Necrotizing Sarcoid Granulomatosis of the Lung in a 12-Year-Old Boy With an Atypical Clinical Course

Serena Panigada, MD,1 Nicola Ullmann, MD,1 Oliviero Sacco, MD,1 Claudio Gambini, MD,2 Andrew Bush, MD,3 and Giovanni A. Rossi, MD1*

Summary. Necrotizing sarcoid granulomatosis (NSG) is a disorder of unknown etiology, rarely described in childhood, belonging to the heterogeneous group of the pulmonary angiitis and granulomatosis. One of the characteristics of NSG is to have typically a benign clinical course with minimal treatment with systemic steroids or even with no therapy at all. Here, we report the case of a boy with a lung consolidation, with morphological and histological features consistent with a diagnosis of NSG. Good clinical and roentgenographic response to high dose prednisone treatment was followed three times by relapses, when steroid treatment was tapered. New lesions were detected in different areas of the lung and not in initially affected area, never previously described in NSG and only rarely in other pulmonary angiitides.

Key words: pulmonary vasculitis; sarcoidosis; children; granulomatosis with polyangiitis.

INTRODUCTION

Necrotizing sarcoid granulomatosis (NSG) is extremely rare in children, characterized by pulmonary nodular infiltrates and, histologically, by granulomatous vasculitis, sarcoid-like granulomas, and necrosis.1 Its etiology and pathogenesis are poorly understood and whether it is a discrete entity or a variant of sarcoidosis is still a matter of debate.2,3 Radiologically, either multifocal nodular pulmonary infiltrates or single pulmonary nodules are seen, with hilar lymphadenopathy described in 10–65% of the cases.4–7 In contrast with “classical” sarcoidosis, extrapulmonary involvement is uncommon in NSG.2–4 The disorder is responsive to corticosteroids and has typically a benign clinical course, even with minimal or no therapy.2–4 Here, we report a case of a boy who presented with an isolated lung consolidation with clinical, roentgenographic and histological features consistent with a diagnosis of NSG, with an unusual clinical course.

CASE REPORT

In March 2009, a 12.2-year-old boy was admitted to the Gaslini Institute with a 6-week history of low-grade fever, cough, and a left-sided chest pleuritic pain, eased with paracetamol. Prior admission, an infiltrate in the left lower lobe had been detected by chest X-ray (Fig. 1A). There had been no improvement with empirical treatment with a variety of antibiotics, including cephalosporins, macrolides, rifampicin, and β-lactams.

On admission, a CT scan showed minor sub-carinal and hilar lymph node enlargement (Fig. 1B), consolidation in the left lower lobe (Fig. 1C) and splenomegaly (Fig. 1D). The laboratory findings showed elevation of the C-reactive protein [4.41 mg/dl (normal ≤0.5)], mild anemia (Hb 9.1 g/dl), normal platelet and white-cell counts, specifically with no eosinophilia. Blood urea nitrogen (BUN) was 10 mg/dl, creatinine 0.5 mg/dl, and electrolytes normal. Urinalysis was negative for protein and blood; microscopic examination revealed no cellular elements or casts. Tuberculin skin test was negative with normal serum IgA, IgG, and IgM levels. Spirometry
demonstrated a restrictive pattern (FVC, FEV₁, and DLCO = 58%, 60%, and 59% of predicted, respectively). A fiberoptic bronchoscopy was performed. No subglottic, tracheal, or endobronchial stenoses were observed. Bronchoalveolar lavage (BAL) cytology showed 64.7% macrophages, 25.2% lymphocytes, and 5.9% neutrophils (normal values in our lab = 86.2% ± 7.8%, 8.7% ± 5.8%, and 0.1% ± 0.2%, respectively). The CD4⁺/CD8⁺ cell ratio was slightly elevated in BAL and normal in blood. BAL culture and molecular microbiology tests, including fungi and mycobacteria, were all negative. Thickened basement membrane and mild mononuclear cell inflammatory infiltrate were detected in bronchial biopsy, with no evidence of granuloma. A video-guided thoracoscopic biopsy was performed. Histological examination of the biopsies showed multiple granulomas of various sizes in the lung parenchyma, including the subpleural and pleural regions, with central necrosis (Fig. 2A). There were cuffs of lymphoid cells in the periphery of the granulomas, surrounded by radially oriented (palisading) histiocytes and scattered multinucleated Langerhans-type giant cells (Fig. 2A and B). Small and medium-sized vessels exhibited luminal narrowing or vascular occlusion with vasculitic infiltrates consisting of lymphocytes and histiocytes (Fig. 2C). Immunohistochemistry revealed a strong predominance of CD4⁺ over CD8⁺ T-cells. Auramine, Ziehl-Neelsen, PAS, Grocott, Giemsa, Gram, and Warthin-Starry stains were negative for acid-fast and other bacteria or fungi. The angiotensin converting enzyme (ACE) serum level was 12 U/L (normal 8–52 U/L). Autoantibodies (ANA, c-ANCA, and p-ANCA) and

