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CASE FOR DIAGNOSIS

A 13-year-old female with shortness of breath and pleuritic chest pain

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CASE HISTORY

A 13-yr-old Caucasian female was referred to the Dept of Paediatric Diseases (Havana, Cuba) with shortness of breath and pleuritic chest pain located in her right hemithorax. The pain had occurred the day before while doing physical activity and lasted ~1 h. The patient reported a 2-month history of recurrent episodes of pleuritic chest pain, which were either self-limited or relieved by paracetamol, as well as growing fatigue in the previous few weeks. Her past history was remarkable for a diagnosis of pneumonia after exposure to fumigation during a dengue haemorrhagic fever epidemic 2 yrs earlier, which was treated with steroids and antibiotics.

On admission, the patient had no weight loss, no fever or dyspnoea. Physical examination showed decreased breathing sounds in the inferior part of both hemithoraces. Cardiovascular, abdominal and neurological examination, as well as ear, nose and ophthalmologic investigations were unremarkable. The chest radiograph showed bilateral pneumonia with moderate right-sided pleural effusion. The leukocyte count was 9.8×10^9 cells·L^{-1} with 54% neutrophils and 32% lymphocytes. The erythrocyte sedimentation rate was 85 mm·h^{-1}. Serum chemistry, renal and liver function tests were in the normal range. Blood cultures were negative. Antibiotic therapy with ceftriaxone and amikacin was started. During the treatment the patient reported 2 days of moderate fever and various episodes of left-sided pleuritic chest pain, which occurred especially during forceful diaphragm contractions (*i.e.* sneezing, laughing and coughing).

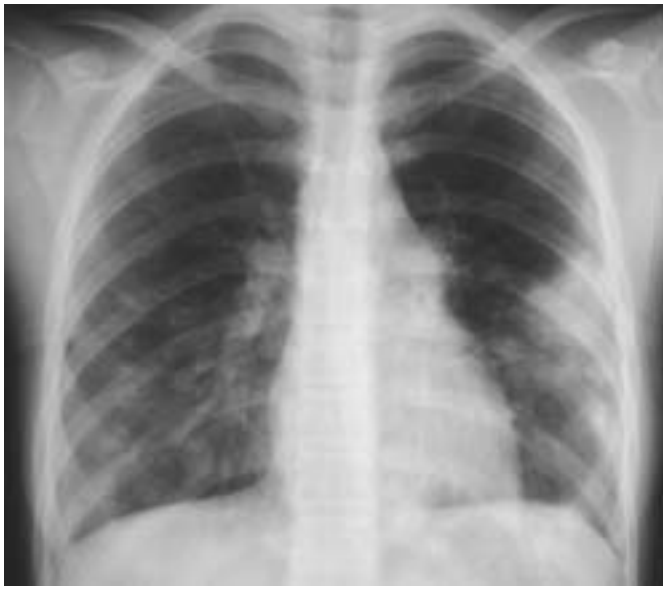

FIGURE 1. Chest radiograph obtained on October 24, 2003 (day 14 from onset).

Following a short stay in the Cuban hospital, the patient was transferred to an Italian hospital (Como). Amikacin was discontinued and clarithromycin added. A new chest radiograph (fig. 1), 14 days after the previous one, and a computed tomography (CT) scan of the thorax were performed. Echocardiography and abdominal ultrasound were both negative. An increased value of the tumour marker CA-125 (220 U·mL^{-1}, *versus* a normal value <35 U·mL^{-1}) was found. Microbiological and blood testing work-up results are shown in table 1.

After 1 week, the patient was admitted to a hospital in Milan where a thoracic CT scan (fig. 2) and whole-body positron emission tomography (PET; fig. 3) were performed. The latter was obtained in order to identify any possible extrapulmonary focus of the disease. Further microbiological and blood testing is shown in table 1.

Pulmonary function tests showed a restrictive ventilatory pattern with a total lung capacity 76% of predicted, a vital capacity of 2.66 L (75% pred), a forced expiratory volume in one second of 2.43 L (82% pred), a transfer factor of the lung for carbon monoxide of 6.52 mmol·min^{-1}·kPa^{-1} (71% pred) and a transfer coefficient of the lung for carbon monoxide of 1.83 mmol·min^{-1}·kPa^{-1}·L^{-1} (94% pred).

