

# Bronchocentric granulomatosis associated with pure red cell aplasia and lymphadenopathy

María A Martínez-López, José M Peña, Joaquín Quirarte, María C Fernández, Juan J González, Mercedes Patrón, Juan J Vázquez

## Abstract

**Bronchocentric granulomatosis developed in a patient with previously diagnosed pure red cell aplasia and lymphadenopathy. There was an excellent response to corticosteroid treatment. An immunological pathogenesis common to bronchocentric granulomatosis and pure red cell aplasia is suggested.**

First described in 1973,<sup>1</sup> bronchocentric granulomatosis is characterised by destructive granulomatous inflammation centred on bronchi and bronchioles. According to the original description the disorder is confined to the lungs, but several case reports since then have recorded bronchocentric granulomatosis in patients with extrapulmonary disorders.<sup>2-8</sup> We report a case of bronchocentric granulomatosis associated with pure red cell aplasia, prolonged fever, and lymphadenopathy.

## Case report

A 22 year old woman, who had never had asthma, was admitted to hospital in June 1987 with recurrent fever, lymphadenopathy, and severe anaemia. She had been well until two months before admission, when isolated severe anaemia developed and a bone marrow aspiration showed the characteristic features of pure red cell aplasia. At that time neither fever nor lymphadenopathy was present, and several units of packed red cells were transfused.

On admission the only abnormal findings were pallor and diffuse lymphadenopathy. Her haemoglobin was 6.5 g/dl, packed cell volume 0.198, mean corpuscular volume 92 fl, reticulocytes 0.79%, white blood cells  $12.3 \times 10^9/l$ , polymorphs 57%, and platelets  $450 \times 10^9/l$ . The Coombs test and tests for rheumatoid factor and antinuclear antibodies gave negative results. Sequential serological tests for hepatitis A and B viruses, Epstein-Barr virus, cytomegalovirus, chlamydia, mycoplasma, legionella, adenovirus, res-

piratory syncytial virus, HIV-1, *Toxoplasma gondii*, salmonella, brucella, and rickettsia all gave negative results. A chest radiograph was normal. Tomograms of the mediastinum were negative for thymoma. Histological examination of a lymph node showed stimulated paracortical T cells, with no abnormal cells. Special stains and cultures for specific pathogens, including acid fast bacilli and fungi, were all negative.

Over the following months the patient continued to have recurrent fever, lymphadenopathy, and transfusion dependent anaemia requiring three units of packed red cells every month. In September 1987 she developed increasing exertional dyspnoea and a productive cough. Physical examination disclosed fever and diffuse lymphadenopathy. Laboratory tests showed that her haemoglobin was 7.5 g/dl, packed cell volume 0.23, white blood cells  $14.6 \times 10^9/l$ , polymorphs 82%, and platelets  $320 \times 10^9$ . Serum immunoglobulins (including total IgE) and complement levels were normal. A chest radiograph showed right upper and middle and left lower zone shadowing (fig 1). Serum precipitins for *Aspergillus fumigatus* and *Candida albicans* were not present. An aspergillus skin-prick test and Mantoux skin test gave negative results. A second bone marrow aspirate and biopsy examination showed normal cellularity, absence of erythroid precursors, and normal leucopoiesis and megakaryocytes.

An open lung biopsy was performed. Histological examination showed necrotising granulomatous inflammation centred on and destroying bronchioles, with sparing of vessels (fig 2), consistent with bronchocentric granulomatosis. Bacterial cultures and special stains and cultures for mycobacteria and fungi were negative.

Treatment with prednisolone 60 mg daily was started. The patient showed rapid improvement, with disappearance of fever and pulmonary symptoms within one week and progressive resolution of lymphadenopathy, anaemia, and pulmonary infiltrates over the ensuing weeks. In April 1988 she was weaned off corticosteroids. At that time a repeat bone marrow examination and chest radiography gave normal results. At the most recent follow

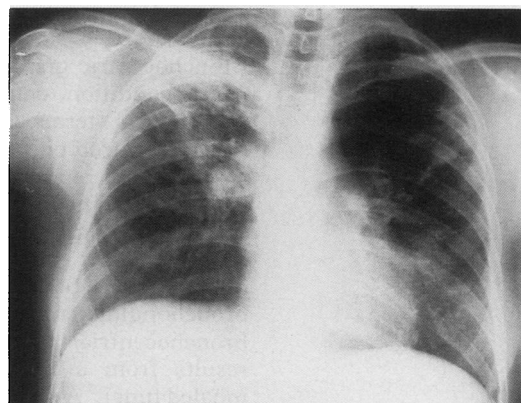


Figure 1 Chest radiograph showing shadowing of the right upper and middle and left lower zones.

