CASE FOR DIAGNOSIS

Rapidly progressing pulmonary nodules in a 14 yr old boy

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Case history

A caucasian male aged 14 yrs was referred to our Institute in December 1996 for the presence of diffuse pulmonary nodules. He had a history of a few viral infections of the upper airways in early childhood, without lower airway involvement. On September 9, 1996 the patient complained of a sudden chest pain, localized in the left mammary region, worsening during respiration. A chest radiograph was taken (fig. 1). Routine blood tests were within normal values and skin tests to mycobacterial antigens were negative. Anti-inflammatory treatment with nimesulide was prescribed and in 3 days the chest pain disappeared.

In the following 2 weeks the patient had intermittent, low degree fever, (37.2–37.4°C). Two additional chest radiographs, performed on October 10 and November 12, demonstrated a rapid progression of the pulmonary lesion. A computed tomography (CT) scan was performed and, in addition to the large nodular infiltrate in the mid portion of the left lung, showed multiple lesions of various sizes in the lower lobes (fig. 2). A fibreoptic bronchoscopy did not detect abnormalities of the airways. Bronchoalveolar lavage (BAL) analysis did not show any cytolological change suggesting malignancies and BAL cultures remained negative for various micro-organisms. A needle biopsy was performed, but the cytolological evaluation of the aspirate demonstrated only necrotic debris.

On admission the patient appeared in good clinical condition. Decreased sounds to percussion were noted over the middle third of the left hemithorax, anteriorly. Transthoracic blood gas determination in room air showed normoxia (arterial oxygen tension (P_a,O_2) 12.6 kPa) and normocapnia (P_a,CO_2) 5.5 kPa). Chest radiograms showed further progression of the pulmonary lesions (major diameter of 9.0 cm). Peripheral blood smear showed a white cell count of 7.96x10^9 cells·L^{-1} (neutrophils 5.91x10^9 cells·L^{-1} lymphocytes 1.16x10^9 cells·L^{-1}, monocytes 0.52x10^9 cells·L^{-1}, eosinophils 0.14x10^9 cells·L^{-1}, basophils 0.05x10^9 cells·L^{-1}). Erythrocyte sedimentation rate was 52 mm·h^{-1}, C-reactive protein was 0.06 g·L^{-1}, while serum protein electrophoresis and immunoglobin (Ig) levels were normal. Biochemical tests were in the normal range. Blood urea nitrogen and creatinine levels were normal, and urine examination did not show any abnormality. Samples of blood, pharyngeal aspirate and urine yielded negative cultures for various micro-organisms. Antinuclear antibodies, anti-neutrophil cytoplasmic antibodies (ANCA), rheumatoid factor and lupus erythematosus (LE) cell test were negative, serum immune complexes were absent; C_3 and C_4 levels were within normal values and no abnormalities in lymphocyte

Fig. 1. – Chest radiograph, performed on September 9, showing the pulmonary lesion.

Fig. 2. – Computed tomography (CT) scan of the lower part of the chest, performed on November 15, 1996.

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subpopulations were found. Skin reactivity to recall antigens and phagocytic oxidative metabolism were also normal.

CT scans of the head did not demonstrate brain lesions or signs of maxillary sinusitis. Ultrasonographic examinations showed no abnormalities in the abdominal organs and ruled out the presence of testis or thyroid tumours.

Diagnostic considerations

In the differential diagnosis of the present case we considered: 1) malignancies (non-Hodgkin’s lymphoma, multiple myeloma, metastatic lung spread of solid tumours (testis, thyroid, bones, kidneys)); 2) infections (histoplasmosis, nocardiosis, actinomycosis, cryptococcosis, mycobacteriosis); and 3) immunological diseases (lymphoid granulomatosis, Wegener’s granulomatosis of the limited type).

Surgical procedure and gross pathologic features

A left thoracotomy was performed and the left large lesion and one of the small left lower lobe nodules, were enucleated. The large nodular mass had a major diameter of 9.2 cm, a solid consistence and a tan-brown cut surface. The small lesion had the same characteristics. The removed tissue was fixed, stained and examined (fig. 3). To exclude infections, Ziehl-Nielsen, Gomori methenamine silver, periodic-acid-Schiff, Brown and Brenn, and Dietler stains were performed, but did not demonstrate the presence of micro-organisms in the resected lung tissues.
Interpretation

Chest radiographs

The posteroanterior chest radiogram, performed on September 9 (fig. 1), demonstrated a pulmonary nodule present in the mid-portion of the left lung. The nodule was well defined, sharply circumscribed, without signs of cavitation. No hilar or mediastinal lymph node enlargement nor pleural involvement can be observed.

Interpretation of computed tomography

The CT scan, performed on November 15, shows the presence of multiple, well defined lesions of various sizes, with bilateral involvement of the lower lobes, which were hidden behind the diaphragm.

Surgical specimens

Histologically the two lung lesions demonstrated similar morphological changes, i.e. broad brands of parenchymal necrosis, bordered by chronic inflammatory granulation tissue, and vasculitis. Inflammatory changes in the alveolar spaces were seen, associated with peribronchiolar lymphoid aggregates, vasculitis and parenchymal fibrosis (fig. 3a). The parenchymal necrosis was largely of the geographic necrobiotic type, with serpiginous border, but in places it was also purulent with microabscesses surrounded by mixed inflammatory infiltrates composed by mononuclear cells, polymorphonuclear leukocytes and multinucleated giant cells (fig. 3b). Around the granulomatous inflammatory lesions, acute and chronic inflammatory changes of the pulmonary vessels were observed, severely reducing the vascular lumen (fig. 3c). Tuberculoid granulomas were not seen. The lymphoid cells showed no atypia and although there was vascular involvement, the appearance was not suggestive of lymphomatoid granulomatosis. Standard histological, cultural and molecular biology tests performed on biopsy materials for detection of fungi, mycobacteria, Pneumocystis carinii, Epstein Barr virus and cytomegalovirus (CMV) were all negative.

