CASE REPORTS

Accelerated Phase of Idiopathic Pulmonary Fibrosis

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The natural history of idiopathic pulmonary fibrosis is characterized by a slow progression resulting in respiratory failure and death. The progression to the fulminant form is rapid in a small percentage of cases, however. Within weeks or months, patients develop respiratory distress, and extensive ground-glass patterns can be seen in computed tomography scans and hyaline membranes in biopsy samples. This is described as an accelerated phase of idiopathic pulmonary fibrosis, in which elevated levels of acute-phase reactants and tumor markers have been reported. To date, the monoclonal tumor marker, CA 15-3 has not been associated with the accelerated phase.

Key words: *Accelerated phase. Idiopathic pulmonary fibrosis. Tumor markers.*

Fase acelerada de la fibrosis pulmonar idiopática

La historia natural de la fibrosis pulmonar idiopática es la lenta evolución hacia la insuficiencia respiratoria y la muerte. Sin embargo, un pequeño porcentaje de casos evoluciona en semanas o pocos meses de forma fulminante con insuficiencia respiratoria, imágenes extensas de vidrio esmerilado y formación de membranas hialinas en las muestras de biopsia; es lo que se denomina "fase acelerada" de la fibrosis pulmonar idiopática, durante la cual se describen incrementos de las cifras de reactantes de fase aguda y marcadores tumorales. Hasta la fecha no se ha relacionado el marcador tumoral monoclonal CA 15/3 con dicha fase acelerada.

Palabras clave: *Fase acelerada. Fibrosis pulmonar idiopática. Marcadores tumorales.*

Introduction

Idiopathic pulmonary fibrosis is a specific type of idiopathic interstitial pneumonia that is characterized by the histologic pattern of usual interstitial pneumonia.[1] Prognosis is poor and the natural history of the disease is characterized by a slow progression resulting in respiratory failure, cor pulmonale, and death within a period of 3 to 5 years. In a small percentage of cases, however, the disease takes an acutely exacerbated form, also known as the accelerated phase of idiopathic pulmonary fibrosis. This phase is characterized by the onset within days or weeks of dyspnea and severe respiratory distress, and computed tomography (CT) reveals ground-glass patterns in the absence of infection or heart failure. Mortality for this phase is higher than 80%.

Tumor markers such as carcinoembryonic antigen (CEA),[2] CA 19-9,[3-5] CYFRA,[6] and other acute-phase reactants are elevated during exacerbation. A bibliographic review of MEDLINE since 1966, however, revealed no association between acute exacerbation of idiopathic pulmonary fibrosis and the CA 15-3 tumor marker, which is linked to breast cancer.

Case Description

The patient was a 71-year-old man who was admitted to our pulmonology department from a private clinic. The patient had no relevant medical or occupational history, did not smoke, drink to excess, or take drugs, and was not taking regular medication until the onset of the symptoms that led to his admission to our department. He had no history of heart or bronchial diseases and was asymptomatic 4 months before admission, when he had a preoperative chest x-ray prior to a cholecystectomy.

A month later, a high-resolution CT scan was performed for suspected interstitial disease. The scan revealed bilateral interstitial consolidation mainly at the periphery and base of the lungs, with septal thickening, subpleural lines, areas of honeycombing, traction bronchiectasis, and enlarged inferior, central lymph nodes in the anterior mediastinum and right paratracheal spaces (Figure 1).

Idiopathic pulmonary fibrosis was suspected and treatment with corticosteroids was initiated. The patient also presented diabetic instability that required treatment with oral antidiabetic drugs. The patient remained asymptomatic until 6 days before his current admission, when he began to present temperature peaks of 38°C and a predominately nocturnal cough at rest in the last 48 hours.