Fibreoptic flexible bronchoscopy did not reveal any endobronchial lesion. Cultures of bronchoalveolar lavage (BAL) for bacteria, including *Mycobacterium tuberculosis*, and for fungi, and a search for malignant cells were negative. In order to obtain a diagnosis, lung biopsy by videothoracoscopy was performed and specimens from the left hemithorax were sent to a pathologist for evaluation (fig. 4).

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TABLE 1 Microbiological work-up and blood determinations

Test	Result
Admission to Como Hospital	
Erythrocyte sedimentation rate	44 $mm \cdot h^{-1}$ (nv)
C-reactive protein	19 $mg \cdot L^{-1}$ (nv <6 $mg \cdot L^{-1}$)
IgM	383 $mg \cdot dL^{-1}$ (nv 50–220 $mg \cdot dL^{-1}$)
Legionella pneumophila urinary antigen	Negative
Streptococcus pneumoniae urinary antigen	Negative
Mycoplasma pneumoniae IgM antibodies	Negative
Epstein–Barr serology	VCA IgG positive EBNA IgG positive, EBV IgM negative
Cytomegalovirus serology	IgG negative IgM negative
Toxoplasma gondii serology	IgG negative IgM negative
Coxiella burnetii serology	IgG negative IgM negative
Histoplasma serology (antigen and antibody)	Negative
Aspergillus serology (antigen and antibody)	Negative
Cryptococcus neoformans serology (antigen and antibody)	Negative
Coxsackievirus B1-6 serology	IgG positive (1:80 titre), IgM positive (1:20 titre)
Tuberculin skin testing	Negative
Mycobacterium tuberculosis gastric aspirate and urine cultures	Negative
Parasite detection in the faeces	Negative
Chloride sweat test	Negative
Blood lymphocyte characterisation	T-cells (CD3 73%, CD4 37.8%; CD8 29.5%), CD4+/CD8+ T-cell ratio 1.28, B-cells (CD19 13.3%), NK cells (CD16–CD56 9.9%)
Admission to Milan Hospital	
Blood cultures	Negative
Chlamydia pneumoniae serology	IgG positive (titre 1:64), IgM negative, IgA positive (titre 1:32)
Legionella pneumophila serology	Negative
Mycoplasma pneumoniae serology	Weak IgM positivity
Proteus serology	Negative
Salmonella typhi and *paratyphi* serology	Negative
Entoameba histolytica, *Schistosoma haematobium*, *Toxocara canis*, *Echinococcus* serology	Negative
Rheumatoid factor and anti-ENA, anti-dsDNA, ANA, AMA, anti-SMA, ANCA antibodies	All negative
Blood lymphocyte characterisation	T-cells (CD5 80%, CD3 77%, CD4 46%, CD8 31%), CD4+/CD8+ ratio 1.47, B-cells (CD19 17%, CD20 16%, HLA-DR 18%), NK cells (3.4% (nv $12 \pm 4\%$))

nv: normal value; Ig: immunoglobulin; VCA: viral capsid antigen; EBNA: Epstein–Barr nuclear antigen; EBV: Epstein–Barr virus; NK: natural killer; ENA: extractable nuclear antigen; dsDNA: double-stranded DNA; ANA: anti-nuclear antibody; AMA: anti-mitochondrial antibody; SMA: smooth muscle actin; ANCA: anti-neutrophil cytoplasmic antibody; HLA-DR: human leukocyte antigen D-related.

