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CASE REPORT

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Alpha-1 Antitrypsin Deficiency with Pulmonary Nodules and Cirrhosis: a Case Report

Déficit de alfa-1 antitripsina con enfermedad nodular pulmonar y cirrosis: reporte de caso

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ABSTRACT

Alpha-1 antitrypsin deficiency (AATD) is an underdiagnosed codominant genetic disorder. The PiZZ phenotype represents the most common form of severe deficiency and is associated with pulmonary and hepatic involvement. In addition to the classic emphysematous phenotype, nodular findings have been described on high-resolution computed tomography (HRCT). We present the case of a 62-year-old nonsmoking man with persistent dry cough and mild dyspnea, in whom the HRCT revealed a dominant solid nodular lesion measuring 24 × 17 mm in the right upper lobe, accompanied by multiple irregular solid nodular opacities of chronic evolution. Abdominal imaging suggested chronic liver disease with normal liver panel and platelet count. Serum alpha-1 antitrypsin level was 69 mg/dL, and the PiZZ phenotype was confirmed. Liver biopsy showed PAS-positive and PAS-D-positive intracytoplasmic inclusions, consistent with alpha-1 antitrypsin polymer accumulation and cirrhosis in the setting of AATD. Granulomatous, infectious, and neoplastic differential diagnoses were considered; available bronchoscopic, cytological and microbiological studies did not show active infection or malignancy, and radiological surveillance was adopted due to lesion stability. Phenotypic confirmation enabled a definitive syndromic diagnosis, identified pulmonary and hepatic involvement, and guided targeted management according to international recommendations.

Key words: alpha-1 antitrypsin deficiency | Pi*ZZ | pulmonary nodules | high-resolution computed tomography | cirrhosis

RESUMEN

El déficit de alfa-1 antitripsina (DAAT) es una enfermedad genética codominante e infradiagnosticada; el fenotipo PiZZ representa la forma más frecuente de déficit grave y se asocia a compromiso pulmonar y hepático. Además del fenotipo enfisematoso clásico, se han descrito imágenes nodulares

en tomografía computarizada de alta resolución (TCAR) de tórax. Presentamos el caso de un varón de 62 años, no fumador, con tos seca persistente y disnea leve, en quien la TCAR mostró una lesión nodular sólida dominante de 24 × 17 mm en lóbulo superior derecho, asociada a múltiples imágenes nodulares sólidas irregulares de evolución crónica. En estudios abdominales se evidenció hepatopatía crónica con hepatograma y plaquetas normales. La alfa-1 antitripsina sérica fue de 69 mg/dL y se confirmó fenotipo PiZZ. La biopsia hepática mostró inclusiones intracitoplasmáticas PAS positivas y PAS-D positivas, hallazgos compatibles con acumulación de polímeros de alfa-1 antitripsina y cirrosis, en el contexto de DAAT. Se consideraron diagnósticos diferenciales granulomatosos, infecciosos y neoplásicos; los estudios broncoscópicos, citológicos y microbiológicos disponibles no evidenciaron infección activa ni malignidad, por lo que, ante la estabilidad de las lesiones, se adoptó vigilancia tomográfica. La confirmación fenotípica permitió un diagnóstico sindrómico definitivo, identificar el compromiso pulmonar y hepático y orientar medidas específicas según recomendaciones internacionales.

Palabras clave: déficit de alfa-1 antitripsina | Pi*ZZ | nódulos pulmonares | tomografía de alta resolución | cirrosis

INTRODUCTION

AATD is an underdiagnosed codominantly inherited genetic disorder.[1,2] The Pi*ZZ phenotype is the most common form of severe deficiency and is associated with both pulmonary manifestations (emphysema, bronchiectasis) and liver disease resulting from the accumulation of alpha-1 antitrypsin polymers within hepatocytes.[1-3] Although emphysema represents the most widely recognized pulmonary phenotype, nodular patterns on HRCT have also been described, potentially posing diagnostic challenges.[4]

