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Case Presentation

Alpha-1-antitrypsin deficiency-associated panniculitis: a case report

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Abstract

Panniculitis is a recognized, but rare complication of α1-antitrypsin (A1AT) deficiency. Less than 60 cases have been reported, mostly in the homozygous PiZZ variant. We report the case of a 55-year old woman with A1AT panniculitis associated with the heterozygous phenotype PiMS and discrete reduction of A1AT serum levels. In addition, the pathophysiology of the disease, clinical and histopathological features, and current treatment possibilities are briefly reviewed.

Keywords: alpha-1-antytripsin, panniculis, neutrophilic panniculitis

Introduction

α1-antitrypsin (A1AT) deficiency is a genetic disorder that increases the risk of chronic pulmonary disease, cirrhosis, and less frequently, panniculitis. A1AT is an important serine protease inhibitor mainly synthesized in the liver and to a small degree in the lung. It regulates the activity of several proteolytic enzymes including trypsin, elastase, chymotrypsin, collagenase, factor VIII, kallikrein, thrombin, and plasmin [1].

A1AT deficiency is inherited as an autosomal co-dominant disorder and more than 100 allelic variants for the gene (located in 14q32) that encodes this protein have been identified. The phenotypes are defined by the protein isoelectrophoretic mobility: M means medium mobility, S means slow mobility, and Z is associated with very slow mobility. The most frequent allele is PiM and homozygous PiMM phenotype is associated with normal serum levels of A1AT. The homozygous phenotype for the Z allele is associated with very low serum levels. Carriers of the Z or S allele have a normal A1AT production and function, but only a small fraction of the enzyme is released from its major production site on the liver. The mutation increases the tendency to polymerize in the Z variant and to a lesser degree in the S variant, including heterozygous phenotypes. Therefore, the polymerized A1AT protein cannot be released from the liver [2]. A1AT heterozygosity (PiMS, PiMZ, PiSZ) affects 10% of general population [3].

Panniculitis is a very rare complication of A1AT deficiency that is mostly associated with homozygous variants, but can also be found in heterozygous types. It has an equal prevalence in both sexes and no racial predominance. It has been reported in all age groups, most commonly between 30-60 years [2].

Case Report

A 55-year-old woman presented with a 9-day history of erythematous plaques on her thighs and abdomen. She reported the occurrence of similar lesions 6 months earlier, which required approximately 2 months for spontaneous resolution. The patient had no history of smoking, alcohol abuse, or drug intake except captopril for high blood pressure. Family history was unremarkable for similar skin lesions, lung disease or liver disease. She had no other constitutional symptoms besides general malaise. The skin lesions were not precipitated by trauma.

On physical examination, the patient was found to have multiple, tender, ill-defined, indurated and erythematous plaques, 1-5 cm in diameter, on the thighs, abdomen, and forearms. There was no ulceration or spontaneous suppuration. Furthermore, the skin displayed atrophic and slightly hyperpigmented scars in locations where previous lesions had spontaneously resolved.

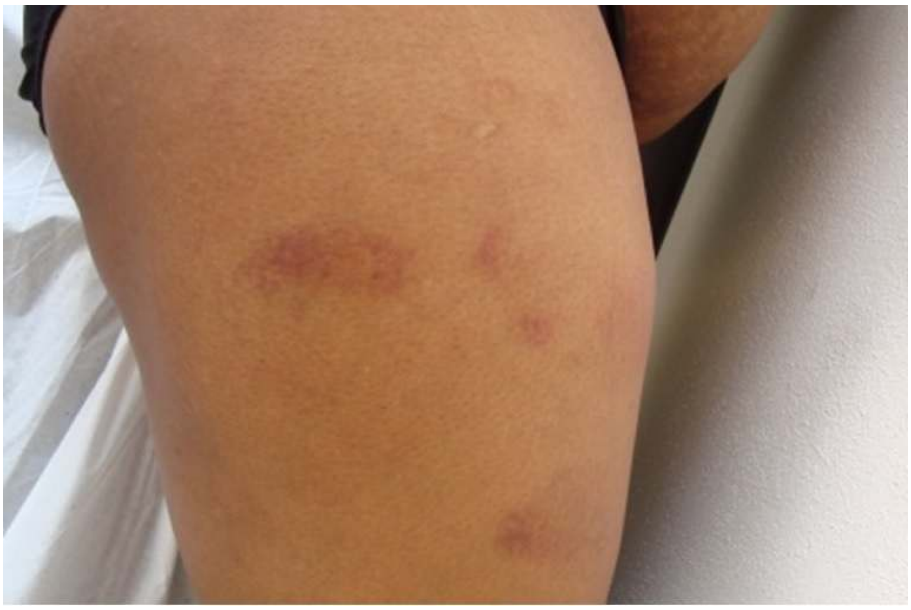

Figure 1. Multiple, ill-defined, indurated erythematous plaques on the proximal extremities (anterior aspect of the thigh)

