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Letter to the Editor

Secondary Pulmonary Alveolar Proteinosis in an Immunosuppressed Patient With Cytomegalovirus Infection

Proteinosis alveolar pulmonar secundaria en un paciente inmunodeprimido con infección por citomegalovirus

To the Editor:

Pulmonary alveolar proteinosis (PAP) is a rare diffuse lung disease in which lipoproteinaceous material accumulates in the alveolar spaces[1,2] and for which 3 types (congenital, secondary, and acquired) have been described. Secondary PAP is often associated with hematological malignancy and immunodeficiency.[3] We report the case of an immunosuppressed patient with secondary PAP and cytomegalovirus (CMV) infection.

A 26-year-old man presented with dyspnea. He reported no fever, expectoration, or hemoptysis. Seven years earlier he had had an allogeneic hematopoietic stem-cell transplant for refractory anemia. He had also had a kidney transplant 3 years earlier for chronic renal failure related to chronic graft-versus-host disease. On examination, the patient appeared anemic but no other abnormalities were found. Laboratory data included a white blood cell count of 5230/μL, with 77% neutrophils, 18% lymphocytes, 3% monocytes, and 2% eosinophils. Arterial blood gas analysis showed a PaO_2 of 58 mm Hg. Chest radiographs showed bilateral reticular patterns of increased opacity sparing the costophrenic angles. High-resolution computed tomography showed diffuse ground-glass attenuation with superimposed intra- and interlobular septal thickening ("crazy-paving" pattern) (Figure). Based on the imaging studies, bronchoalveolar lavage (BAL) was performed by fiberoptic bronchoscopy. Macroscopically, the BAL fluid had a milky appearance. Microscopically, the fluid was seen to contain lipid-laden macrophages and a large amount of periodic acid-Schiff–positive and diastase-resistant material. Additionally, we found a high level of CMV DNA in BAL fluid cells using real-time polymerase chain reaction. With the diagnosis of PAP confirmed, whole-lung lavage was performed. The patient showed great improvement. It was therefore decided that monitored outpatient treatment would be carried out and another lung lavage would be scheduled if indicated. CMV infection was treated with antiviral drugs and anti-CMV immune globulin.

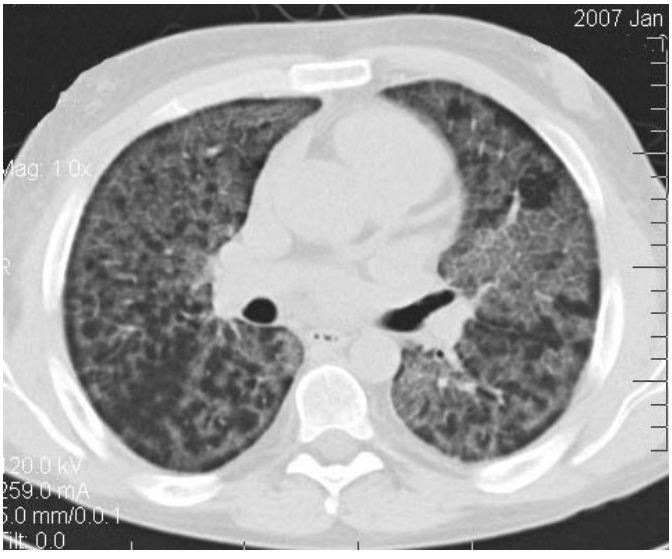

Figure. The high-resolution computed tomography scan shows diffuse geographic ground-glass attenuation with superimposed interlobular septal and intralobular interstitial thickening in a mosaic pattern (the so-called "crazy paving" appearance).