CASE REPORT

A 62-year-old man, never-smoker, employed as a baker, with a history of presumed ocular sarcoidosis treated with prolonged corticosteroid therapy, insulin-dependent type 2 diabetes mellitus, and liver cirrhosis secondary to alpha-1 antitrypsin deficiency presented with persistent dry cough and dyspnea classified as grade 1 on the mMRC scale (modified Medical Research Council dyspnea scale). The patient was being followed by the Pulmonology Service for long-standing pulmonary nodular lesions. HRCT showed multiple solid pulmonary nodules, predominantly involving the right lung, some with irregular margins and diffuse distribution. Several lesions were associated with pleuropulmonary fibrotic sequelae. A dominant lesion measuring 24 × 17 mm was identified in the posterior segment of the right upper lobe. Subsequent follow-up evaluations over 2 years demonstrated no significant evidence of disease progression.

Flexible bronchoscopy with bronchoalveolar lavage (BAL) was performed and revealed no endobronchial abnormalities. The CD4/CD8 ratio was within normal limits, without lymphocytosis. Cytologic analysis was negative, and cultures for common bacterial pathogens, mycobacteria, and fungi yielded negative results. Serial chest CT examinations demonstrated no significant changes in the size or morphology of the pulmonary lesions.

Available lung function testing was limited to spirometry, which showed an FVC (forced vital capacity) of 3.33 L (77%), FEV_1 (forced expiratory volume in the first second) of 2.29 L (74%), and a FEV_1/FVC ratio of 73%. Measurements of lung volumes and diffusing capacity of the lung for carbon monoxide (DLCO) were not available, limiting the comprehensive assessment of pulmonary impairment related to AATD. Abdominal MRI demonstrated a heterogeneous liver with lobulated margins, a hepatic nodular lesion measuring approximately 35 mm, splenomegaly, and collateral venous circulation. Liver biochemical tests and platelet count were within normal limits. In the absence of hepatotropic virus infection or alcohol-related liver disease, the alpha-1 antitrypsin level was measured at 69 mg/dL, and the Pi*ZZ phenotype was confirmed.

Liver biopsy revealed hepatocytes containing PAS-positive and PAS-D positive intracytoplasmic inclusions, findings consistent with alpha-1 antitrypsin deficiency. In addition, chronic steatohepatitis with moderate inflammatory activity (Ishak score, 6/18; portal inflammation, grade 2) and advanced fibrosis/cirrhosis characterized by portoportal bridging and nodular regeneration were identified. No documentation of family screening for AATD was available in the medical record. Given the hereditary nature of the disease, genetic counseling was provided, and screening of first-degree relatives was recommended via serum alpha-1 antitrypsin quantification and potential phenotypic and/or genotypic confirmation. Further pulmonary evaluation with measurement of lung volumes, DLCO, and longitudinal assessment of FEV_1 was proposed to better define the extent of pulmonary involvement and determine potential eligibility for alpha-1 antitrypsin augmentation therapy.[1-3] The clinical course was complicated by multiple liver disease-related events, and the patient ultimately died.

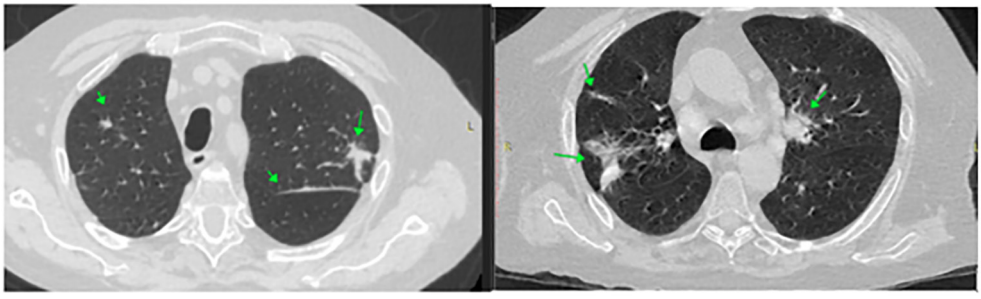
DISCUSSION

AATD is an underdiagnosed genetic disorder whose pulmonary manifestations are classically associated with emphysema (frequently panacinar) and, to a lesser extent, bronchiectasis.[1-3] Current clinical guidelines and consensus statements recommend maintaining suspicion of AATD in adults presenting with compatible lung disease or otherwise unexplained liver disease, quantifying serum alpha-1 antitrypsin levels and confirming the diagnosis via phenotype or genotype to guide targeted management strategies.[1-3]