On admission, the patient had a blood pressure of 110/60 mm Hg, a heart rate of 120 beats/min, severe tachypnea (>40

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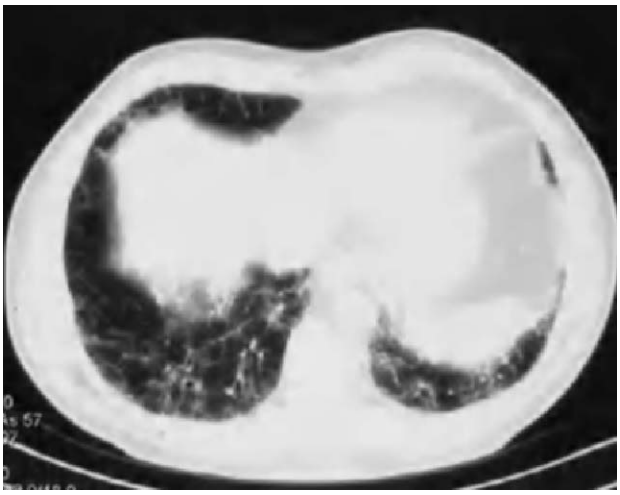

Figure 1. Radiological pattern typical of idiopathic pulmonary fibrosis, with predominately basal and peripheral interstitial involvement, thickening of the septa, subpleural lines, areas of honeycombing, and traction bronchiectasis.

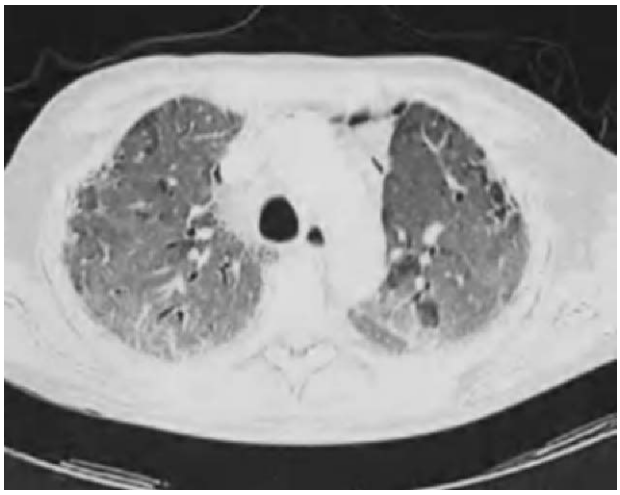

Figure 2. The image shows a diffuse, bilateral, ground-glass pattern superimposed on images of septal and subpleural thickening.

breaths/min.), and oxygen saturation was 80% with 50% oxygen supplied through a Ventimask. A new high resolution CT scan revealed widespread bilateral ground-glass opacities superimposed on the chronic pattern of interstitial thickening and honeycombing that the patient had presented previously (Figure 2). Empirical treatment was started with corticosteroids at a dosage of 2 mg/kg/d, and with levofloxacin and co-trimoxazole. As blood gases (arterial oxygen saturation, <80% breathing air from a 10-L reservoir) and clinical symptoms had not improved after 24 hours, it was decided to admit the patient to the intensive care unit for a telescoping catheter brush and bronchoalveolar lavage (BAL). Samples were sent for microbiology as the examination was interrupted due to severe desaturation and poor tolerance of the BAL. The patient remained in intensive care for 5 days, during which time treatment with co-trimoxazole was suspended and azathioprine was added at an initial dosage of 1 mg/kg/d. No inotropic drug or ventilation support was required. The patient returned to the ward with similar blood-gas parameters and clinical status and persistent refractory respiratory failure and severe tachypnea.

Biochemistry results were normal (including the hepatic series), with lactate dehydrogenase levels of 798 U/L (reference values, 230-460 U/L) and a slightly elevated white blood cell count (13 300/mL), with normal composition. The erythrocyte sedimentation rate was 76 mm/h, rheumatoid factor was normal, and antinuclear and anti-DNA antibodies were negative. Tumor-marker values were as follows: CA 15-3, 560 U/mL (reference values, 0-25 U/mL); CA 19-9, 0.8 U/mL (reference values, 0-35 U/mL); and CEA, 6.8 ng/mL (reference values, 0-5 ng/mL). Precipitins for the usual lung allergens and serology results for atypical bacteria and viruses (influenza, parainfluenza, adenovirus, and respiratory syncytial virus) were negative. Fungal and virus cultures and auramine and toluidine blue staining of the BAL sample were negative. The culture revealed aerobic gram-positive cocci, which were identified as *Rothia mucilaginosa* resistant to levofloxacin and sensitive to cephalosporins, and *Peptostreptococcus anaerobius*.

