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Case Report

Response to Inhaled Granulocyte-Macrophage Colony-Stimulating Factor in a Patient With Alveolar Proteinosis

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ABSTRACT

Pulmonary alveolar proteinosis is a rare disease characterized by the accumulation of lipoproteinaceous material derived from alveolar surfactant in the alveoli, with a consequent deterioration in gas exchange. Pathogenesis is related to impaired phagocytic function of alveolar macrophages. In recent years, a new treatment for pulmonary alveolar proteinosis—consisting of subcutaneous administration of granulocyte-macrophage colony-stimulating factor (GM-CSF)—has become available. The commonly accepted treatment, and the one to have shown greatest efficacy in pulmonary alveolar proteinosis, is whole lung lavage. Instead of subcutaneous administration, GM-CSF can also be inhaled as an aerosol. This route of administration of GM-CSF is safe and effective in the treatment of pulmonary alveolar proteinosis and represents an alternative to subcutaneous administration or whole lung lavage. We present a patient with pulmonary alveolar proteinosis who was treated with inhaled GM-CSF and describe her clinical and functional outcome after 1 year of treatment.

Proteinosis alveolar. Respuesta al tratamiento con factor estimulante de colonias de granulocitos y macrófagos por vía inhalada

Palabras clave:
Proteinosis alveolar pulmonar
GM-CSF
Aerosolterapia

RESUMEN

La proteinosis alveolar pulmonar (PAP) es una rara enfermedad que se caracteriza por la acumulación en el alvéolo pulmonar de un material lipoproteico derivado del surfactante alveolar, lo que provoca el consiguiente deterioro del intercambio gaseoso. Su patogenia está relacionada con alteraciones en la capacidad fagocítica del macrófago alveolar. Desde hace pocos años existe un nuevo tratamiento para la PAP consistente en la administración de factor estimulante de colonias de granulocitos y macrófagos (GM-CSF) por vía subcutánea. El tratamiento comúnmente aceptado y que ha demostrado mayor eficacia en la PAP es el lavado pulmonar total. Una alternativa a este tratamiento es la administración por vía inhalada en aerosolterapia de este factor. La administración del GM-CSF por vía inhalada es segura y eficaz para el tratamiento de la PAP y supone una alternativa al tratamiento con lavado pulmonar total y GM-CSF por vía subcutánea. Presentamos un caso de PAP tratada con GM-CSF por vía inhalada y su evolución clínica y funcional tras un año de tratamiento.

Introduction

Pulmonary alveolar proteinosis is a rare disease characterized by the accumulation of lipoproteinaceous material derived from alveolar surfactant in the alveoli, with the consequent deterioration in gas exchange. The annual incidence of the disease is estimated to be 0.36/1 000 000 population and its prevalence 3.7/1 000 000 population.[1] In its most common form of presentation, it affects previously healthy young adults, who develop progressive exercise-induced dyspnea, hypoxemia, and characteristic radiological abnormalities.[2] The recommended treatment consists of whole lung lavage with physiological saline solution to remove the proteinaceous material occupying the airways and thereby achieve clinical and functional improvement.

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The pathogenesis is related to impaired phagocytic function of alveolar macrophages. In recent years, a new treatment for pulmonary alveolar proteinosis consisting of the subcutaneous administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) has become available and outcomes have been promising.[3] As an alternative to subcutaneous administration, this agent can be inhaled as an aerosol.

We present a patient treated with inhaled GM-CSF and describe her clinical and functional outcome after 1 year of treatment.

Case Description

The patient was a 31-year-old female ex-smoker (with a cumulative cigarette consumption of 13 pack/years) who reported a 4-month history of persistent dry cough, progressive dyspnea that had reached grade 2 of the Medical Research Council (MRC) scale,[4] and slight fever, associated with a weight loss of 2 kg. On physical examination, inspiratory crackles were detected in both lung bases and clubbing was apparent; otherwise findings were normal.

The laboratory tests yielded the following results: hemoglobin, 16.9 g/dL; hematocrit, 48%; white blood cell count, 9200/μL; neutrophils, 66.8%; platelet count, 260 000/μL, erythrocyte sedimentation rate, 52 mm/h; and lactate dehydrogenase, 770 U/L. Tests for rheumatoid factor, thyroid hormones, antinuclear and anticytoplasmic antineutrophil antibodies, and angiotensin converting enzyme were all negative. Serology for atypical pneumonia was also negative.