Fig. 1. A: Chest X-ray performed before admission, demonstrating the presence of a pulmonary infiltrate in the left lower lobe. CT scan performed on admission, showing small subcarinal and hilar lymphadenopathies (B), consolidation in left lower lobe (C) and splenomegaly (D).

Fig. 2. Light microscopy of lung biopsy. A: Low-power view showing large zone of necrosis (°) with palisading histiocyte (→) surrounded by an intense inflammatory reaction consistent of multiple noncaseating granulomas (>) (Hematoxylin-eosin. Original magnification ×25). B: Medium-power view showing a granuloma consisting of confluent clusters of epithelioid cells, giant cells, and scattered lymphocytes (Hematoxylin-eosin. Original magnification ×100). C: Low-power view showing a vein with extensive inflammatory granulomatous infiltration of its wall (Weigert elastic fiber stain. Original magnification ×40).
rheumatic factor were all negative. Sinonasal CT scan was performed and did not show any bony destruction of the nasal cavity or any abnormal change of the paranasal sinuses, of the mastoid cells, or of the orbits. Consistently, fluorodeoxyglucose (FDG) PET scan was positive only for the pulmonary consolidation. On the basis of the clinical and roentgenographic features and of the histological characteristics, a diagnosis of NSG was made and treatment with an initial daily dose of prednisone 50 mg daily (1 mg/kg body weight) was started, to be progressively tapered after 3 months to a maintenance dose of 5 mg, every other day. He went in complete symptomatic remission.

He was re-evaluated 6 months later, in September 2009. He complained of right-sided chest pain for the past month, after the dose of prednisone had been reduced to 10 mg daily. Pulmonary function had improved slightly (FVC, FEV\(_1\), and DLCO = 70%, 70%, and 69% of predicted). Chest CT scans showed nearly complete resolution of the lower left lobe lesion, but detected “new” multiple nodular infiltrates in the right lung. No lymphadenopathy was seen (Fig. 3A and B). Blood tests were nondiagnostic and a fiberoptic bronchoscopy was again performed. BAL fluid was again negative for infections and malignant cells. Prednisone treatment was increased to 50 mg daily, with progressive remission of symptoms.

In January 2010, complete regression of the pulmonary lesions was demonstrated by CT scan, associated with a further improvement of lung function (FVC, FEV\(_1\), and DLCO = 80%, 80%, and 81% of predicted). The prednisone dose was progressively tapered to a maintenance dose of 10 mg daily.

In August 2010, when on treatment with prednisone 10 mg daily, he again complained of intermittent right-sided chest pain, localized to the right antero-lateral chest wall. Chest pain was progressively increasing in intensity and frequency. He was readmitted in September 2010. A significant deterioration of lung function (FVC, FEV\(_1\), and DLCO = 71%, 70%, and 74% of predicted)
was associated with a “new” single subpleural nodular lesion in the right middle lobe on CT scans (Fig. 3D). Methotrexate (15 mg/m², weekly) was added to prednisone, to try to facilitate steroid tapering.

He was re-evaluated in June 2011, when on treatment with 15 mg/m² methotrexate weekly and 15 mg prednisone daily. Right-sided chest pain recurred, whenever the daily prednisone dose was decreased below 15 mg daily. Lung function improved (FVC, FEV₁, and DLCO = 103%, 100%, and 115% of predicted) with resolution of the subpleural nodular lesion in the right middle lobe, but a new single similar nodular lesion in the right upper lobe was shown in the CT scan (Fig. 3E). The patient was discharged on prednisone dose of 50 mg daily (1 mg/kg) for 6 weeks with a program of progressive tapering at 2.5 mg each week, until a daily maintenance dose of 0.25 mg/kg is reached. The patient has a follow-up visit scheduled for December 2011 and so far demonstrates again a good clinical response to prednisone with symptoms’ resolution.

