Necrotizing sarcoid granulomatosis with an uncommon manifestation: clinico-pathological features and review of literature

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ABSTRACT

We report a rare case of an incidental diagnosis of necrotizing sarcoid granulomatosis (NSG) in a 60-year-old non smoker male. The patient was admitted to the hospital for sudden back pain. Chest X-ray revealed areas of parenchymal consolidation and high resolution computed tomography demonstrated a pulmonary nodular pattern without any lymph node enlargement. All laboratory and pulmonary function tests were normal. Bronchoscopy with bronchoalveolar lavage showed no sign of infection or specific inflammation. The diagnosis of NSG was made by histopathological examination of a lung surgical biopsy and by excluding other causes of granulomatous disease. In pauci/asymptomatic patients, as was our case, therapy is not necessary with a good prognosis and complete recovery. NSG is a rare systemic disease lying in between sarcoidosis and Wegener's granulomatosis with a benign clinical course that should always be kept in mind in patients with nodular pulmonary lesions even with subclinical or uncommon features.

KEY WORDS: Back pain, Pulmonary nodules, Granulomatous disease, Histopathology, Sarcoidosis, Wegener's granulomatosis.
Necrotizing sarcoid granulomatosis (NSG) is an uncommon systemic disease of unknown etiology and incidence. NSG is more common in females than males and most subjects are smokers. The age of presentation varies with distribution of cases between the second and the sixth decade of life [1]. It was described for the first time in 1973 by Liebow as a lung granulomatous disease characterized by sarcoid-like granulomas, vasculitis and a variable degree of necrosis [2]. Since then several case reports have documented the existence of NSG, mainly reporting lung involvement [1, 3-10]. The etiology and pathogenesis are both still unknown.

Up to today it has not yet been defined whether this disease is a specific entity, a variant of sarcoidosis or pulmonary vasculitis (Churg-Strauss syndrome or Wegener’s disease), or a hypersensitivity reaction, as some features are found in all these diseases. NSG is diagnosed on the basis of morphological features and shares common histological and clinical patterns with sarcoidosis.

The radiological pattern consists of multiple bilateral nodules and infiltrates or appears as a solitary mass. Evidence of cavitation and hilar lymphadenopathy is occasionally seen.

The clinical presentation can be extremely variable: cough is the most common manifestation, followed by chest pain, dyspnea, weight loss and fatigue. Subclinical or uncommon manifestations, as in our case, have rarely been described [1, 3, 4].

We report a case of NSG in which the final diagnosis was based on an accurate radiological and overall morphological approach. A brief review and update of the literature is also provided mainly focusing on lung NSG.
CASE REPORT

A 60-year-old non-smoker caucasian male presented at the hospital with sudden back pain (eased with paracetamol). At admission he did not report any other symptoms as fever, malaise or any kind of trauma and careful medical history was taken to rule out whatever ingested or injected factors. Physical examination was quite unremarkable except for a reduced breath sounds at the right lung base. Chest X-ray was performed and showed bilateral lower lobe areas of consolidations associated with linear atelectasis. High resolution computed tomography (HRCT) was performed and multiple bilateral nodular lesions, mostly localized in the lower lobes (>2 cm of maximum diameter), and with a prevalent subpleural distribution (Figure 1) were detected. Some lesions had the “halo sign” but no cavitations were detected. Abdominal ultrasound was normal.

Laboratory analysis revealed a low number of white blood cells (3760 µ/L) and low lymphocytes (720 µ/L) especially of the CD4 subset. Erythrocyte sedimentation rate, C-reactive protein, electrophoresis of proteins, angiotensin-converting enzyme concentration, serum immunoglobulins and autoantibodies (anti-nuclear antibodies, anti-extractable nuclear antigen antibodies, anti-neutrophil cytoplasmatic antibodies) were normal. Microbiological investigation including HIV test (blood), Quantiferon-TB gold (blood), Aspergillus fumigatus (bronchoalveolar lavage), Histoplasma capsulatum (urine and blood), Chlamydia (bronchoalveolar lavage and blood), were negative.

Pulmonary function tests revealed normal lung volume with a mild (74%) reduction in diffusing capacity of the lung for carbon monoxide (DLco).

Bronchoscopy and bronchoalveolar lavage fluid was negative for infections and malignant cells. Differential cell count was normal (CD4/CD8 ratio 1.8 %).

Transbronchial biopsy was carried out, but unfortunately it did not give any diagnostic
information, thus a thoracoscopic lung biopsy was performed.

Histological analysis showed a severe, mostly inflammatory architectural rearrangement (Figure 2). The inflammatory infiltrate was mainly characterized by aggregates of epithelioid granulomas with surrounding chronic inflammation. Granulomas were primarily located in subpleural areas and along bronchovascular bundles. Many granulomas showed a confluent pattern with extensive central areas of necrosis. Transmural lymphocytic vasculitis was also seen. All special stains including Gomori methenamine silver, Giemsa, Gram, Warthin-Starry and periodic acid-Schiff did not reveal any bacteria or fungi. Atypical and typical Mycobacteria, investigated also by nested polymerase chain reaction, were negative. No foreign body was identified by examination with polarized light microscopy.

The histological analysis led to a final diagnosis of NSG.

