue" nodules (A). Higher magnification shows a polymorphous mononuclear infiltrate (B, C) with vascular involvement (D) and areas of diffuse alveolar damage (E).
However, the outcome is poor and most patients with LYG succumb to the disease after a short period of time. In addition, patients often respond initially, but relapse is very common and the immunosuppressive effects of therapy may actually worsen the condition. During therapy, a close follow-up for possible superimposed infections is required.

Since this is an EBV-driven process, grade I LYG is often treated with interferon alpha (starting dose of 7.5 million units subcutaneously administered 3 times per week, then dose-escalation to best response or complete remission and therapy continued at that dose for a year beyond) (7, 10-13). By contrast, grade II and III should be considered high-grade lymphomas, requiring a more aggressive treatment including cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) combined with the anti-CD20 monoclonal antibody rituximab (R-CHOP). Etoposide, prednisone, vincristine, cyclophosphamide doxorubicin and rituximab (DAEPOCH-R) was also considered an effective treatment strategy in grade III LYG (7, 10-13, 30-37). Of note, patients with grade I LYG can relapse with grade II or grade III disease, but this is sampling-dependent due to the presence of discordant disease at different sites. Re-biopsy should then be highly recommended in patients who are progressing on therapy in order to switch in treatment strategy. At a median follow-up time of 5 years, the progression-free survival (PFS) of patients with grade I LYG was 56% with a median time to remission of 9 months (7, 10-13). Almost all deaths are recorded in the first 36 months after diagnosis. Grade II-III disease at diagnosis treated with immunotherapy, PFS was 40% with a median follow-up of 28 months (7, 10-13).

**Discussion**

LYG is an angiocentric large B-cell lymphoproliferative disorder due to a defective immune response to EBV and characterized by a mixed polymorphic mononuclear infiltrate with small and large lymphocytes, plasma cells and histiocytes arranged in ill-defined nodules with transmural angiocentric infiltration leading to an angiodestructive process (7, 10-13, 22, 23). The disease generally occurs in middle-aged patients (mean, 40-50 years; range, 2-85 years) with systemic symptoms (fever, malaise, arthralgia, weight loss) mimicking infections (especially tuberculosis and acute histoplasmosis), vasculitides (Wegener’s granulomatosis) or malignancies (7, 10-13, 16, 22, 23). Given the rarity of LYG and the non-specific symptoms, correct diagnosis is frequently delayed, requiring a mean time of 8 months from disease onset (14, 30). When LYG is restricted to lungs, fever is the main and often unique symptom, followed by general malaise, weight loss, arthralgia, but clinical manifestations are mainly organ-related (skin, central nervous system, kidney) (7, 10-13). Lungs are almost always involved by LYG, but respiratory symptoms may be absent in 20% of cases, while imaging studies invariably show parenchymal nodules, opacities or poorly-defined masses with a peculiar tropism for bronchoalveolar bundles and interlobular septa without mediastinal lymphadenopathy (15-21). Otherwise, LYG may appear as pulmonary cystic disease, pleural-based mass or prominent interstitial process (15, 18). Patients with LYG should be investigated for alterations of cytotoxic T-cell function, since a significant association between LYG and immunodeficiencies has been well-demonstrated (i.e., AIDS, Wiskott-Aldrich, post-transplantation, collagen-vascular diseases treated with methotrexate, sarcoidosis, hematologic and solid malignancies, chronic liver and cutaneous diseases, medications) (3, 7, 8, 10-13, 24, 25, 27). Interestingly, recent observations by Yamashita et al. (38) suggested that some cases of EBV-negative grade 1 LYG are indistinguishable from pulmonary IgG4-related sclerosing disease, an autoimmune disorder affecting several organs and characterized by elevated serum IgG4 titer, increased IgG4-positive plasma cells in tissues with vascular involvement and dramatic clinical response to steroids.
Lymphomatoid granulomatosis

TAKE HOME MESSAGES

➢ LYG is an EBV-driven lymphoproliferative disease, ranging from grade I to grade II and III, these latter being consid-ered as a form of diffuse large B-cell lymphoma (“T-cell rich diffuse large B-cell lymphoma”). LYG primarily occurs in the lungs, less frequently involving skin and central nervous system.

➢ Mean age at diagnosis is 48 years with a male prevalence. Cough, dyspnoea, fever and malaise are the main symptoms.