**DISCUSSION**

We here report the case of boy with a lung consolidation characterized by clinical, roentgenographic and presenting features consistent with a diagnosis of NSG. However, he had an unusual clinical course, characterized by response to “high dose” prednisone but by relapse of symptoms and of the pulmonary lesions, when treatment was tapered. Unusual also is the observation that the recurrence of the pulmonary infiltrates involved lung sites, different from the initially affected area.

NSG, a very rare in childhood,⁸–¹⁰ belongs to the group of the noninfective pulmonary angiitis and granulomatosis disorders, which include granulomatosis with polyangiitis (GPA), Churg–Strauss syndrome, bronchocentric granulomatosis, and lymphomatoid granulomatosis.⁴ However, from a histological and clinical point of view, the most important differential diagnosis of NSG is sarcoidosis.⁶ Histological studies in classic sarcoidosis usually show less vasculitis and no widespread zones of predominantly coagulative necrosis. Furthermore, pleural involvement is rare in sarcoidosis and serum ACE levels are often elevated.⁶–⁷ Finally, significant involvement of the hilar lymph nodes and extrapulmonary manifestations are more frequent in sarcoidosis than in NSG.⁶–¹⁰

Another important radiologic feature distinguishing NSG from classic sarcoidosis is the propensity of pulmonary lesions to cavitate.²–⁵,⁷,⁹

Cough is the most common clinical manifestation of NSG, followed by chest pleural pain, dyspnea, fever, and constitutional symptoms of weight loss.²–⁵ However, approximately 15–40% of patients are asymptomatic.

In addition to sarcoidosis, GPA is an additional disorder to be considered in the differential diagnosis of NSG. According to the PRES/EULAR criteria,¹¹ three of the following six features should be present for the diagnosis of childhood GPA: (a) abnormal urinalysis (hematuria and/or significant proteinuria); (b) granulomatous inflammation on biopsy; (c) nasal sinus inflammation; (d) subglottic, tracheal, or endobronchial stenosis; (e) abnormal chest X ray or CT; (f) PR3 ANCA or C-ANCA staining. Since our patient had only two features (abnormal chest CT and granulomatous inflammation on biopsy) he did not meet the criteria for the diagnosis of childhood GPA. Unlike those with granulomatosis with polyangiitis, patients with NSG have no upper airway disease, no subglottic, tracheal, or endobronchial stenosis, or glomerulonephritis, or systemic vasculitis and extrapulmonary manifestations occur infrequently.³–⁵ In addition, although the radiographic manifestations of NSG and GPA, may be similar, pleural involvement and mediastinal adenopathy are more frequent in NSG than in PGA.⁵,¹²,¹³ Finally, the histological distinction of NSG from PGA is usually not difficult because non-necrotizing granulomas are not present in PGA and the vasculitis seen in PGA is characteristically more necrotizing and often suppurative.¹⁴

Treatment of NSG typically consists of corticosteroid therapy alone. Because the clinical course of the disease is usually benign, even with minimal or no therapy, immunosuppressive and cytotoxic agents are not considered appropriate options.²–⁶ Of note is that in our patient methotrexate was not beneficial.

In the case here reported, the clinical presentation, the initial radiologic features on CT scans, the blood test results, the histological characteristic of the lung tissue and the response to prednisone, all fit with a diagnosis of NSG. Relapse of symptoms (pleuritic pain) and the appearance of new pulmonary lesions in three occasions, when the dose of prednisone was tapered, has not previously been described. In addition in non-infectious pulmonary angiitis and granulomatosis, relapse tends to occur in previously involved lung areas and involvement in new sites has been described only rarely in granulomatosis with polyangiitis.¹⁵ NSG “diagnosis of exclusion,” but in this case we consider that sarcoidosis and of other vasculopathies have been excluded. Although atypical presentations of other rare conditions cannot be excluded, we believe that a novel course of NSG best fits this clinical course of this child.
ACKNOWLEDGMENTS

We thank Professors Andrew Nicholson and David M. Hansell (Royal Brompton Hospital, London, UK) for reviewing the histology and the CT scans of this case.

REFERENCES