Secondary PAP develops in the context of functional impairment or reduced numbers of alveolar macrophages[4] in such conditions as hematological disorders (eg, leukemia or lymphoma), immunodeficiency disorders (eg, AIDS), or after solid organ transplantation.[2,3] Mycobacterial, CMV, or *Pneumocystis carinii* infections have also been associated with PAP.[2] Secondary PAP is also a rare complication occurring late after hematopoietic stem-cell transplantation.[5]

In our patient, secondary PAP developed in association with immunodeficiency and CMV reactivation. CMV interstitial pneumonia is a severe complication in immunocompromised hosts such as patients who have received a transplant. CMV reactivation, which affects alveolar macrophages, has been suggested as an inducer of PAP,[6] while other reports suggest that opportunistic infections are superimposed on preexisting PAP.[2] Infection is a common feature during the course of PAP but in secondary PAP, it is unclear whether PAP is the cause or consequence of infection. High-resolution computed tomography demonstrates the crazy-paving pattern. Although this radiologic appearance is not pathognomonic of PAP, it is highly suggestive. The typical radiographic findings of CMV (small or poorly defined nodules and dense consolidations) were not present in our patient, although we cannot rule out that the ground-glass attenuation observed might be due to the CMV infection.

In conclusion, this case highlights the importance of considering PAP as a cause of diffuse pulmonary infiltrates in an immunosuppressed patient.

References

1. Du EZ, Yung GL, Le DT, Masliah E, Yi ES, Friedman PJ. Severe alveolar proteinosis following chemotherapy for acute myeloid leukemia in a lung allograft recipient. J Thorac Imaging. 2001;16:307-9.
2. Ioachimescu OC, Kavuru MS. Pulmonary alveolar proteinosis. Chron Respir Dis. 2006;3:149-59.

3. Birsak CA, van Rossem RN, Nijhuis-Heddes JM, Maartense E. Pulmonary alveolar proteinosis: a complication in patients with hematologic malignancy. Neth J Med. 2000;56:193-7.
4. Goldstein LS, Kavuru MS, Curtis-McCarthy P, Christie HA, Farver C, Stoller JK. Pulmonary alveolar proteinosis: clinical features and outcomes. Chest. 1998; 114:1357-62.
5. Coy DL, Ormazabal A, Godwin JD, Lalani T. Imaging evaluation of pulmonary and abdominal complications following hematopoietic stem cell transplantation. Radiographics. 2005;25:305-17.
6. Ohyashiki JH, Nagate A, Ojima T, Abe K, Yamamoto K, Ohyashiki K. Quantification of human cytomegalovirus using bronchoalveolar lavage cells in pulmonary complications associated with hematologic neoplasia. Int J Mol Med. 2003;11:779-83.

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Sleep Apnea-Hypopnea Syndrome at the Onset of Acromegaly Due to Ectopic Secretion by a Pancreatic Neuroendocrine Tumor

Síndrome de apneas-hipoapneas durante el sueño como forma de inicio de acromegalia por secreción ectópica a tumor neuroendocrino pancreático

To the Editor:

Sleep apnea-hypopnea syndrome (SAHS) is common in patients with acromegaly and both conditions are independently associated with hypertension and insulin resistance, conditions which increase morbidity and mortality.[1] Acromegaly caused by ectopic oversecretion of growth hormone is unusual (with an incidence of <1%[2]) and has not been reported in association with SAHS. We describe a case in which SAHS was the first sign of ectopic acromegaly secondary to a pancreatic neuroendocrine tumor metastasized to the liver.

