

THE MASQUERADES OF BILATERAL MULTIPLE PULMONARY NODULES

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Description of two Cases

A 26 year-old South American woman presented with a four week history of productive cough, fevers, sweats, weight-loss, tender cervical lymphadenopathy and hepatosplenomegaly. Investigations revealed abnormal liver function, pancytopenia and patchy, rounded infiltrates with widened mediastinum on chest X-ray. Provisional diagnosis of lymphoma and tuberculosis were considered. Broad spectrum antibiotics were commenced. Lymph node and bone marrow biopsies proved negative for both malignancy and bacterial, fungal, viral, mycobacterial and other opportunistic infections. HIV serology was negative. Serial CT imaging of the chest revealed mediastinal and hilar adenopathy with bilateral, multiple poorly- defined nodules of variable size. Multiple bronchoscopies with broncho-alveolar lavages (BAL) and endoscopic transbronchial biopsies (TBB) were inconclusive. A PET scan showed increased uptake in both lung nodules and lymph nodes on both sides of the diaphragm. Meanwhile, her symptoms, fever and pancytopenia spontaneously resolved and, after six weeks of inconclusive investigations, the patient self-discharged. She represented within three weeks with recurrent fever. A video-assisted thoracoscopic lung biopsy (TLB), performed some three months after initial presentation, made the diagnosis of lymphomatoid granulomatosis.

In comparison, a 78 year-old man with rheumatoid arthritis, bronchiectasis and bronchiolitis had a history of six inpatient admissions in twelve months for management of infective exacerbations of airways disease and "pneumonia". Multiple investigations including bronchoscopies with BAL and TBB proved inconclusive. Serial chest imaging revealed persistent mediastinal lymphadenopathy and multiple pulmonary nodules of variable sizes, which changed in appearance and extent over time. Lymphomatoid granulomatosis was eventually diagnosed with a TLB, following which the patient succumbed with MRSA septicaemia and multi-organ failure.

Review of medical records reveal that these are the only two documented cases of lymphomatoid granulomatosis diagnosed at Liverpool Hospital over the last ten years.

Key Questions for Discussion

1. What is the definition and the epidemiology of lymphomatoid granulomatosis?
2. Describe the typical clinical and radiological manifestations.
3. Does Epstein Barr Virus play a role in the pathogenesis ?
4. What are the histological features and classification?
5. Is lymphomatoid granulomatosis a lymphoproliferative disorder ?
6. What is the best method used for diagnosis ?
7. Describe the treatments available.
8. What is the prognosis ?

Relevant Literature Review

Lymphomatoid granulomatosis (LG) was originally described by Liebow and Carrington in 1972 as a variant of limited Wegener's granulomatosis (1). The World Health Organisation currently defines LG as an angiocentric and angiodestructive lymphoproliferative disease involving extranodal sites, composed of atypical B cells usually positive for Epstein Barr virus (EBV) and admixed with reactive T cells [2]. This is a rare and unusual condition, with only

600 cases having been described in the literature. The lung is the most commonly affected organ. LG generally presents between the ages of 30 and 50 with a male predominance [3].

Primary presenting symptoms are typically fever, cough, malaise, weight loss, dyspnoea and night sweats. However, neurological symptoms such as mental changes, ataxia, diplopia and mono or polyneuropathies or cutaneous involvement may also occur when these systems are involved. The classical radiological description of LG is bilateral multiple pulmonary nodules of variable sizes distributed along the bronchovascular bundles or interlobular septa commonly in the mid to lower zones. Conglomeration of nodules can occur but solitary nodules and cavitation are rare [3]. As demonstrated in our cases, serial imaging may demonstrate change in size and position of the nodules ("wax and wane") [4].

The diagnosis of LG is histological, requiring the presence of polymorphic lymphoid infiltrates, transmural infiltration of arteries and veins ("angiitis") and focal areas of necrosis within the lymphoid infiltrates ("granulomatosis"). The progressive histopathological stages (Grade 1 to Grade 3) reflect the increasing presence of atypical, EBV-positive, large B lymphocytes. Grade 3 has the worst outcome and most closely resemble the clinical and pathologic features of diffuse large B cell lymphoma [3]. It is now generally accepted that LG is an EBV-associated lymphoproliferative disease (2). However a direct causal link between EBV & LG has, as yet, not been demonstrated.

Since the diagnosis is histological, LG usually requires a surgical biopsy, most commonly of the lung. Bronchoscopic transbronchial biopsy has low diagnostic yield therefore a thoroscopic lung biopsy is usually required to establish the diagnosis. Not surprisingly, the diagnosis is often delayed possibly due to dissociation between symptomatology, radiology, clinical signs and the disinclination to perform an invasive surgical procedure.

LG has a high mortality rate (>50%) with reported median survivals from diagnosis varying between 14 and 72 months. Nevertheless, spontaneous resolution can occur in approximately 20% of patients without specific treatment (4). Thus, in relatively asymptomatic patients with low-grade histology a reasonable case can be made to just observe. Otherwise, there is no consensus on "best treatment" but combined corticosteroids and cytotoxic therapy have been reported to achieve complete remission in approximately 50% of cases (5). Other proposed therapies such as interferon alfa-2b, anti CD-20 and autologous haematopoietic stem cell transplantation remain unproven.

Key References

1. Lieblow, AA, Carrington CR, Friedman, PJ. Lymphomatoid granulomatosis. *Hum Pathol* 1972 3: 457-558
2. Jaffe, ES, Wilson WH. Lymphomatoid granulomatosis: In: World Health Organisation Classification of Tumours. IARC Press, Lyon, France. 2001 P185
3. Lee JS, Tuder R, Lynch DA. Lymphomatoid Granulomatosis: Radiologic features and Pathologic correlations. *American Journal of Roentgenology* 2000: 175, 1335-1339
4. Bolaman Z, Kadikoylu G, Polatli M, Barutca S, Culhaci, Senturk T. Migratory Nodules in the Lung : Lymphomatoid Granulomatosis. *Leukemia and Lymphoma* 2003, Vol 44 (1) 197-200
5. Fauci, AS, Haynes BF, Costa, J et al. Lymphomatoid Granulomatosis. Prospective clinical and therapeutic experience over 10 years.. *N Eng J Med* 1982 306: 68-74