The histological pattern of the lung samples suggested a diagnosis of Wegener's granulomatosis. This conclusion was confirmed by B. Corrin, Brompton Royal Hospital, London, U.K.

Diagnosis: "Wegener's granulomatosis of the limited type".

Treatment and clinical course

Classic treatment of Wegener's granulomatosis includes corticosteroids and cyclophosphamide. After an unsuccessful 10 day therapy with trimethoprim-sulphamethoxazole, the patient was treated with prednisone (1 mg·kg⁻¹·day⁻¹) and cyclophosphamide (5 mg·kg⁻¹·day⁻¹, for 4 days, every 28 days). After five courses of cyclophosphamide, this treatment was followed by an almost complete remission of all the pulmonary infiltrates (i.e. >90% decrease of the two major diameters of the only lesion, still detectable on lung CT scans, in the right lower lobe).

Discussion

Wegener's granulomatosis is a systemic disease, characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract, in combination with vasculitis and focal necrotizing crescentic glomerulonephritis [1]. The pathogenesis of Wegener's granulomatosis is unclear: the presence of granulomas with well-defined multinucleated giant cells suggests delayed hypersensitivity, but direct evidence for this mechanism is lacking. Although it typically affects adults in their fifth decade, with a slightly higher frequency in males than females, Wegener's granulomatosis can be seen at any age and occasionally even before adolescence [1–3].

The majority of patients present with complaints referable to the nose, paranasal sinuses or chest. Indeed, upper and/or lower airways are almost always involved initially. Renal manifestations occur in the majority of the cases at some time in the course of the disease, but they are rarely the presenting clinical feature [1, 3]. Relatively mild forms of disease, without renal involvement at presentation, have been described in 20–30% of the patients and are termed “Wegener's granulomatosis of the limited type” [1].

The typical radiographic pattern of lung lesions is represented by multiple, bilateral, rounded opacities, usually sharply circumscribed, ranging from a few millimetres to 9–10 cm in diameter (as in our patient). Some of these nodules may cavitate [3]. Pulmonary infiltrates are initially present in nearly 50% of the cases and may be associated with respiratory symptoms, including cough, haemoptysis and pleuritis, although one third of patients with radiographical, biopsy-proven pulmonary abnormalities may be asymptomatic [1]. Indeed, the present patient had, as presenting symptom, a localized chest pain, possibly related to involvement of the visceral pleura, that resolved rapidly with anti-inflammatory drugs.

Most patients with active Wegener's granulomatosis have leukocytosis, elevated erythrocyte sedimentation rate, anaemia and trombocytosis. Typically, more than 90% of patients with active disease develop classic anti-neutrophil cytoplasmic antibodies (c-ANCA) [1, 4]. The temporal relation between disease activity and changes in serum c-ANCA levels (reported in some studies, but not in others) and the presence of neutrophil-related products in the airways of individuals with lung lesions has led to the hypothesis that neutrophils might be involved in the pathogenesis of Wegener's granulomatosis [4–5].

Most patients with untreated, or ineffectively treated, generalized Wegener's granulomatosis experience a rapidly progressive, fatal illness, usually within a few months after the onset of clinically apparent renal disease [1–3]. In contrast prospective studies have demonstrated that low-dose daily cyclophosphamide and glucocorticosteroids can effectively treat patients with Wegener's granulomatosis, although disease relapse, morbidity and drug toxicity have been frequently reported [1, 6]. Since drug toxicity is mainly related to cyclophosphamide-induced side effects
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(i.e. cystitis, bladder cancer and myelodysplasia), alternative therapies have been tested, such as the "intermittent high dose intravenous (pulse) cyclophosphamide" treatment, associated with daily prednisone [7]. With this "less toxic" treatment protocol, more than half of the patient achieved remission.

More recently, anecdotal reports have indicate beneficial results with sulfamethoxazole-trimethoprim [8], raising speculations regarding a possible pathogenetic role for infectious agents, at least as disease activity inducers [8, 9]. However, the use of concurrent immunosuppressive therapies and failure to rule out infections for which trimethoprim-sulphamethoxazole may be an effective antimicrobial, cast serious doubts on efficacy. Only a few patients show prolonged improvement with trimethoprim-sulphamethoxazole [1]. In the present patient, a 10 day treatment period with trimethoprim-sulphamethoxazole did not induce any clinically relevant response. However, the majority of the patients with Wegener's granulomatosis experience secondary bacterial infections of the respiratory tract, often associated with ANCA titre elevation, further suggesting an important role for infectious agents in the induction of relapses of the disease [10]. For this reason, prophylactic treatment with trimethoprim-sulphamethoxazole has been proposed in patients with Wegener's granulomatosis [1, 10].

In conclusion, Wegener's granulomatosis of the limited type should also be included in the differential diagnosis of solitary or multiple pulmonary lesions in paediatric patients. The low frequency of this uncommon disorder in children raises questions on the severity of the prognosis and, therefore, on the need for aggressive, prolonged treatment with cytotoxic drugs in this age group.

Keywords: Childhood, cyclophosphamide, Wegener's granulomatosis.

References