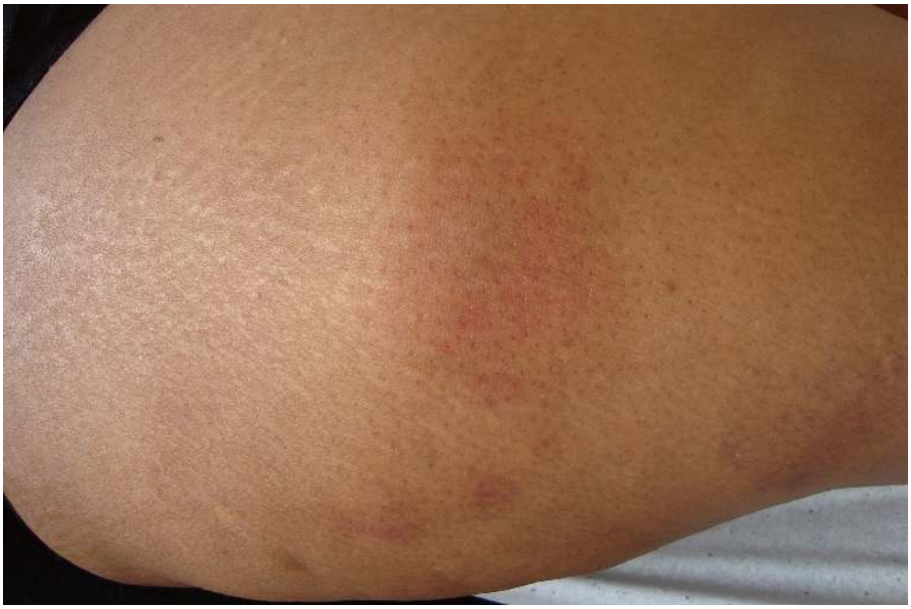

Figure 2. Multiple, ill-defined, indurated erythematous plaques on the proximal extremities (posterior aspect of the thigh)

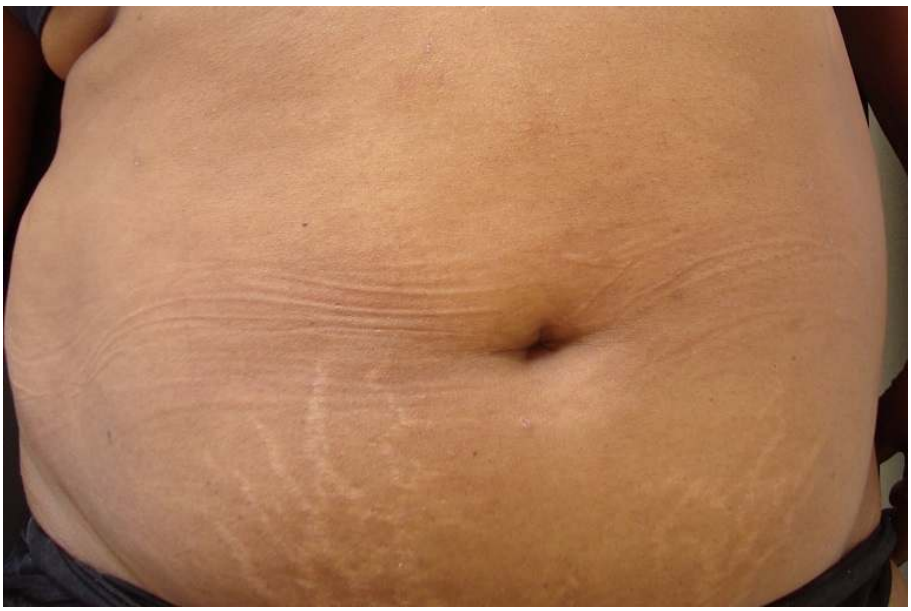

Figure 3. Multiple, ill-defined, indurated erythematous plaques on the abdomen; neither ulceration nor spontaneous suppuration were seen

Serum amylase and lipase levels were normal. Rheumatoid factor, antinuclear antibody, and antineutrophil cytoplasmatic antibody were all normal. The A1AT level was decreased at 107 mg/dL (reference range: 140-320 mg/dL). The A1AT phenotype was PiMS. Chest X-ray and chest and abdominal computed tomography were normal.

An incisional biopsy from a fresh lesion on the patient's thigh was taken and an oily brown discharge from the site of the incision was noted. Histopathological examination revealed a mostly lobular panniculitis without vasculitis, with focal necrosis of adipocytes and an intense infiltration of neutrophils. Special stains for organisms were negative. The correlation between clinical, laboratorial, and histopathological features allowed the diagnosis of A1AT deficiency-associated panniculitis.

