

EDUCATIONAL CASE

A rare cause of fever and PET-positive nodules in the lungs**Case history**

Between November 2006 and January 2007, two non-smoking women, 58-year-old (case 1) and 51-year-old (case 2), respectively, presented with recurrent fever partly responsive to steroids and resistant to antibiotics. Routine laboratory tests were unremarkable. Both patients were immunocompetent without history of autoimmune diseases. Chest X-rays and CT-scan showed bilateral irregular nodules in the lungs. Case 1 showed several, peripherally located, poorly defined nodules of different diameter with a tendency to confluence, distributed along the bronchovascular bundles with thickening of the interlobar septa (Fig. 1A), while case 2 showed infiltration of the bronchovascular bundles, subpleural opacities with air-bronchogram associated with mediastinal lymphadenopathy (Fig. 1B). In both cases, the opacities showed intense fluorine-18 2-fluoro-2-deoxy-D-glucose uptake at PET examination (Fig. 1C). Bronchoalveolar lavage was negative for infection and tumor cells, while a not informative transbronchial biopsy was performed in case 2. The patients then underwent video-assisted thoracoscopic biopsies.

What is the diagnosis?

Histology was characterized by poorly defined pulmonary nodular lesions along the bronchovascular bundles and interstitial inflammatory infiltrates consisting of lymphocytes, plasma cells, histiocytes and intermediate-to-large centroblast-like lymphoid cells. Vascular and bronchiolar involvement by lymphoid infiltrates was noted (Fig. 1D). At immunohistochemistry, a population of large B-cells (CD20+, PAX5+ and CD79a+) intermingled with small T-lymphocytes (CD3+), predominantly with helper phenotype (CD4+) and CD68+ histiocytes, was observed. *In situ* hybridization for EBV-encoded RNA (EBER) revealed a consistent number of EBV+ large B-cells (Fig. 1E),

while molecular analyses demonstrated B-cell clonality by immunoglobulin gene rearrangement in both cases. A diagnosis of lymphomatoid granulomatosis (LYG), grade 2 according to the World Health Organization grading system (1), was made in both cases. MRI of the brain and total body CT scan, together with a bone marrow biopsy confirmed that LYG was limited to the lungs. The patients underwent four cycles of chemotherapy with R-CHOP [Rituximab, Cyclophosphamide, Hydroxydaunorubicin (Adriamycin), Oncovin (Vincristine) and Prednisone] regimen in both cases with complete clinical responses (Fig. 1F and 1G). Patient 1 has no evidence of disease at 21 months follow-up, while patient 2 died of brain stroke after 16 months with no evidence of disease recurrence.

Discussion

LYG is a misnomer coined by Liebow in 1972 (2) actually designating an EBV-driven lymphoproliferative disorder with different aggressiveness ranging from low-grade to high-grade angiocentric lymphoma likely secondary to a defective immune response to EBV (1, 3-5). LYG generally occurs in middle-aged patients (range 2-85 years) with systemic symptoms mimicking infections (especially tuberculosis), vasculitides (Wegener's granulomatosis in particular) or malignancies, and correct diagnosis is frequently delayed, requiring a mean time of 8.5 months from initial symptoms (6, 7). When LYG is restricted to lungs, fever is the main and often unique symptom, followed by general malaise, weight loss and arthralgia, but clinical manifestations are mainly organ-related (skin, central nervous system, kidney and liver *in primis*). 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 and medications) (6, 7). Interestingly, Yamashita *et al.* (8) suggested that some cases of EBV-negative grade 1 LYG are indistinguishable from pulmonary IgG4-related sclerosing disease (8), an autoimmune disorder affecting several organs and characterized by elevated serum IgG4 titer, increased IgG4-positive plasma cells in