➢ CT key features: bilateral, round, poorly defined nodules ranging from 0.5 to 8 cm in diameter with basal predominance and peribronchovascular distribution. The nodules may coalesce and cavitate, and even show “reversed halo sign”, while “migratory” nodules due to “waxing and waning” may occur.

➢ Diagnosis always relies on histology and cannot be made on cytology. Morphologic examination requires the presence of a polymorphic, angiocentric lymphoid proliferation including a background of T-cells, plasma cells and histiocytes intermingled by varying numbers of large B-cells. Necrosis may be focal to extensive and surrounding parenchyma frequently shows acute lung injury. Demonstration of EBV genome in large B-cells is mandatory and determines the grade of disease. Grade II and III contain clusters of EBV-positive large B-cells. Of note, grade I is very rare and usually represents an unsampled or poorly sampled grade II or III lymphoma.

➢ Prognosis in grade II and III is dismal, median survival ranging from 14 months to 4 years from the diagnosis. Mortality rate ranges from 53% to 64%.

➢ Therapy depends on disease grade. Grade I is usually treated with immunomodulators, namely interferon alpha, whi-le grade II and III require immunochemotherapy combining chemotherapeutic agents with rituximab.

Diagnosis of LYG obligatorily requires an accurate histopathologic examination on generous biopsies. Bronchoalveolar lavage cytology does not permit a confident diagnosis, basically evidencing a non-specific mixed inflammatory infiltrate. Transbronchial or transhilaric CT-guided biopsies may be diagnostic when sampling a large amount of pathologic tissue and in the hands of expert pathologists. By the way, in the majority of cases diagnosis is performed on surgical specimens and tissue sampled should be entirely analyzed, since correct diagnosis mainly depends on a careful examination of various areas of the pathologic process coupled to adequate immunohistochemical stains and molecular analysis (22, 23). In other words, LYG may actually show grade I and grade III disease in different pathologic areas of the same case. Based on the number of EBV-positive large B-cell counted x high-power-field, LYG is subdivided in III grades (7, 8). According to recent observations by Katzenstein et al. (22) and Colby (23), grade I LYG is a formidable challenging diagnosis and probably represent a early or poorly sampled lymphoma. Grade II/III LYG likely raise the suspicion of a malignant lymphoproliferative disease even in the hands of general pathologist. Sharing these complicated cases with more expert colleagues and performing EBER-EBV analysis on multiple sections or blocks is very helpful in discriminating LYG from other mimicking processes.

Differential diagnosis at histology includes other lymphoproliferative (primary or secondary) and inflammatory diseases (22, 23). Knowledge of a previous diagnosis of lymphoma (Hodgkin or large B-cell lymphomas) is mandatory before performing a diagnosis of LYG. Since post-transplant lymphoproliferative disorder and iatrogenic immunodeficiency-associated lymphoproliferative disorder are quite similar to LYG, such a diagnosis should be posed with caution in patients receiving organ transplant or those heavily treated with methotrexate or other immuno-suppressive agents (7, 22).

The main differentials is with Wegener’s granulomatosis (WG). However, WG shows a true granulomatous inflammation with scattered multinucleated giant cells, dirty “blue” necrosis and/or granulocytic microabscesses. Neutrophils, plasma cells and eosinophils represent the major cellular components in the necrotic background (1, 2, 22, 23). Vascular infiltration of WG takes the form of an inflammatory necrotizing vasculitis with a mixture of granulocytes and mononuclear cells with or without giant cells leading to at least segmental vessel wall necrosis (1, 2, 22, 23).

Special stains for mycobacteria and fungi should be performed in all cases before considering a diagnosis of LYG.

Spontaneous remission or waxing-and-waning course has been reported in grade I LYG, while grade II and III LYG are basically a unique variant of “T-cell-rich diffuse large B-cell lymphoma”, mortality ranging from 50% to 90% with an overall median survival of 14 months (3, 7, 8, 10-13, 22, 23). No standard therapies are available at now for patients with LYG. Monotherapy using steroids, rituximab or interferon-alpha has been adopted mainly in grade I LYG (10). Combined chemotherapy with CHOP ± rituximab in patients with grade II-III LYG seems to represent the best therapeutic option at now (3, 10-14, 29, 30, 32, 34).

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