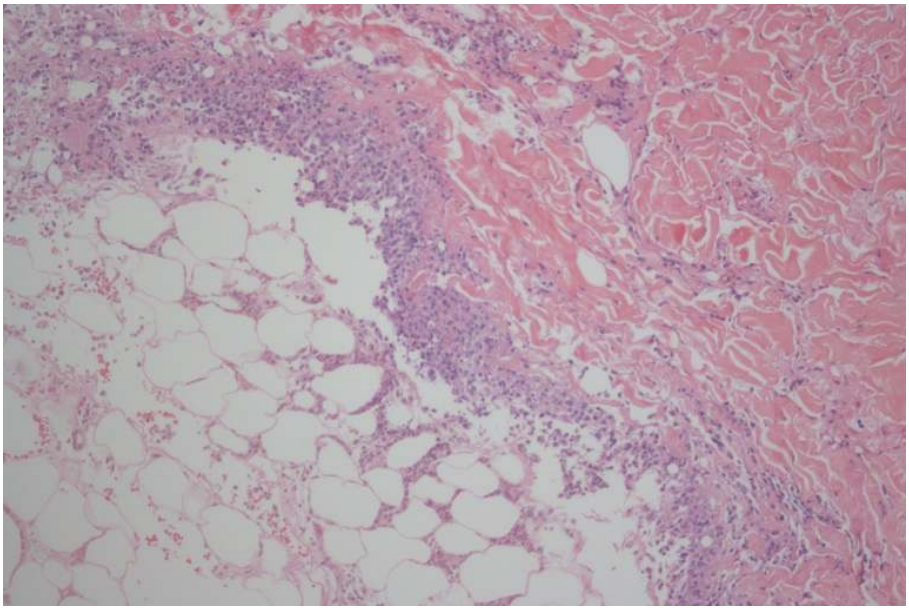

Figure 4. Histopathological examination of a plaque: mostly lobular panniculitis without vasculitis, with focal necrosis of adipocytes surrounded by an intense infiltrate of neutrophils (Hematoxylin-eosin, original magnification x100)

Treatment with dapsone was not considered because of a decreased serum level of glucose-6-phosphate-dehydrogenase. The patient was started on oral colchicine therapy 2 mg daily and all skin lesions resolved within 4 weeks and healed with scarring. The colchicine dose was gradually reduced to 0.5 mg daily without recurrence of the symptoms after 3 years of follow-up.

Discussion

Panniculitis is a much less frequent complication of A1AT deficiency than lung and liver disease, but can be its presenting sign; less than 60 cases have been reported [1].

The pathogenesis of A1AT deficiency panniculitis may be explained by several mechanisms: 1) increased degradation of elastin and subsequent tissue damage related to A1AT deficiency and also conformational changes in elastin induced by fatty acids; 2) lack of inhibition of membrane-bound serine proteases resulting in activation of lymphocytes and phagocytes and accumulation of neutrophils that release unopposed serine proteases within local tissue damage; 3) oxidation of A1AT by neutrophil myeloperoxidase that decreases its function [2].

The lesions occur predominantly on the trunk and proximal extremities. The patients often present with painful, erythematous nodules or plaques that frequently ulcerate and drain an oily material. They tend to heal with atrophic scars. Chronicity and recurrences are not uncommon. In one third of cases, previous trauma at lesion locations is described [4,5,6].

The diagnosis is made by skin biopsy and blood testing for A1AT. Histopathological examination reveals a mostly lobular panniculitis but may also show septal involvement. In early stages, neutrophils are interstitially arranged between collagen bundles of the deep reticular dermis, followed by a neutrophilic mixed panniculitis with lobular necrosis. There are foci of normal fat adjacent to necrotic areas. As the amount of necrosis increases, fewer neutrophils are seen and the number of fibroblasts increases with subsequent scar formation. Vasculitis has been described in association with significant neutrophilic infiltration [7].

The differential diagnosis should include other causes of panniculitis that ulcerate and drain. These include pancreatic, infectious, and factitial panniculitis and also erythema induratum. Histopathologic findings of intense neutrophilic infiltrate phases may be confused with findings typically seen in neutrophilic dermatoses [1,2,3].

Multiple drugs have been tried in the treatment of A1AT deficiency panniculitis because it is refractory to many treatments, including corticosteroids, immunosupressants, and antimalarials. Doxycycline and minocycline can be effective in mild cases as a result of the anticollagenase activity of the tetracyclines. Dapsone has been used with good results in some cases by inhibiting the migration and myeloperoxidase activity of neutrophils. Colchicine was useful in very few cases but we also had a good outcome in our patient [2,3]. For severe cases with associated lung and liver disease, augmentation therapy with A1AT from human pooled plasma of normal donors via intravenous infusions must be considered. Replacement therapy has proven to be useful in these aggressive cases [8]. The role of gene therapy is under development.

Our patient presented with a slightly decreased serum level of A1AT associated with classic clinical and histologic features and an abnormal phenotype (MS). Only a few cases of A1AT deficiency panniculitis associated with heterozygous variants have been reported to date. The frequency of S and Z alleles in the general population is also quite high relative to the rare incidence of panniculitis. These findings suggest that other etiopathogenetic factors may play a role in A1AT deficiency panniculitis, including other unrelated genetic or environmental factors.

Conclusion

Proper knowledge of A1AT deficiency genetics and epidemiology is important for interpretation of serum levels and phenotype. Testing can only be of diagnostic value with adequate clinical and histological correlation in the setting of a panniculitis.

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