

Cutaneous Manifestation of α_1 -Antitrypsin Deficiency: Panniculitis Absent on Biopsy

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Practice Points

- α_1 -Antitrypsin (AAT) deficiency with a ZZ phenotype has the lowest serum levels of AAT and presents with systemic manifestations such as pulmonary and liver disease; rarely, AAT deficiency can present with cutaneous findings.
- Panniculitis may be absent on histopathology during the early phase of skin lesions of AAT deficiency.
- One should consider checking serum AAT levels if ulcerative nodules are noted on the trunk and proximal extremities in the setting of systemic findings such as dyspnea and lower leg edema, even if the classic findings of panniculitis are absent on histopathology.

Patients with α_1 -antitrypsin (AAT) deficiency may develop cutaneous manifestations of the disorder that histologically appear as panniculitis. Algorithms consistently emphasize measuring AAT levels when both clinical and histological features of deficiency are present; however, the patient's medical history and a physical examination alone can be extremely helpful in guiding the physician to the diagnosis of AAT deficiency. We describe a patient who presented with the classic clinical findings of AAT deficiency—associated panniculitis with surprising absence of panniculitis on repeated deep incisional biopsies. We propose a triad of classic findings that should alert the clinician to check the patient's serum AAT levels, even in the absence of panniculitis on histologic

evaluation. Consideration of this clinical triad may prevent delays in the diagnosis of AAT deficiency, as early lesions may not yet demonstrate subcutaneous fat involvement.

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A glycoprotein produced in the liver, α_1 -antitrypsin (AAT) is a potent inhibitor of serine proteases such as trypsin, chymotrypsin, and neutrophil elastase. More than 120 different alleles for the gene have been discovered, which are categorized into subtypes based on the protein's electrophoretic mobility.¹ The normal variant of AAT is the M subtype; the A to L variants migrate faster and the N to Z variants migrate slower than M-type AAT.² Most commonly, these subtypes are classified into 4 main categories: F, fast; M, medium; S, slow; Z, very slow.

The ZZ phenotype is associated with the lowest serum AAT levels and presents with systemic manifestations such as pulmonary and liver disease. Rarely, the ZZ phenotype of AAT also manifests as panniculitis, which presents as erythematous to violaceous subcutaneous nodules or plaques that can develop into ulcerative lesions, most commonly located on the trunk and proximal extremities.³ The most common

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histopathologic feature of AAT deficiency–associated panniculitis is an infiltrate of neutrophils involving septal and lobular areas with fat necrosis.³⁻⁵

Classically, the diagnostic approach to AAT deficiency–associated panniculitis includes consideration of the clinical and histologic features along with evaluation of serum AAT levels. We describe a patient who presented with the classic clinical picture of AAT deficiency–associated panniculitis that was surprisingly absent on repeated deep biopsies.

Case Report

A 55-year-old woman presented to her primary care physician after developing multiple tender, erythematous to violaceous nodules on the upper left arm that she suspected were from insect bites. The patient had no constitutional symptoms such as dyspnea, fever, chills, or gastrointestinal tract involvement. The patient noted that she had vacationed in Brazil 1 month prior to the development of the lesions. Her primary care physician suspected an infectious etiology and treated her empirically over the next few weeks with multiple courses of antibiotics and oral prednisone with no improvement. The patient was subsequently referred to infectious disease and dermatology clinics for further diagnosis and management.

Physical examination 1 month later revealed several discrete red to violaceous nodules and plaques, primarily located on the trunk and proximal arms and legs (Figure 1); some were ulcerated and resembled pyoderma gangrenosum (Figure 2). The lesions began as erythematous macules that developed bullae and ruptured, releasing an oily yellowish exudate, and were primarily located on the trunk and proximal arms and legs. Edema of the bilateral lower legs also was noted.

Five biopsies, including deep incisional biopsies to fascia, were performed over several weeks, and stains and cultures were all negative for fungal or bacterial organisms. The histology showed a mixed acute and chronic inflammatory infiltrate, which was localized primarily to the dermis; a prominent panniculitis was not seen despite good sampling of the subcutaneous fat (Figure 3). The superficial dermis showed areas of inflammation between collagen bundles (Figure 4). Superficially, there were foamy macrophages, eosinophils, lymphocytes, and neutrophils present.