Because of the high levels of CA 15-3, a mammogram and abdominal and pelvic ultrasound scans were performed but no findings indicative of cancer were revealed.

The patient's clinical symptoms deteriorated progressively. An attempt was made to apply noninvasive ventilation with pressure support but was discontinued after a few hours due to intolerance and the patient's distress. The patient died 16 days after admission following sedation with morphine chloride and midazolam.

The autopsy revealed ectasis in both lower lobes and areas of diffuse alveolar damage, with inflammation, congestion, and interstitial edema, lining of the alveolar walls with hyalin membranes, and reactive type-II pneumocyte hyperplasia. There were also interspersed areas of alveolar damage in the process of healing, with fibrosis and thickening of the alveolar septa. The autopsy also showed abdominal incidentalomas (renal cysts and adrenal adenoma), with no enlarged lymph nodes or images indicating tumors in the abdomen or pelvis.

Discussion

This is a case of accelerated phase of idiopathic pulmonary fibrosis, as confirmed by the autopsy.

The cause of onset of the acute phase is often unknown, though it is reasonable to exclude an infectious etiology due to the absence of bacterial or viral growth in the serology and BAL cultures. Performing BAL and thoracic surgery are occasionally cited as causes.

The finding of *R mucilaginosa* (implicated in periodontal and other oral infections) in the BAL sample, together with other anaerobic bacteria, suggests that food particles may have been drawn in from the mouth on performing BAL on a patient with severe tachypnea and poor tolerance of the procedure. Furthermore, the patient's condition worsened progressively despite varying the antibiotic treatment to provide coverage against these bacteria. The 3-month high resolution CT findings (extensive ground-glass opacities[9,10]) were highly indicative of a diagnosis of an accelerated phase of idiopathic pulmonary fibrosis, considering that the patient had previously been diagnosed with idiopathic pulmonary fibrosis, had experienced considerable deterioration of symptoms and blood-gas levels, and did not respond to treatment with corticosteroids and immunosuppressants,

once other infectious agents that cause the same pattern (eg, cytomegalovirus or *Pneumocystic carnii*) had been ruled out.

The radiologic findings were paradoxical because the diffuse ground-glass pattern is rare at the initial diagnosis of idiopathic pulmonary fibrosis and it may suggest an alternative diagnosis such as lymphoid interstitial pneumonia, desquamative interstitial pneumonia, cellular forms of nonspecific interstitial pneumonia, or allergic alveolitis—all of which present a better response to corticosteroids as they are, in theory, extended manifestations of alveolitis.

There is evidence regarding the increased levels of acute-phase reactants (C-reactive protein, erythrocyte sedimentation rate, and γ-globulins), immunological markers (rheumatoid factor, antinuclear antibodies in 20% of cases of idiopathic pulmonary fibrosis), and tumor markers such as CEA, CA 19-9, and CYFRA in inflammatory lung diseases.[2-6] We believe that the originality of our case lies in the high serum levels of CA 15-3, which have not been reported to date in the absence of breast involvement (verified by mammography) or of tumors in other organs (as shown by autopsy).

In summary, the severe acute phase of idiopathic pulmonary fibrosis is an uncommon form of evolution with no clear etiology. It has a high mortality rate, and response to treatment with corticosteroids and immunosuppressants is poor.[11] It may be associated with high levels of acute-phase reactants and tumor markers. We believe that high levels of tumor markers in patients with an accelerated phase of idiopathic pulmonary fibrosis should not cause us to prioritize the diagnostic process to search for possible tumors. In particular, aggressive procedures for this purpose should be avoided.

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