A restrictive pattern was detected in lung function tests, with forced vital capacity (FVC) of 2270 mL (52%), forced expiratory volume in the first second (FEV_1) of 2230 mL (61%), FEV_1/FVC of 98%, total lung capacity measured by helium dilution of 3550 mL (62%), residual volume measured by helium dilution of 1110 mL (69%), and diffusing capacity of lung for carbon monoxide (DLCO) corrected for alveolar volume of 43%. Arterial blood gas analysis showed PaO_2 of 60 mm Hg, $PaCO_2$ of 34 mm Hg, and pH of 7.42. The distance covered in the 6-minute walk test was 570 m. The electrocardiogram showed sinus rhythm with no abnormalities. In the chest radiograph, a ground-glass alveolar pattern could be discerned in both lung fields, mainly in the lower lobes. High-resolution computed tomography revealed areas of ground-glass appearance with interlobular septal thickening, more marked in the subpleural area, and slight interstitial thickening around the bronchial vasculature. No macroscopic findings were apparent in the fiberoptic bronchoscopy examination. Bronchoalveolar lavage returned a milky, proteinaceous fluid, positive for periodic acid Schiff reaction and oil red O staining. Microbiological cultures—which included fungi and mycobacteria—were negative. A diagnosis of idiopathic alveolar proteinosis was reached.

In the next 2 months, the patient's clinical and functional condition deteriorated markedly, with dyspnea worsening to grade 3 of the MRC scale, progression of the radiological abnormalities, and marked respiratory failure (PaO_2, 53 mm Hg; $PaCO_2$, 33 mm Hg; and pH, 7.40), FVC of 45%, and DLCO of 25%. Two whole lung lavages were undertaken, 2 months apart, with clinical and functional improvement (PaO_2, 64 mm Hg; FVC, 60%; and DLCO, 61%). Five months after the second lavage, the patient presented increased dyspnea, progression of radiological involvement (Figure 1), and marked deterioration in gas exchange, with PaO_2 of 40 mm Hg, $PaCO_2$ of 32 mm Hg, pH of 7.37, and DLCO of 23%. In the 6-minute walk test, she covered 338 m with a minimum saturation of 75% and presented dyspnea of 8 out of 10 points on a visual analogue scale. Serum concentrations of antibodies against GM-CSF were measured and found to be high (4.43 nM). In view of the deterioration in her clinical state and gas exchange despite the 2 whole lung lavages, treatment was started with inhaled GM-CSF in the form of an aerosol (sargramostim) at a dose of 250 μg every 12 hours on alternate

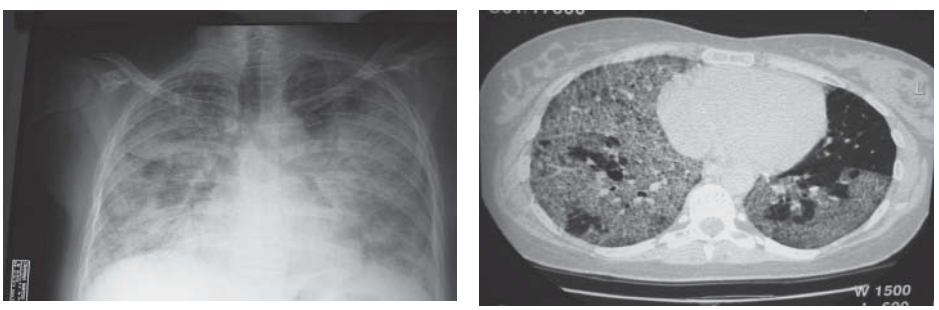

Figure 1. Chest radiograph 5 months after second whole lung lavage, before starting treatment with inhaled granulocyte-macrophage colony-stimulating factor.

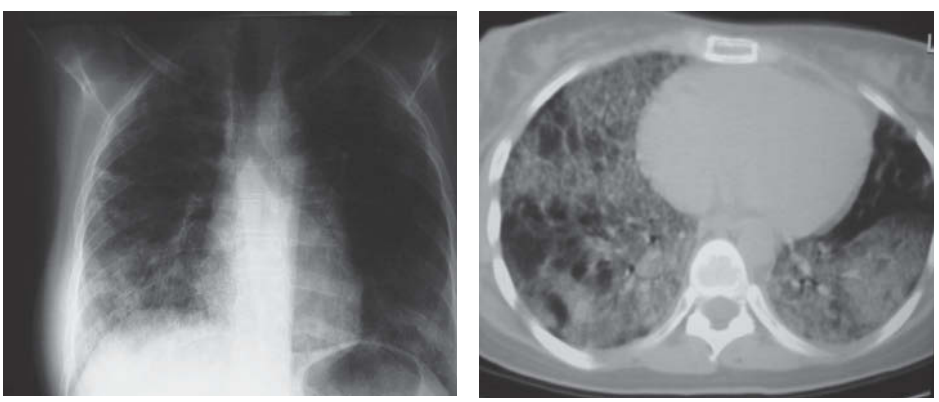

Figure 2. Radiological outcome after 12 months of treatment with inhaled granulocyte-macrophage colony-stimulating factor.