Six weeks after the initial presentation of the skin lesions, the patient was admitted to the hospital because of acute dyspnea and worsening cutaneous lesions. Given the patient's recent trip to Brazil, leishmaniasis was suspected and azithromycin was initiated. The patient proceeded to develop worsening edema of the lower legs and recurrent bilateral pleural effusions that required multiple thoracenteses



Figure 1. Edematous inflammatory plaque on the proximal left arm.



Figure 2. Ulcerated lesion on the posterior aspect of the right shoulder resembling pyoderma gangrenosum.

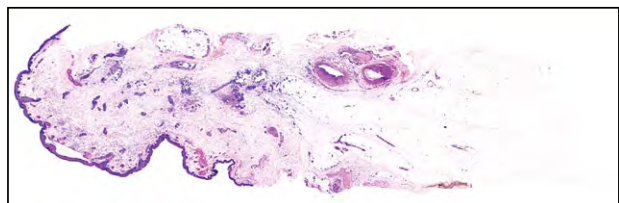


Figure 3. Representative biopsy of a cutaneous lesion clearly demonstrating sampling of the subcutaneous fat without evidence of panniculitis (H&E, original magnification $\times 4$).

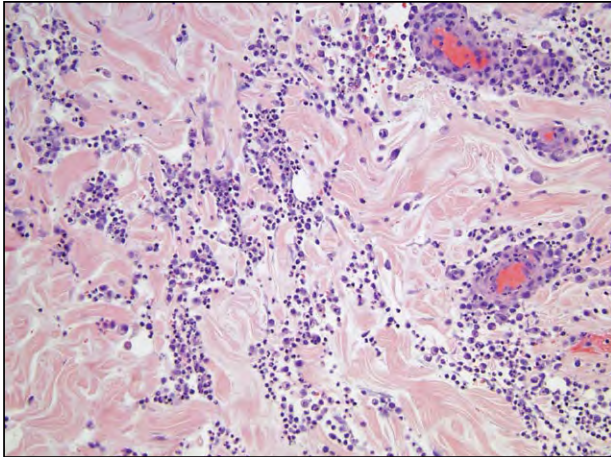


Figure 4. Neutrophils between collagen bundles in the reticular dermis, commonly described as splaying of neutrophils (H&E, original magnification $\times 10$).

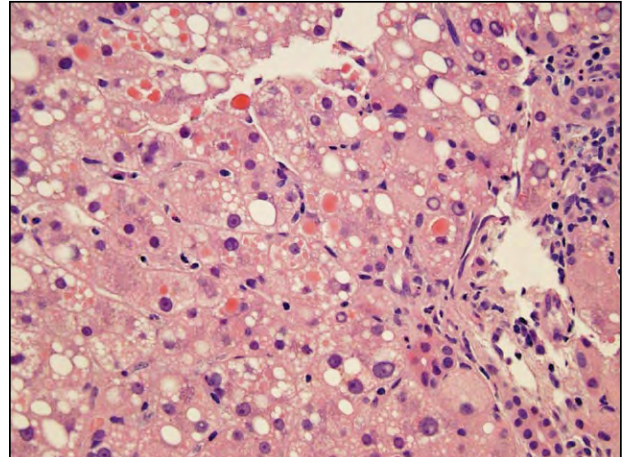


Figure 5. Liver biopsy showed classic round to oval eosinophilic inclusions within hepatocytes (H&E, original magnification $\times 40$).

during her hospital admission. Laboratory evaluation included negative serologies for deep fungal infections, *Leishmania* IgG, antinuclear antibody, human immunodeficiency virus, and rapid plasma reagin. Angiotensin-converting enzyme and alkaline phosphatase levels were within reference range.

Initially, AAT deficiency was ruled out based on the absence of panniculitis on histology; however, given the morphology and distribution of the skin lesions, pulmonary involvement, and swelling of the lower legs, poor clinicopathologic correlation was considered and a serum AAT level was ordered. Results revealed an extremely low AAT level (36 mg/dL [reference range, 78–200 mg/dL]) with ZZ phenotype.

Due to the recurrent pleural effusions and persistent lower extremity edema, there was concern about possible hepatic cirrhosis secondary to AAT deficiency and a liver biopsy was ordered. The liver biopsy was consistent with cirrhosis and revealed large parenchymal nodules devoid of portal tracts and central veins. Prominent eosinophilic globules were seen within the zone 1 hepatocytes (Figure 5). Immunohistochemical stains of the liver biopsy for AAT confirmed the diagnosis (Figure 6). Dapsone 50 mg daily was initiated with notable improvement of cutaneous lesions after 1 week of treatment. Future AAT replacement therapy was pursued.