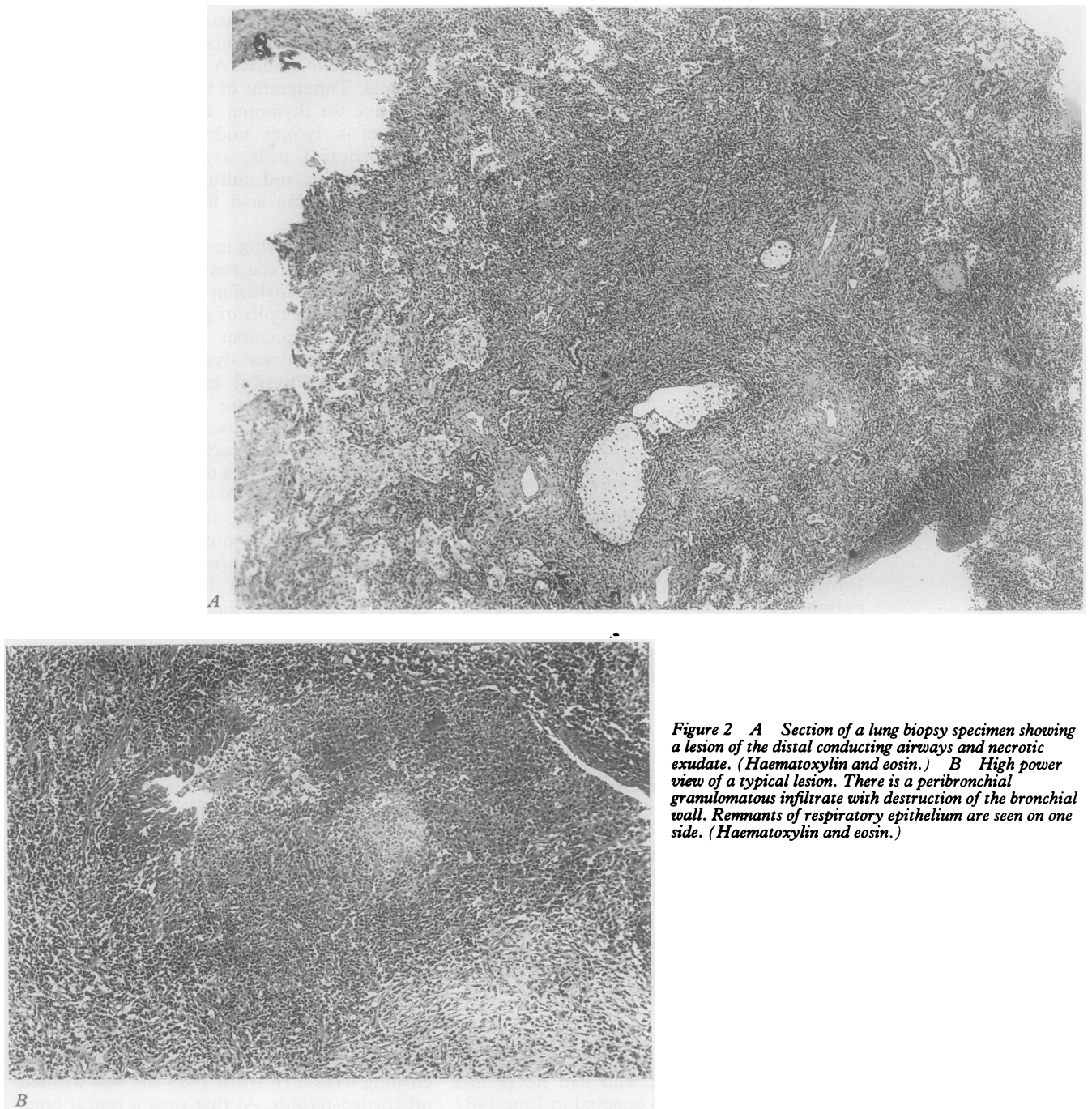
Departments of Internal Medicine, Haematology, and Pathology, Hospital "La Paz," Universidad Autónoma de Madrid, Spain