The patient was a 40-year-old man referred to our sleep clinic for snoring, witnessed apneas, and a 6-month history of mild daytime sleepiness. Twenty-one months earlier, asymptomatic hypertension (220/140 mm Hg) was detected. A pseudonodular lesion at the head of the pancreas and 20 nodular lesions on the liver were also identified; after resection, the lesions were diagnosed as a pancreatic neuroendocrine tumor and hepatic metastases. Three months before coming to the sleep clinic, the patient had begun treatment with lanreotide in gel form at a dosage of 120 mg/mo after he was diagnosed with acromegaly secondary to ectopic secretion by the tumor of 811 μg/L of type 1 insulin-like growth factor, 2.7 μg/L of growth hormone after an oral glucose tolerance test, and 1273 pg/mL of growth-hormone releasing factor. Noteworthy findings of physical examination included a score of 9 on the Epworth sleepiness scale, blood pressure of 140/90 mm Hg, a body mass index of 28.4 kg/m^2, a neck circumference of 43 cm, a Mallampati class III score, upper airway narrowing due to soft palate hypertrophy, and mild prognathism. Nighttime polysomnography demonstrated sleep efficiency of 86%, abnormal sleep architecture with a reduced percentage of rapid eye movement sleep (2.3%) and a high percentage of superficial sleep stages (stage 1-2, 64%; stage 3-4, 33.7%), apnea-hypopnea index of 30 events/h due to obstructive apneas, an arousals at a rate of 28/h, arterial oxygen saturation of 92% with 16 desaturations/h, and 0.6% of sleep time with oxygen saturation less than 90%. Continuous positive airway pressure (CPAP) was adjusted in incremental steps during the second part of the night, until most events were corrected with a flow of 7 cmH_2O (Figure). With a diagnosis of SAHS related to acromegaly due to ectopic secretion by a metastatic neuroendocrine tumor, nighttime CPAP treatment through a nasal canula was started. Tolerance and adherence were good. A year later, under controlled conditions, treatment with analogs was withdrawn and polysomnographic abnormalities were once again demonstrated. Four years after the initial diagnosis, the patient was alive and continued to use CPAP, even though hepatic metastases were persistent.

The prevalence of SAHS in patients with acromegaly is approximately 60%, with rates ranging from 19% to 93% in different series.[3] Most patients with acromegaly and SAHS have obstructive apneas, although central apneas have been described in a third of cases and are possibly attributable to a direct effect on respiratory drive of elevated growth hormone, or insulin-like growth factor, or somatostatin levels.[4] Patients with central apneas and acromegaly also have a more marked response to hypercapnic hypoxia.[4] Acromegaly leads to important structural changes in para- and retropharyngeal soft tissues and these can disrupt the balance of forces during inspiration, enhancing pharyngeal collapsibility during sleep.[5] The relationships between craniofacial changes, hormone activity in acromegaly, and treatment with somatostatin analogs, and the presence and severity of apneas are disputed.[3,6,7] The treatment of acromegaly (surgery, radiotherapy, or somatostatin analogs) improves but rarely cures SAHS, which persists if growth hormone secretion is not halted, possibly because structural changes in the soft tissue and bony structures of the upper airway are irreversible.[3] Sleep studies are therefore needed in order to start treatment as soon as possible, as prognosis may be affected even though mortality has not been shown to decrease.[5] SAHS in association with ectopic acromegaly has not been described in the literature, possibly because the incidence is low and survival as in our patient's case may be exceptional. We emphasize the presence of symptoms of SAHS as the initial manifestation of ectopic acromegaly even before SAHS was diagnosed, and also the fact that the patient continues to require CPAP treatment in spite of therapeutic control of the underlying disease. The explanation may be the metastases that were not removed or the presence of irreversible changes in craniofacial structures and soft tissues caused by ectopic secretion of growth hormone.

References

1. Sze L, Schmid C, Bloch KE, Bernays R, Brändle M. Effect of transsphenoidal surgery on sleep apnoea in acromegaly. Eur J Endocrinol. 2007;156:321-9.
2. Lucas T, Catalá M, en nombre del grupo de trabajo de Neuroendocrinología de la Sociedad Española de Endocrinología y Nutrición. Guía clínica del diagnóstico y tratamiento de la acromegalia. Endocrinol Nutr. 2005;52:18-21.
3. Bottini P, Tantucci C. Sleep apnea syndrome in endocrine diseases. Respiration. 2003;70:320-7.
4. Grunstein RR, Ho KY, Berthon-Jones M, Stewart D, Sullivan CE. Central sleep apnea is associated with increased ventilatory response to carbon dioxide and hypersecretion of growth hormone in patients with acromegaly. Am J Respir Crit Care Med. 1994;150:496-502.
5. Colao A, Pivonello R, Marzullo P, Aurriemma RS, de Martino MC, Ferone D, et al. Severe systemic complications of acromegaly. J Endocrinol Invest. 2005;28:65-77.