

# Ulcerative panniculitis with fevers and pleural effusions: A unique case of $\alpha_1$ -antitrypsin deficiency

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**Key words:**  $\alpha_1$ -antitrypsin deficiency; fever; panniculitis; *PiZZ* phenotype; pleural effusions; ulcerative panniculitis.

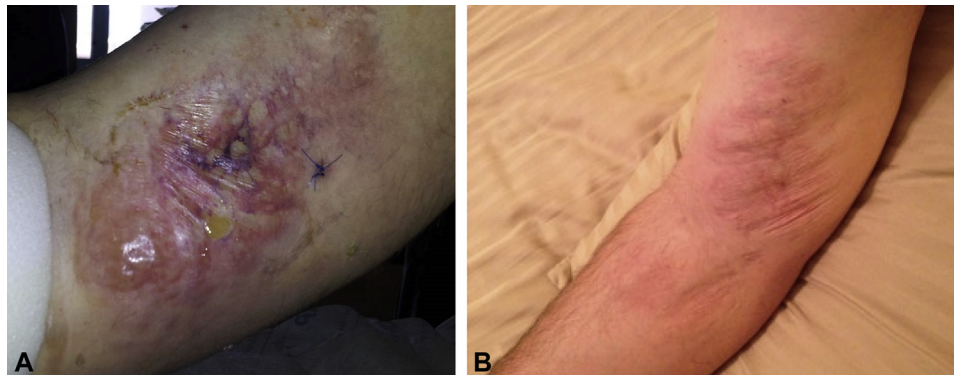
**A**lpha<sub>1</sub>-antitrypsin (AAT) is a serine protease inhibitor that prevents enzymatic degradation of normal human tissue.<sup>1</sup> The Z allele of the AAT gene locus (designated *PI*) is the most frequent deficient mutation, with the *PiZZ* phenotype responsible for 95% of severe AAT deficiency cases.<sup>2</sup> Severe deficiency is often underdiagnosed and classically leads to pulmonary and hepatic disease. Panniculitis is an unusual complication of AAT deficiency with prevalence of less than 0.1%.<sup>3</sup> The panniculitis is characterized by refractory, painful nodules that ulcerate with oily or sanguineous drainage.<sup>4</sup> We describe a unique inflammatory presentation of AAT deficiency that was characterized by recurrent fevers, ulcerative panniculitis, and pleural effusions. The classic findings of emphysema, bronchiectasis, and overt liver injury were absent.

*Abbreviation used:*

AAT:  $\alpha_1$ -antitrypsin

## CASE REPORT

A previously healthy, 38-year-old man (with distant smoking history) presented with 5 months of severe fatigue, fever, myalgias, arthralgias, and joint swelling, which began shortly after a fishing trip. These symptoms were accompanied by painful, ulcerating plaques of his upper and lower extremities (Fig 1, A). The patient's condition was refractory to numerous courses of intravenous antibiotics and systemic corticosteroids. Physical examination of the ankles and arms found several ill-defined, purpuric, ulcerative, edematous plaques with yellow serous drainage. Clinical



**Fig 1.** Panniculitis of AAT deficiency. **A**, Tender, ill-defined, edematous, violaceous plaque with flaccid bulla and small central ulceration with serous drainage on upper extremity. **B**, Progression to atrophic scars after 3 infusions of augmentation therapy in combination with dapsone.

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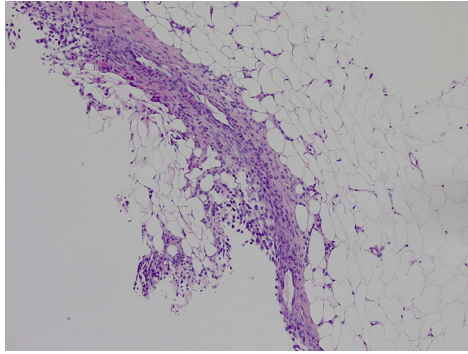
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**Fig 2.** Histopathologic features of AAT deficiency–related panniculitis. Septal panniculitis with a lymphocyte predominant inflammatory infiltrate, scattered histiocytes, and septal widening of the subcutaneous fat. No evidence of vasculitis or well-formed granulomas. (right arm; hematoxylin-eosin stain; original magnification:  $\times 10$ .)

differential diagnosis was broad, including infectious, inflammatory, vasculitic, thrombotic, and embolic etiologies. An extensive rheumatologic and infectious workup was negative, including serologies and blood and tissue cultures.

Skin biopsy showed a septal panniculitis with a lymphocyte-predominant infiltrate. Scattered necrotic keratinocytes were observed in the epidermis and acrosyngia (Fig 2). Vasculitis and necrosis were not found. Infectious stains were negative.

The patient was found to have an AAT level of 43 mg/dL (normal, 83-199 mg/dL). Subsequent genetic testing showed that the patient was homozygous for the Z allele. Accordingly, AAT deficiency PiZZ phenotype was diagnosed. Results of liver function tests were normal. A computed tomography scan of the abdomen and pelvis showed minimal hepatic steatosis. Chest computed tomography showed no evidence of emphysema or bronchiectasis. However, the patient later developed recurrent and bilateral, neutrophil predominant, exudative pleural effusions that required multiple thoracenteses.

The patient was treated initially with dapsone, 100 mg by mouth daily, resulting in slight clinical improvement. Remarkable systemic and dermatologic improvement was observed after initiation of intravenous  $\alpha_1$ -proteinase inhibitor replacement protein administered at 60 mg/kg/wk. The patient's ulcerated plaques progressed to atrophic scars after 3 infusions of augmentation

therapy (Fig 1, B), and the patient's pleural effusions resolved.

## DISCUSSION

AAT deficiency is an underdiagnosed genetic disorder that rarely first presents on the skin.<sup>5</sup> Morphology is nonspecific and can resemble cellulitis, vasculitis, or chronic ulcers.<sup>1,4</sup> Fever commonly leads to misdiagnosis as infection. Similarly, histopathology can be variable, as septal panniculitis may be present with or without lobular involvement and fat necrosis.<sup>4</sup> Although the characteristic feature of AAT deficiency-related panniculitis is the presence of neutrophils and liquefactive necrosis of the dermis and fibrous septa,<sup>4</sup> this may not necessarily be observed in early lesions. Dapsone at 50 to 150 mg by mouth daily for several weeks alone or combined with intravenous infusions of AAT ameliorates panniculitis in AAT-deficient patients.<sup>5</sup>

Although our patient possessed the severe phenotype of the disease, he lacked numerous diagnostic features of AAT deficiency: (1) a neutrophilic infiltrate and necrosis on biopsy of the panniculitis, (2) emphysema or bronchiectasis, and (3) evidence of liver injury or cirrhosis. Instead, our patient exhibited recurring, neutrophil-rich bilateral pleural effusions, which are uncommon in AAT deficiency. This case highlights that unexplained panniculitis in the setting of fever and other signs of systemic inflammation should prompt suspicion for AAT deficiency.

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