Comment

The lesions of panniculitis may be the first manifestation of AAT deficiency, as seen in our patient. Clinically, panniculitis associated with AAT deficiency presents as erythematous plaques and nodules

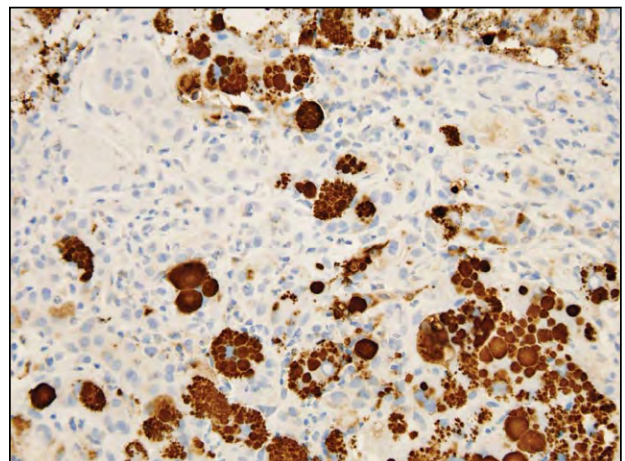


Figure 6. Immunohistochemical stain of the liver biopsy was positive for α_1 -antitrypsin (original magnification $\times 40$).

most commonly located on the trunk and proximal extremities.³ The subcutaneous nodules develop into deep necrotic ulcers with an oily discharge.^{3,6}

Noncutaneous manifestations of AAT deficiency primarily include pulmonary and hepatic involvement. Individuals with the ZZ phenotype of AAT have limited ability to inhibit the widespread proteolytic activity produced from neutrophils during inflammatory processes and often develop panacinar emphysema as a result. Recurrent sterile pleural effusions such as those seen in our patient also have been reported in prior cases.⁶ Unlike the elastase-mediated mechanism of disease in the lungs, hepatic involvement results from the accumulation of the

defective AAT protein in the endoplasmic reticulum of hepatocytes. Although all individuals with the ZZ phenotype accumulate misfolded AAT proteins, only 10% develop cirrhosis.³ Histopathology of cutaneous lesions associated with AAT deficiency generally reveals a panniculitis with neutrophils involving lobular and septal areas.^{6,9} Neutrophils are seen between collagen bundles in the reticular dermis (splaying of neutrophils).⁴ Panniculitis adjacent to normal fat (skip lesions) also is a common characteristic of AAT deficiency.^{5,6} Destruction of elastic tissue in the areas of inflammation may be present. Repeated deep incisional biopsies of our patient's cutaneous lesions failed to show panniculitis. Neutrophils were present between collagen bundles in the superficial dermis consistent with splaying of neutrophils. Geller and Su⁴ proposed the progression of histopathologic findings of AAT deficiency-associated panniculitis. The earliest finding is the splaying of neutrophils between collagen bundles throughout the reticular dermis followed by progression to the fibrous septa of the subcutaneous fat. Late in the process, widespread neutrophilic infiltration of the dermis and subcutaneous fat with prominent panniculitis is observed.⁴

The lack of panniculitis on our patient's multiple biopsies may have several explanations. Although unlikely, it is possible that some of the biopsy specimens were too superficial, leading to inadequate sampling of the subcutaneous fat; however, subcutaneous fat was present on several biopsies and panniculitis was not observed. The evolutionary nature of inflammatory diseases also complicates the picture. Panniculitides generally are dynamic processes, and the inflammatory infiltrate may evolve over a matter of days. It is plausible that we biopsied during the early phases of AAT deficiency-associated panniculitis described by Geller and Su⁴ and only saw splaying of neutrophils in the collagen fibers without obvious panniculitis.

The absence of panniculitis on multiple biopsies led to a delay in diagnosis in our patient. Algorithms consistently emphasize measuring AAT levels when both clinical and histological features of deficiency are present; however, the patient's medical history and a physical examination alone can be extremely helpful in guiding the physician to the diagnosis of AAT deficiency.

Conclusion

We propose a triad of classic findings that should alert the clinician to check serum AAT levels, even in the absence of panniculitis on histologic evaluation: (1) recurrent ulcerative subcutaneous nodules or plaques with serosanguineous drainage; (2) lesions presenting primarily on the trunk and proximal extremities; and (3) systemic findings of shortness of breath and/or limb swelling. Consideration of this clinical triad may prevent delays in the diagnosis of AAT deficiency, as early lesions may not yet demonstrate subcutaneous fat involvement.

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