Without any therapy the patient’s symptoms disappeared within four weeks following the biopsy. Serial clinical and radiological follow-up were scheduled, and chest X-ray one month after the surgery showed a significant reduction of remaining pulmonary infiltrates. To date there is no evidence of progression of the lesions.
DISCUSSION

Since the first report by Liebow several authors have described the existence of NSG [1, 3-10, 12-21], mostly involving lung parenchyma (Table 1). The etiology and pathogenesis are both unknown and for final diagnosis a biopsy specimen is required.

Clinical presentation is quite variable and nonspecific. Cough is the most common clinical manifestation of NSG, followed by pleural chest pain, dyspnea, fever and constitutional symptoms of weight loss [6, 18]. However approximately 25% of patients are pauci/asymptomatic [20]. Limited information is available in the literature about laboratory tests. The most important clinico-radiological differential diagnoses of NSG are Wegener’s granulomatosis, rheumatoid arthritis, sarcoidosis and metastasis. It is important to distinguish NSG from systemic vasculitis or metastasis because of differences in prognosis and response to treatment.

Unlike subjects with Wegener’s granulomatosis, patients with NSG have no upper airway disease, nephritis or systemic vasculitis. Moreover the round opacity typically demonstrates thick patchy wall cavitation areas that in our case were completely absent [22, 23].

Uveitis or cutaneous lesions, involvement of hilar lymph nodes and increased ACE levels, usually frequent in sarcoidosis, are rare in NSG, as in our case.

Although NSG and sarcoidosis seem to have different presentations, there is still debate whether the two diseases are distinct entities [18]. Indeed there are some similarities between sarcoidosis and NSG. Both diseases have a favorable prognosis, similar immune mechanism and distribution of granulomas [24]. Furthermore 5% of patients with sarcoidosis show the typical histology of NSG [25, 26].

The HRCT of rheumatoid lung nodules shows well defined nodules with lobulated margins. The size of isolated nodular lesions may increase during the acute phase of the disease.
proportional to the antibody titer. The hypothesis of rheumatoid lung disease was excluded in our case because all antibody titers were negative and in the clinical history no arthralgias were reported.

In our case the nodules were mainly peripheral with a predilection for the lower lobes, thus also lung metastasis had to be considered. Metastatic opacities usually have regular and well-defined margins but sometimes are hazy with a halo sign, as in choriocarcinomas and angiosarcomas. Cavitations or calcifications depend on the histologic pattern of the primary tumor. We excluded metastatic disease especially because no primary tumor had been detected and the patient had a relatively stable condition.

Biohumoral analysis and HRCT scans may now more sensitively suggest the disease, however lung biopsy is the cornerstone for establishing the diagnosis of NSG. This is particularly true in cases with subclinical or uncommon presentation as in our patient.

Indeed, back pain could be due to degenerative discopathy (spondyloarthrosis) or more likely to the subpleural lower lobe localization of nodules (pleuritic chest pain).

From a pathological point of view the most important differential diagnoses are Wegener's granulomatosis and infection. Well-formed non necrotizing sarcoid granulomas are rarely seen in Wegener's granulomatosis. Moreover the vasculitis of Wegener's is more necrotizing and often suppurative [18, 19, 27]. The differential diagnosis with infection is more difficult: the application of conventional microbiological analysis and overall tissue ancillary techniques such as special stains, immunohistochemistry and molecular analysis (the latter for mycobacterial detection) are important. Above all the application of a high specific and sensitive molecular technique as nested PCR for mycobacterial detection is mandatory. This is particularly true in cases with subclinical or uncommon features as in the case presented here.
The prognosis of NSG patients has been described as favorable. Indeed the clinical course is generally benign with a good responsiveness to steroid treatment or even with no therapy [1, 6, 17]. The most known case reports/series of lung NSG are listed in table. In many cases no medical treatment was required as was in our case. Treatment seems to be associated with relapse and should be indicated only when symptoms are severe.

We have presented a case of NSG with an uncommon clinical manifestation whose final diagnosis was based on a multidisciplinary approach and overall on accurate morphological and molecular analysis. Our case supports the fact that the disease has a benign clinical course with complete spontaneous recovery especially when tissue lesions are not extensive and there are no constitutional symptoms.

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LEGENDS

Figure 1 High resolution computed tomography.
(a) HRCT shows multiple bilateral nodular lesions mostly localized in the lower lobes and with a prevalent subpleural distribution. (b) Some lesions have the “halo sign”. (c) At left lower lobe a larger nodule is adherent to the left costovertebral space.

Figure 2 Histology.
(a) Granuloma with a large central area of parenchymal necrosis with coagulative pattern; bar scale: 500µm. (b) Foci of organizing pneumonia; bar scale: 150 µm. (c) Lymphocitic vasculitis involving small arteries; bar scale: 150 µm.
Table 1. Lung necrotizing sarcoid granulomatosis: literature review.

<table>
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<tr>
<th>Author/Year</th>
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<th>Night sweats</th>
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* Others include shoulder pain, subcutaneous nodule, sore throat, conjunctivitis, headache, VI-VII left cranial nerve palsy, diarrhea, lower limb weakness, neurological symptoms, weight loss, shortness of breath and malaise.

** Symptoms were reported in 64/93 cases, thus different symptom percentages were calculated in 64 patients. Treatment information was available in 63 patients, thus no treatment percentage was calculated in 63 cases.

F, female; M, male