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Single Case

Acute Disseminated Panniculitis Associated with Alpha-1 Antitrypsin Deficiency

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Abstract
Alpha-1 antitrypsin deficiency, although one of the most common genetic diseases, is a very rare and often undiagnosed cause of panniculitis. The authors present a case characterized by an acute involvement of several areas in the thorax, abdomen, and limbs, occurring after repetitive trauma of the perineal area caused by a long period of cycling. After performing the differential diagnosis and establishing etiology, the patient was started on augmentation therapy with plasma-derived synthetic human alpha-1 proteinase inhibitor and the disease has been under control since then. We recommend lifelong treatment with this medication. At the end of a 10-year follow-up, there has been no evidence of pulmonary emphysema or liver disease. The authors perform a concise review of the genetic and pathogenic mechanisms behind this disease, with a special focus on panniculitis and its treatment.

Introduction

Alpha-1 antitrypsin deficiency (AATD) is an autosomal codominant genetic condition that causes decreased concentration and activity of alpha-1 antitrypsin (AAT) in blood and body tissues. AAT is mainly synthesized in the hepatocytes and, in smaller numbers, in intestinal and pulmonary alveolar cells, neutrophils, macrophages, and cornea [1]. AAT is responsible

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for almost 90% of total plasma protease inhibition activity against enzymes such as trypsin (from leukocytes in the lung, pancreas, and other organs), elastase, and others [2].

As AAT inhibits neutrophil proteases during acute-phase response, its severe deficiency predisposes to early-onset pulmonary emphysema, primarily in smokers, and less frequently systemic vasculitis and neutrophilic panniculitis [3]. AAT trapped in the liver due to point mutations can induce organ disease through toxic "gain of function" and its persistence as endoplasmic reticulum inclusions within hepatocytes can lead to fibrosis, cirrhosis, and cancer [4]. AAT polymers may also arise within the lung, in response to local inflammation and tobacco exposure, and have been found in the bloodstream of patients with chronic obstructive pulmonary disease [5] and in the skin of patients with panniculitis [6].

The AAT gene (*SERPINA1*) is located in chromosome 14, and around 100 allelic variants are known [7]. *SERPINA1* mutations lead to the synthesis of misfolded or dysfunctional AAT. Depending on their electrophoretic mobility, variants are referred to as F (fast), M (medium), S (slow), and Z (very slow). The genotypic classification of AAT variants uses the *Pi* (protease inhibitor) system followed by the two letters of the alleles. The normal genotype is *Pi*MM [8]. Deficient alleles cause decreased plasma AAT levels; the Z allele is responsible for the least amount of AAT; and the seldom-seen "null" alleles have no detectable AAT protein. Serum levels of AAT <100 mg/dL are an indication for phenotyping and genotyping, in order to assess AATD in patients and their families [1].

Acute panniculitis is associated with a variety of conditions but rarely so with AATD, research finding just 50-odd references worldwide [9]. Although several drugs, like dapsone and doxycycline, have been proposed as treatment, the results were unsatisfactory. In severe cases, such as our patient with disseminated acute panniculitis, augmentation therapy with intravenous plasma-purified AAT is nowadays the most successful tool [10].

Case Report

A 38-year-old nonobese white man, a forest engineer, was admitted to our Unit on September 28, 2010. His past medical history was irrelevant. He denied smoking habits and drank alcohol only socially. He was a father of three healthy children and, as for his family history, his own father had died with diabetes type 2 and alcoholic liver cirrhosis.

Two months before, during a 72-km-long bicycle ride, the patient had started complaining of pain in the perineum and buttocks. The symptoms gradually worsened, with intense muscle pain and weakness in the thorax, lumbar area, as well as the upper and lower limbs. Over the next few days, his condition deteriorated and he noted inflammation on the buttocks, perineum, and thighs. A course of nonsteroidal anti-inflammatory drugs and other painkillers was ineffective. In 2 weeks, there was an exacerbation and he noticed a maculopapular erythematous rash in the lumbar area and left axilla, as well as pubic edema. He went to several emergency departments; his bloodwork repeatedly showed elevated inflammatory parameters. Soft tissue ultrasonography confirmed an intense inflammatory process around the perineal area. Nonsteroidal anti-inflammatory drugs and antibiotics (ciprofloxacin/ceftriaxone) were unsuccessful. The symptoms persisted and the patient started reporting shortness of breath after minor efforts, dry cough, and central pleuritic chest pain. Evaluation at his local hospital emergency departments was nondiagnostic. The situation got worse 6 days later, with fever (38–39°C), inflamed right scapula, and painful right foot and left leg. He was admitted at his local hospital for investigation. Apart from elevated C-reactive protein (12.72 mg/dL), a complete work-up of tumor markers and bacterial, viral, and autoimmune diseases was normal. Contrast-enhanced body CT scan (shown in Fig. 1a–d) revealed significant inflammatory abnormalities in muscular and adipose tissues (right supraclavicular area, both axillae, dorsal and lumbar areas, buttocks,