Although emphysema remains the most widely recognized pulmonary phenotype, the radiologic spectrum of AATD may include nonclassical findings. Specifically, the prevalence and radiological evolution of pulmonary nodules have been evaluated in AATD cohorts, highlighting the importance of integrating clinical context, lesion morphology, and temporal changes before indicating routine invasive procedures.[4] Furthermore, atypical presentations of AATD with findings that mimic infection or malignancy have been reported, reinforcing the need for a stepwise diagnostic approach.[5]

In our patient, the pulmonary nodular pattern prompted the consideration of granulomatous, infectious, and neoplastic differential diagnoses. Sarcoidosis was considered because of the patient's ophthalmologic history and chronic radiologic pattern. However, bronchoscopic evaluation did not demonstrate lymphocytosis or a significant alteration in the CD4/CD8 ratio. Given the history of chronic immunosuppression, diabetes mellitus, and prior infectious complications, infectious etiologies, including mycobacterial and fungal disease, were also investigated. No microbiologic evidence of active infection was identified in the available studies. Malignancy was likewise considered because of the presence of a dominant irregular solid pulmonary nodule. Nevertheless, negative cytology, absence of significant radiologic progression, and overall clinical context favored a conservative approach with serial imaging surveillance. Although flexible bronchoscopy with BAL do not definitively exclude a malignancy in peripheral pulmonary lesions, the risk-benefit assessment supported initial observation, consistent with international recommendations for the

Image 1. High-resolution computed tomography (HRCT) of the chest: dominant solid nodular lesion associated with multiple irregular, solid nodular and pseudonodular opacities.



management of selected (non-smoker) incidental pulmonary nodules based on clinical risk and radiologic characteristics.[6]

Concomitantly, liver involvement associated with the PiZZ phenotype may be present despite normal liver biochemical tests and platelet counts. Therefore, phenotypic confirmation and histopathologic correlation remain essential when imaging findings suggest advanced fibrosis or portal hypertension.[1-3] In this patient, reduced serum alpha-1 antitrypsin levels, confirmation of the PiZZ phenotype, and liver biopsy findings demonstrating PAS/PAS-D positive inclusions and cirrhosis facilitated a definitive syndromic diagnosis and guided subsequent hepatologic management. The decision to initiate augmentation therapy requires adequate characterization of pulmonary involvement, ideally including serial spirometry, DLCO measurement, and assessment of lung volumes. The absence of comprehensive physiologic testing at initial evaluation, together with incomplete data regarding family screening, represents a limitation of the present report.[1-3]

CONCLUSION

Alpha-1 antitrypsin deficiency due to the Pi*ZZ phenotype must be considered in the presence of atypical pulmonary findings, including nodular patterns, particularly when concurrent imaging suggests liver disease despite normal liver function tests and platelet counts.[1-4] In clinically stable patients, the absence of tomographic progression on serial monitoring warrants the consideration of a conservative, surveillance-based approach. This strategy requires integrating the patient's risk profile, differential diagnoses, and available microbiologic and cytologic studies, in accordance with international recommendations for incidental nodules.[6] Phenotypic confirmation, histopathologic correlation when indicated, complete pulmonary function testing, and genetic counseling are fundamental to establishing a definitive syndromic diagnosis, guiding subsequent follow-up and targeted clinical interventions.[1-3]

Conflict of interest

Authors have no conflicts of interest to declare.

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High-resolution computed tomography (HRCT) of the chest: dominant solid nodular lesion associated with multiple irregular, solid nodular and pseudonodular opacities.

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