M A Martínez-López  
J M Peña  
J Quirarte  
M C Fernández  
J J González  
M Patrón  
J J Vázquez

Reprint requests to:  
Dr M A Martínez-López,  
Avda Llano Castellano 3,  
5 B, 28034 Madrid, Spain

Accepted 25 July 1991





**Figure 2** A Section of a lung biopsy specimen showing a lesion of the distal conducting airways and necrotic exudate. (Haematoxylin and eosin.) B High power view of a typical lesion. There is a peribronchial granulomatous infiltrate with destruction of the bronchial wall. Remnants of respiratory epithelium are seen on one side. (Haematoxylin and eosin.)

up, three and a half years after diagnosis, she was still symptom free.

### Discussion

Bronchocentric granulomatosis is a rare idiopathic condition, defined by Liebow<sup>1</sup> in pure pathological terms as necrotising granulomatosis centred on peripheral conducting airways. Recent reports emphasise that it should be considered not as a disease but as a descriptive pathological diagnosis.<sup>9</sup> About 50% of reported cases of bronchocentric granulomatosis have been associated with allergic bronchopulmonary aspergillosis. In this group bronchocentric granulomatosis probably results from a hypersensitivity reaction to inhaled fungi.<sup>3</sup> A second group consists of non-asthmatic patients in whom the features of aspergillus hypersensitivity are absent. The

origin of bronchocentric granulomatosis in this latter group remains unknown. Our patient was not asthmatic and lacked evidence of hypersensitivity to fungi. An invasive infection was excluded by vigorous investigation.

Extrapulmonary features were originally considered not to be part of the spectrum of bronchocentric granulomatosis; but several case reports since the original report have described articular lesions<sup>3-7</sup> (particularly rheumatoid arthritis), and lesions of the eye<sup>2</sup> and, possibly, kidney<sup>8</sup> in association with the pulmonary manifestations. Interestingly, Hellems *et al*<sup>5</sup> reported a case of bronchocentric granulomatosis associated with rheumatoid arthritis in which arthralgia and vasculitis occurred during exacerbations of the bronchocentric granulomatosis, suggesting that bronchocentric granulomatosis might be part of a systemic disease process.

Although mild to moderate anaemia is common in patients with bronchocentric granulomatosis, severe anaemia due to pure red cell aplasia has not previously been described in this condition. Pure red cell aplasia is an uncommon disease for which an autoimmune aetiology has been proposed in view of the presence of serum immunoglobulin inhibitors of erythropoiesis in many patients and the frequent association of the condition with other immune disorders.<sup>10</sup> The association of fever and lymphadenopathy with pure red cell aplasia in our patient may suggest a common infectious (presumably viral) pathogenesis. Nevertheless, the following facts argue against this origin: (1) the appearance of lymphadenopathy and fever two months after the diagnosis of pure red cell aplasia was made; (2) the chronic course of the severe anaemia; (3) no evidence of acute infection from sequential tests for serum antibodies to multiple viruses; and (4) the excellent response to corticosteroid treatment.

Although we cannot exclude a causal relation, the temporal association of pure red cell aplasia, lymphadenopathy and prolonged fever with bronchocentric granulomatosis in our patient, and the rapid resolution of all features with corticosteroid treatment, supports the idea that bronchocentric granulomatosis is part of a systemic disease process, as suggested by others.<sup>5</sup> We suggest that both bronchocentric granulomatosis and extrapulmonary disease might reflect a widespread disordered immunological reaction to an as yet unidentified

antigen. The association of bronchocentric granulomatosis with pure red cell aplasia, a disorder for which an autoimmune pathogenesis has been proposed, would seem to support our hypothesis. Further studies are needed to identify the antigen responsible and assess the immune system in patients with bronchocentric granulomatosis, especially in those patients with associated extrapulmonary features.

This work was supported by a grant from the Caja de Ahorros y Monte de Piedad de Madrid.

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