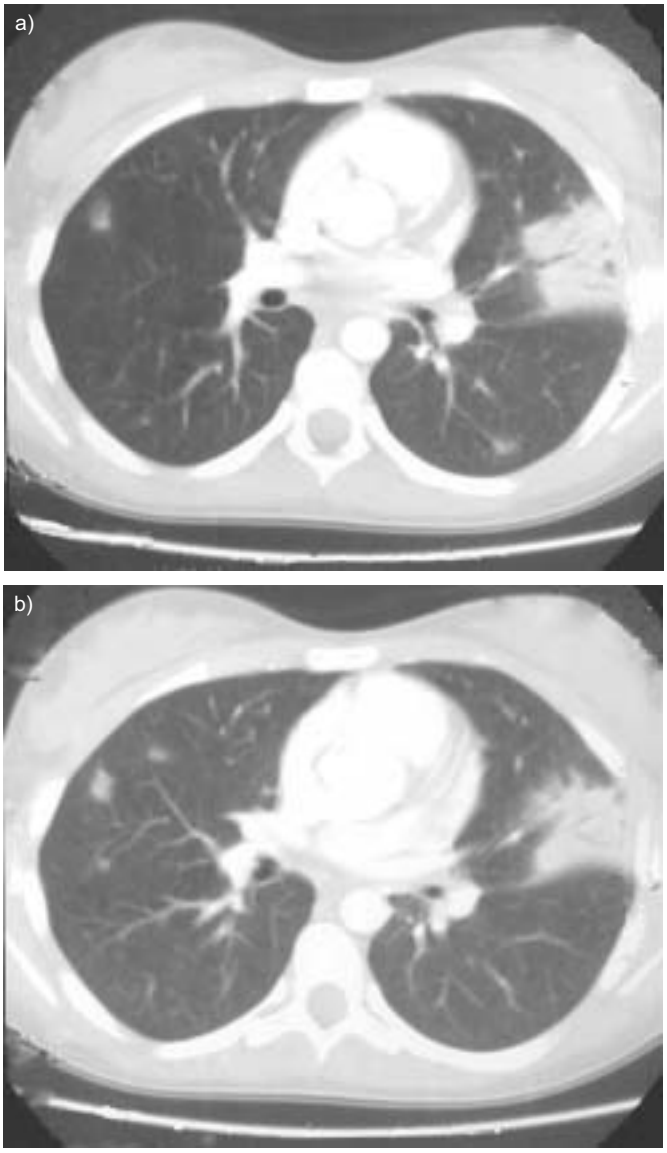

FIGURE 2. Two windows of the same chest computed tomography scan obtained on October 31, 2003 (day 21 from onset).

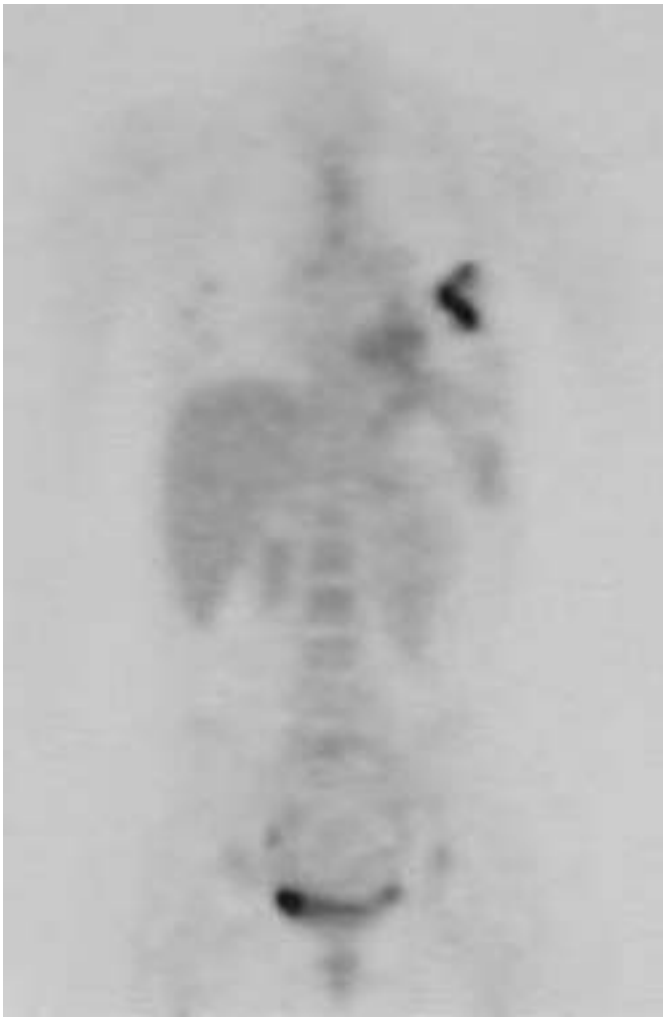

FIGURE 3. Total body positron emission tomography obtained on October 31, 2003 (day 21 from onset).