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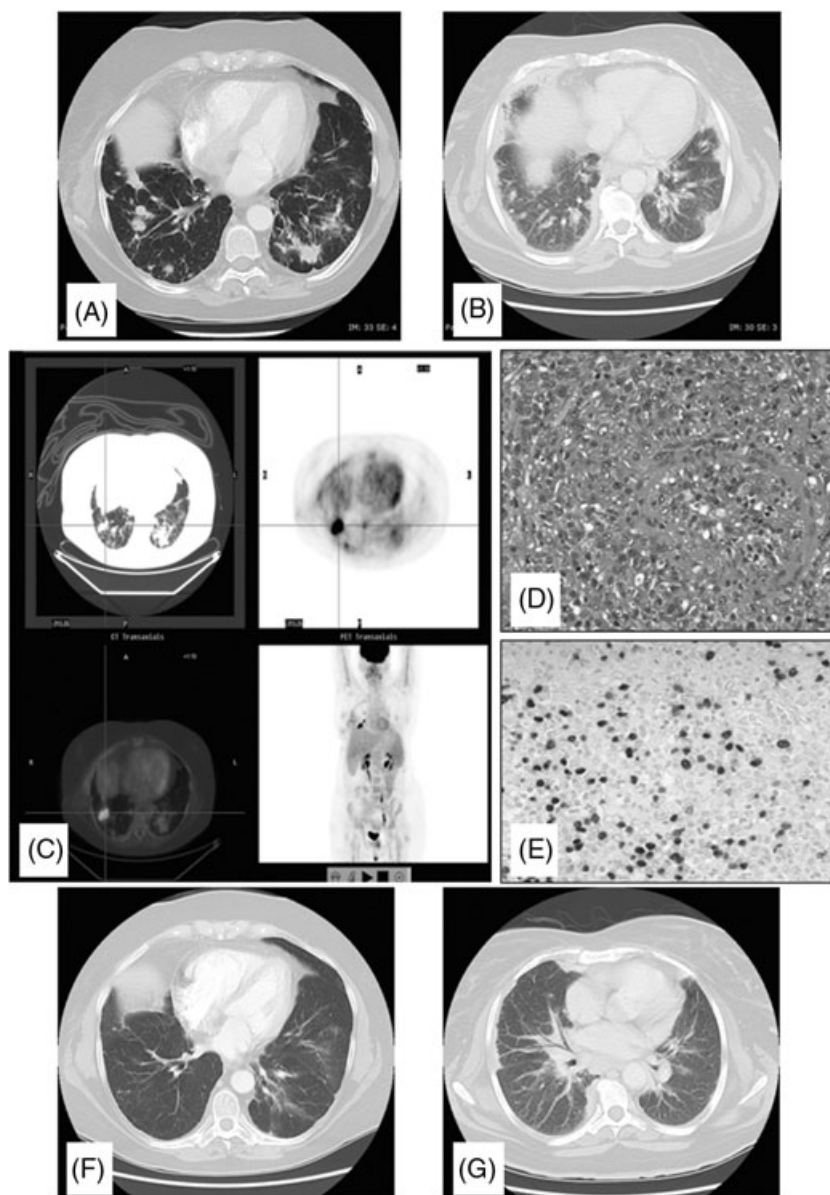


Figure 1. Chest CT of case 1 (A) and case 2 (B) at diagnosis showing several irregular nodular opacities along the bronchovascular bundles. PET scan in case 1 revealing intense Fluorine-18 2-fluoro-2-deoxy-D-glucose uptake (C). Histology showing a mixed lymphoid infiltrate with vascular involvement (D; haematoxylin-eosin X200) with several medium-to-large lymphoid cells displaying positive nuclear staining for EBV (E; EBER probe, *in situ* hybridization X200). Chest CT of case 1 (F) and case 2 (G) after chemotherapy showing resolution of pulmonary parenchymal nodules.

tissues with vascular involvement and dramatic clinical response to steroids.

Lungs are almost always involved by LYG, but respiratory symptoms may be absent, while imaging studies invariably show parenchymal nodules, opacities or poorly defined masses with a peculiar tropism for bronchoalveolar bundles and interlobular septa with or without mediastinal lymphadenopathy (9). Otherwise, LYG may appear as pulmonary cystic disease, pleural-based mass or prominent interstitial process. Diagnosis of LYG requires an accurate histopathologic examination, mainly depending on extensive sampling of generous biopsies, with the help of immunohis-

tochemical stains and molecular analysis. Grade 2/3 LYG generally raise the suspicion of a malignant lymphoproliferative disease even in the hands of general pathologist, whereas grade 1 LYG may result a formidable challenging diagnosis. Sharing these complicated cases with more expert colleagues and performing EBER-EBV analysis on multiple sections or blocks should be helpful in discriminating LYG from other mimicking processes. Based on the number of EBV-positive large B-cell counted per high-power field, LYG is graded on three grades. Spontaneous remission or waxing-and-waning course has been reported in grade 1 LYG, while grade 2 and 3 LYG are basically a

variant of T-cell-rich histiocyte-rich large B-cell lymphoma, mortality ranges from 50% to 90% with an overall median survival of 14 months (6, 7). No standard therapies are available now for patients with LYG. Monotherapy using steroids, rituximab or interferon-alpha has been adopted mainly in grade 1 LYG, the less common and more controversial form of this disease, while CHOP \pm rituximab in patients with grade 2–3 LYG seems the best therapeutic option at now.

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