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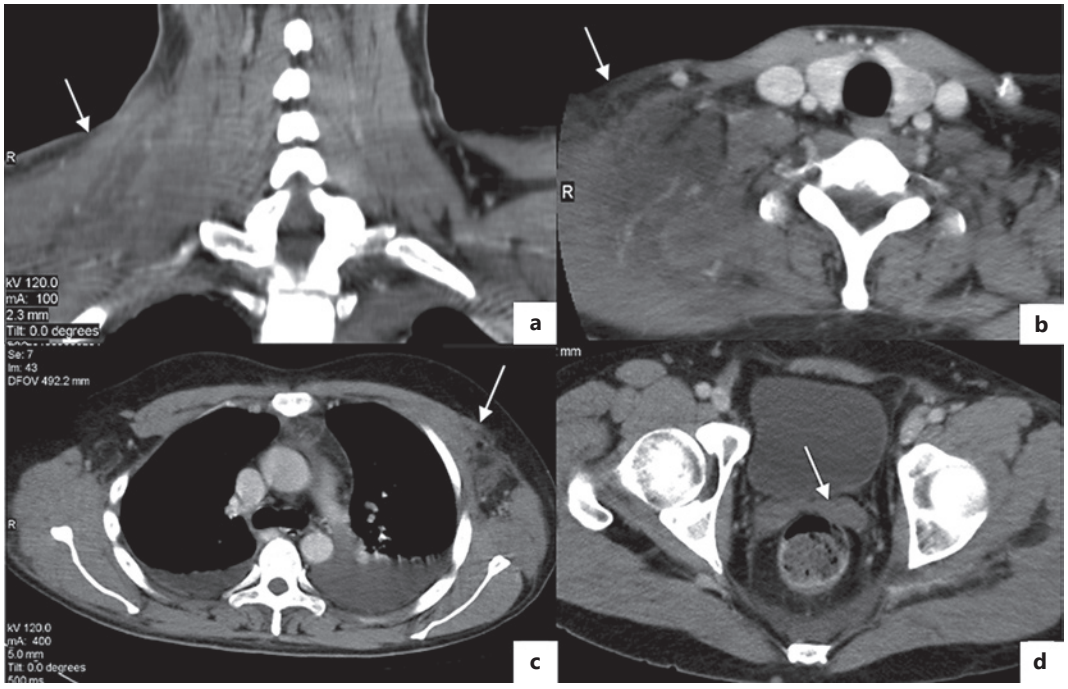

Fig. 1. Body CT showing inflammatory signs: right supraclavicular area (**a**, **b**); mediastinal and left axillary areas (**c**); pelvic area (**d**).

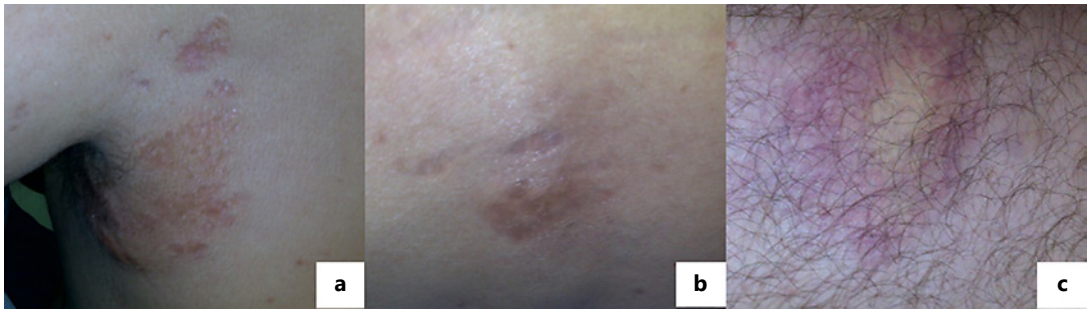

Fig. 2. Violaceous lesions: nodular form, left axilla and lumbar area (**a**, **b**); maculopapular appearance, right thigh (**c**).

presacral area and obturator muscles, and the mediastinum adipose tissue) but no changes in lung parenchyma. The patient was treated with ceftriaxone and doxycycline for 10 days and became afebrile, eventually being discharged. Nonetheless, he still complained of thoracic pain while swallowing and eructing and noticed the appearance of new nodular erythematous/violaceous skin lesions in various areas such as right and left arms, right and left thighs, lumbar region, and left axilla (shown in Fig. 2a–c).