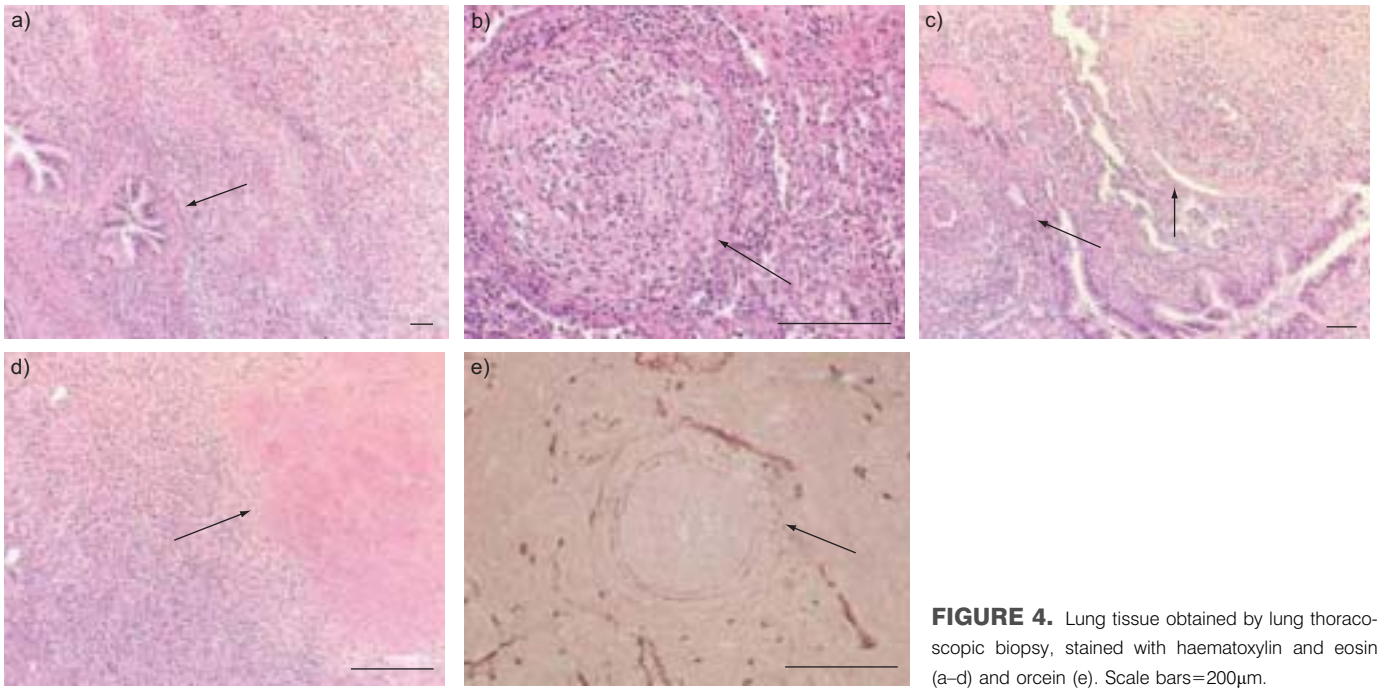

FIGURE 4. Lung tissue obtained by lung thoracoscopic biopsy, stained with haematoxylin and eosin (a–d) and orcein (e). Scale bars=200μm.

BEFORE TURNING THE PAGE, INTERPRET THE PATIENT'S HISTORY, CHEST RADIOGRAPH, COMPUTED TOMOGRAPHY SCANS, POSITRON EMISSION TOMOGRAPHY SCAN AND HISTOLOGY SLIDES, AND SUGGEST A DIAGNOSIS.

INTERPRETATION

Chest radiography

The postero-anterior chest radiograph of the lungs (fig. 1) shows resolution of the right pleural effusion and the presence of a subpleural homogeneous lung opacity, with an irregular contour located in the left middle field. No hilar lymphadenopathy was detectable.