On admission in our Unit, his vital signs, heart, and lung sounds were normal. His abdomen was nontender and there were no organomegalies. After 24 h, he exhibited dry cough and fever (39.5°C) that lasted for 6 days. Chest radiograph disclosed moderate left pleural effusion, with no obvious signs of infection or neoplasia. Thoracentesis was performed, draining 1,000 mL of clear, lymphocyte-predominant fluid without bacterial or neoplastic elements. Pleural biopsy showed mild nonspecific inflammation. Over 2 weeks, inflammatory parameters

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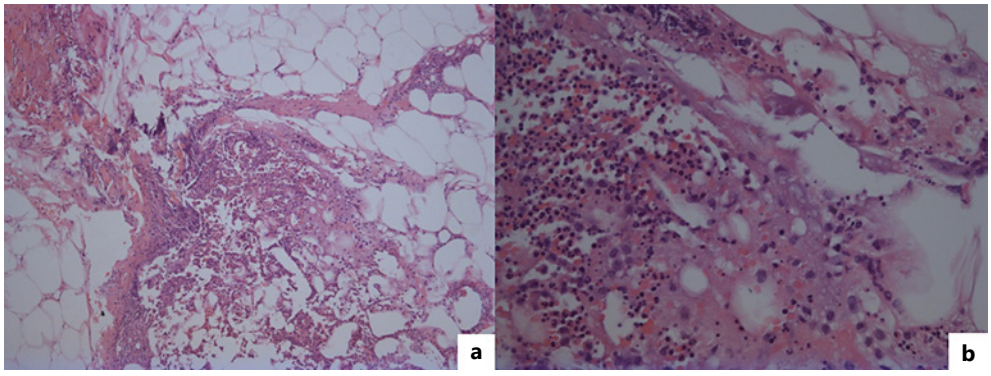

Fig. 3. Microscopic aspects of acute neutrophilic lobular panniculitis, with neutrophils interstitially arranged between collagen bundles of the deep reticular dermis (**a**, **b**).

returned to normal. After the pleural effusion was dealt with, oxygen levels and pulmonary function tests were also normal. Liver parameters and angiotensin-converting enzyme levels were within normal range and we excluded bacterial/viral/parasitic respiratory infections, autoimmune conditions, and endocrine diseases. Serum protein electrophoresis, however, revealed a very low alpha-1 globulin band, a result which suggested the possibility of AATD.

The serum AAT, via immunoturbidimetry method, was 8 mg/dL (90–200), thus confirming the diagnosis of AATD. Molecular biology analysis with enzymatic amplification of genomic DNA using specific oligonucleotides studied our patient's genotype. He was found to be homozygote for the *Gln342Lys* mutation in the AAT gene, in accordance with a *Pi**ZZ genotype. A deep incisional skin biopsy of one lesion showed acute lobular panniculitis with predominantly neutrophilic infiltrate (shown in Fig. 3a, b), accepted as acute disseminated panniculitis due to AATD. Because of the common association of AATD with lung emphysema, we proceeded to a thoracic CT scan with volumetric acquisition, which did not show tomographic evidence of pulmonary emphysema (Table 1). Since both legs developed new lesions with oily discharge, and considering the clinical course had been prolonged and severe, with widespread lesions in adipose tissue, we decided to initiate augmentation therapy with plasma-derived synthetic human AAT (*Prolastin*®, the only available licensed drug in Portugal at the time), on a weekly iv dose of 60 mg/kg. A serum "protective threshold" of 80 mg/dL was obtained and we advised the patient to maintain lifelong therapy. The skin lesions eventually healed, leaving no atrophic scars.

Along the last decade, the patient did not show an evolution to significant pulmonary emphysema. There was an apparent worsening in 2013, but it was temporary, most likely related to intense exposure to smoke from local forest fires, after which he returned to previous levels (Table 1). Until now, 11 years after discharge (April 2022) the patient has had no new bouts of panniculitis or other symptoms. Lung function tests remain normal.

He has been fully vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), using a mRNA-based vaccine, and did not contract COVID-19 until now. We also recommended yearly prevention of influenza infection and the immunization against pneumococcal disease every 5 years. He was instructed to avoid tobacco or any kind of smoke exposure. And finally, we performed a liver biopsy which did not show pathologic aspects of hepatic disease due to AATD.

A genealogical study coupled with serum AAT immunoturbidimetry showed these results: mother – *PI*SZ* (AAT 59 mg/dL), brother #1 – *PI*MS* (106 mg/dL), brother #2 – *PI*MZ* (123 mg/dL), wife – *PI*MS* (108 mg/dL), daughter – *PI*MZ* (92 mg/dL), son #1 – *PI*MS* (106 mg/dL), son #2 – *PI*SZ* (64 mg/dL). All were healthy. His deceased father probably had a *PI*MZ* genotype. The ones with *S* allele had a *Glu264Val* mutation.