Contrast-medium CT

The contrast-medium CT scan (fig. 2) revealed a triangular lung infiltrate in the anterior segment of the left superior lobe between the apical segment of the inferior left lobe and the lingula with its base on the pleura.

A further area of lung consolidation was present in the left inferior lobe area and numerous subpleural nodular alterations could be seen bilaterally in the inferior and middle lobes distal to the peripheral vascular divisions. On both lung fields, particularly in the middle and lower areas, a large number of nodular lesions with no enhancement and a benign aspect was present.

Whole-body PET

Diffuse high-glucidic-metabolism lesions were apparent in both lungs (fig. 3). Considering the plurifocality of the lesions and the high glucose captation of active granulomas, the PET scans are compatible with a diagnosis of granulomas.

Diagnostic considerations

In the differential diagnosis of the present case, the current authors considered the following diagnoses: 1) immune-derived granulomata (*e.g.* Wegener's granulomatosis); 2) infective granulomata; 3) metastatic lesions; and 4) cryptogenic organising pneumonia.

Surgical specimens

Macroscopic features

The lung subpleural specimen was 5 cm in greatest dimension, with yellowish nodules ranging 0.3–1.5 cm in diameter on the cut surface.

Microscopic features

Figure 4 shows the histological evaluation of the resected pulmonary lobe specimens. Figure 4a shows an intense peribronchial and vascular chronic inflammatory infiltrate consisting mainly of lymphocytes and plasma cells, and granulomas with multinucleated giant cells. Figure 4b shows a noncaseating granuloma of tightly clustered epithelioid cells and interspersed multinucleated giant cells. Vasculitis with diffuse lymphocyte and plasma cell infiltrates and granulomas with multinucleated giant cells were seen in the peribronchial areas (fig. 4c). Large areas of necrosis (on the right-hand side of fig. 4d) were seen in the centre of nodules composed of confluent granulomas. Vasculitis with chronic inflammatory infiltrates of plasma cells and lymphocytes and/or granulomatous reaction was mainly observed in areas with intense granulomatous reaction and is easily evident with special stains highlighting the wall of the vessels (fig. 4e).

Possible rare filamentous, Gram-positive and weakly periodic acid-Schiff positive, alcohol- and acid-resistant microorganisms were found in some of the sections. PCR assays were negative for both typical and atypical mycobacteria and Actinomyces. Thus, the organisms were considered innocent bystanders.

Diagnosis: Necrotising sarcoid granulomatosis.

CLINICAL COURSE

The patient was discharged with no therapy and remained asymptomatic. A CT scan taken 3 months later showed complete resolution of the opacities located in the middle and lower fields of both hemithoraces. There was a reduction in the size of the subpleural opacity in the left lower lobe. The erythrocyte sedimentation rate was 14 mm (after 1 h) and 24 mm (after 2 h); leukocyte count and C-reactive protein values were in the normal range.

DISCUSSION

Necrotising sarcoid granulomatosis (NSG), first described by LIEBOW in 1973 [1], is a rare form of pulmonary vasculitis and granulomatosis that mainly occurs in middle-aged females (40–50 yrs) [2–4]. NSG in childhood, to the current authors' knowledge, has been described in literature only four times and in only two of these cases [5, 6] was the pulmonary involvement isolated, as in the case described here. In the other two cases [7, 8] neurogical and ophthalmological lesions were encountered as well.

NSG is currently included in the group of pulmonary angiitis and granulomatosis, along with four other distinct clinical syndromes: Wegener's granulomatosis, lymphomatoid granulomatosis, bronchocentric granulomatosis, and allergic angiitis and granulomatosis (Churg–Strauss syndrome). The aetiology and pathogenesis of NSG is still unknown. Diagnosis can be reached only by pathological investigation [2, 9], through identification of sarcoid-like granulomas (fig. 4b), granulomatous vasculitis (fig. 4c) and necrosis (fig. 4d).

Cough, dyspnoea and chest pain are nonspecific pulmonary symptoms that may be present, either with or without systemic involvement, such as fever, weight loss and weakness [4]. However, 25% of patients are asymptomatic. The presentation of NSG in the 13-yr-old female was remarkable for several reasons, including the previous history of recurrent pleuritic chest pain and the onset of an ''atypical'' bilateral pneumonia. A large discrepancy was in fact present between the mild clinical presentation and the extensive radiological involvement. The recurrence of chest pain episodes and the occurrence of fever during antibiotic treatment prompted thorough diagnostic investigations to identify possible underlying diseases. This strategy was later borne out when the pneumonia was resolved but underlying chest radiography and CT opacities persisted.

The typical radiographic findings with NSG are single or multiple lung opacities [10], with common involvement of the pleura [5, 11], as was observed in this case (figs 2a and b). Lymphadenopathy in NSG is reported in 10–65% of cases [11, 12], whereas previous reports in adult [13] and paediatric patients [5] found no hilar or mediastinic lymph node enlargement, as occurred in the current case. No typical laboratory and radiographic/functional findings can be of help in diagnosing NSG. The erythrocyte sedimentation rate was elevated in this patient, a finding present in some [9], but not

all papers in the literature [6]. Pulmonary function tests showed a restrictive pattern, as in other previous cases [5, 11], but this finding is not universal [4, 6]. The CD4+/CD8+ ratio in the peripheral blood of the current patient was normal; however, in a previous case [6] this value was reported to be reduced early in the disease, but later normalised. The CD4+/CD8+ T-cell ratio in the BAL was normal too. Serum levels of immunoglobulin M were increased in the current patient, as in the case described of another 12-yr-old female with NSG [8].

Immunopathological findings are strikingly common between NSG and sarcoidosis. Whether NSG should be considered a distinct entity [14, 15] or a subform of sarcoidosis [3, 12, 16–18] with a similar immunopathological basis [19] remains, to date, an open question. Nonnecrotising granulomas and angiitis may be detected both in NSG and sarcoidosis, particularly in the less severe forms of the latter. In addition, 5% of patients with sarcoidosis show histological characteristics typical of NSG [3, 20]. Hilar lymphadenopathy and extrapulmonary manifestations are more frequent in sarcoidosis [11, 15], as is the presence of an elevated serum angiotensin-converting enzyme (ACE) level. In the present case, ACE could not be assessed, but in most of the previously reported cases of NSG [4–6, 13] it was in the the normal range. In terms of outcome, both diseases generally show a benign clinical course with a favourable prognosis.

Differential diagnoses include tuberculosis, Wegener's granulomatosis, lymphomatoid granulomatosis, neoplasms, hypersensitivity pneumonitis or Churg–Strauss syndrome. Roughly 20% of Wegener's granulomatosis cases show sarcoid-like granulomata; in the current case, this possibility was ruled out by the absence of anti-neutrophil cytoplasmic autoantibodies and the subsequent benign clinical course.

Cultural and serological studies ruled out most common infectious diagnoses. Antibodies to *Mycoplasma pneumoniae* were detected, suggesting this agent as the cause of the bilateral pneumonia in the current patient. Evidence of *Chlamydia pneumoniae* infection has previously been reported in a 14-yr-old female NSG patient [5]. On this basis some authors have hypothesised that NSG could be a form of hypersensitivity pneumonitis [9]. Other authors found Aspergillus antigen upon immunohistochemical staining of granulomas [9]. Although so far undetected in NSG, immune complexes may be involved in its pathogenesis [21].

The clinical course of NSG is usually benign [13, 16], and in most cases treatment is not required. The patient reported was discharged without any treatment and 3 months later complete clinical and radiographic resolution of the disease was witnessed. A favourable outcome was also seen in an 8-yr-old patient whose symptoms and radiographic findings disappeared in the absence of therapy [6]. Experience in terms of therapy is unfortunately still limited. Data from adults suggest that corticosteroids and immunosuppressive therapy should be restricted to patients with progressive or severe NSG, particularly in cases with central nervous system involvement [4, 7, 9, 22, 23].

In conclusion, the current authors present the clinical features of a 13-yr-old child with a diagnosis of necrotising sarcoid granulomatosis. The disease showed spontaneous remission in the absence of treatment. In the differential diagnosis of lung granulomatous lesions, necrotising sarcoid granulomatosis should be kept in mind in paediatric patients in addition to adults.

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