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Table 1. Eight-year evolution of thoracic CT scans with volumetric acquisition

Date	Evidence of parenchymal emphysema	ED in lung parenchyma	ED: aortic arch	ED: tracheal bifurcation	ED: lower border of inferior pulmonary veins
Oct 2010	None	<10%			
Nov 2011	None	13.9% (15th percentile)	7.6% (15th percentile)	13.1% (15th percentile)	12.7% (15th percentile)
Nov 2012	None	19.1% (15th percentile)	12.3% (15th percentile)	16.2% (15th percentile)	17.8% (15th percentile)
Nov 2013[a]	None	28.4% (15th percentile)	20.5% (15th percentile)	29.2% (15th percentile)	35% (15th percentile)
Nov 2014	None	22.7% (15th percentile)	16.3% (15th percentile)	24% (15th percentile)	26.3% (15th percentile)
Aug 2018	None	17.7% (15th percentile)	9.1% (15th percentile)	19.8% (15th percentile)	19.6% (15th percentile)
Dec 2019	None	17.7% (15th percentile)	9.1% (15th percentile)	20% (15th percentile)	19.6% (15th percentile)

ED, emphysematous density.
[a]Significant exposure to smoke from forest fires during August 2013.

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Discussion

Panniculitis related to AATD is extremely rare. Data regarding symptom prevalence are scarce, with just over 50 references to AATD-associated panniculitis [9]. It presents as recurrent erythematous plaques and subcutaneous nodules on the trunk, buttocks, and extremities, eventually ulcerating and resulting in an oily discharge, healing with atrophic scarring [11]. Around one-third of lesions are preceded by trauma, excessive activity, or surgery [12]. Deep skin biopsy shows excessive fat necrosis and dense lobular neutrophilic infiltration to the dermis and connective tissue. The presence of extensive collagenolysis and elastolysis, resulting in "floating fat," separated from the surrounding reticular dermis and the pannicular septa, is a characteristic finding [13]. Hemorrhage at the lesions' periphery is common, but blood vessels do not reveal primary disease or vasculitis. These findings prompt further work-up to investigate the underlying cause of panniculitis [3]. AATD should always be considered in any biopsy revealing lobular neutrophilic or necrotizing panniculitis [14]. Differential diagnoses include factitial panniculitis, foreign body reactions, infectious diseases (bacteria, fungi, protozoa), and pancreatic panniculitis [15].

Intravenous infusion of AAT from pooled human plasma is extremely useful for treatment of serious AATD-associated panniculitis [9]. The rationale for use of augmentation therapy is that it corrects the protease imbalance in areas of panniculitis and modulates neutrophil activation and degranulation, the end result being a decreased inflammatory cytokine burden and downstream proteolysis [16]. Although this is an expensive therapy, we believe it is indicated for severe cases of AATD-associated panniculitis because of its safety and efficacy.

In terms of AATD-associated lung disease, the most important prophylactic measure is smoking cessation. When possible, continuous passive smoking should also be avoided, as should every persistent exposure to other potentially harmful substances [17]. Prophylaxis for pulmonary diseases is strongly recommended. This is especially paramount regarding SARS-CoV2 because some studies point that the genotypes associated with lowest levels of AAT, such as *Pi**ZZ, seem to have a higher risk of COVID-19 [18, 19] and AAT itself may lend protection from SARS-CoV2 infection [20].

Several authors consider that augmentation therapy is yet unproven as an effective prevention and treatment for lung emphysema and does not warrant generalized use due to economic concerns. More than a decade after the diagnosis was made and AAT substitution was started, our patient is yet to show any evolution toward lung emphysema. His biggest protecting factor is the fact that he was never a smoker, but we propose that augmentation therapy can contribute to slowing (or even preventing) a hypothetical progression of the disease to lung emphysema. Further investigation is required in this area.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and the accompanying images. Study approval statement was not required for this study in accordance with local guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. António Guilherme Murinello is the main author. He made the most substantial contribution toward the conception, design, and draft of this paper. He also participated in the acquisition, analysis, and interpretation of data. He performed research and literature review and revised the intellectual content of the document. He gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Dr. Helena Sá Damásio and Dr. Ana Serrano participated in the acquisition of data for the paper, as well as the draft. They gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Dr. Pedro Guedes made a significant contribution regarding the design and draft of this paper. He also participated in the acquisition, analysis, and interpretation of data. He performed literature review and revised the intellectual content of the document. He gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Dr. António Manuel de Figueiredo and Dr. Adriana Santos participated in the acquisition and analysis of data for the paper, as well as the draft. They gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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