Treatment of α_1-Antitrypsin–Deficiency Panniculitis With Minocycline

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A small proportion of patients with α_1-antitrypsin (α_1AT) deficiency experience recurrent ulcerating panniculitis. Studies suggest that α_1AT-deficiency panniculitis reflects an uncontrolled inflammatory process because of the serum's incapacity to neutralize proteolytic enzymes released by leukocytes in the skin. Dapsone is considered the treatment of choice for this entity, but it is limited by its side effects, especially hematologic ones. Tetracyclines have anticollagenase and anti-inflammatory activity and have been used successfully to treat this type of panniculitis.

We report the case of a 42-year-old woman with recurrent α_1AT-deficiency panniculitis who did not tolerate the side effects of dapsone or systemic corticosteroid. Minocycline treatment led to disappearance of lesions, and long-term administration prevented recurrences without evident negative side effects. We consider minocycline a safe treatment that allows control of α_1AT-deficiency panniculitis.

Panniculitis in patients with α_1-antitrypsin (α_1AT) deficiency is at least partially caused by deficient inhibition of various proteases released by leukocytes in the course of an inflammatory reaction. Dapsone and systemic corticosteroids are the treatments most consistently effective, but, unfortunately, they have significant undesirable side effects. Recently, treatment with tetracyclines has been proposed because of their anticollagenase activity.[1] Tetracyclines can be used over long periods and are thus suitable for treatment of patients who frequently suffer flares. We report the case of a patient with α_1AT-deficiency panniculitis successfully treated with minocycline. The patient initially responded well to treatment with oral prednisone,[2] but the drug was discontinued because of side effects. Subsequent treatment with minocycline led to disappearance of lesions, and long-term administration prevented recurrences without evident negative side effects.

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Case Report

A 42-year-old woman was referred to us with relapsing nodular lesions in subcutaneous fat that were first noted 2 years previously and diagnosed as panniculitis due to α_1AT deficiency. Initially, she had been treated unsuccessfully with minocycline and potassium iodide. Dapsone had been effective but had to be discontinued because of hematologic alterations. Dermatologic examination revealed subcutaneous nodules of inflammatory appearance that spontaneously ulcerated, releasing a serosanguineous fluid, which left hyperpigmented residual lesions (Figures 1 and 2). Results of histopathologic studies revealed nonspecific lobular panniculitis. Results of Mantoux testing showed an induration 15 mm in diameter. Abdominal ultrasonography revealed slight splenomegaly and a hypo-echogenic mass in the liver; needle biopsy indicated these were caused by a nonspecific inflammatory response. The serum α_1AT level was determined as 31 mg/100 mL (normal range, 90 to 200 mg/100 mL). The α_1AT phenotype was ZZ. Other standard tests (ie, blood count, coagulation tests, serum biochemistry, serum amylase, urine analysis, levels of complement fragments C3 and C4, CH50, antinuclear antibodies, rheumatoid factor, chest radiography, functional respiratory test, serologic test for syphilis, bacterial and fungal cultures of tissue from the lesion) gave normal or negative results.

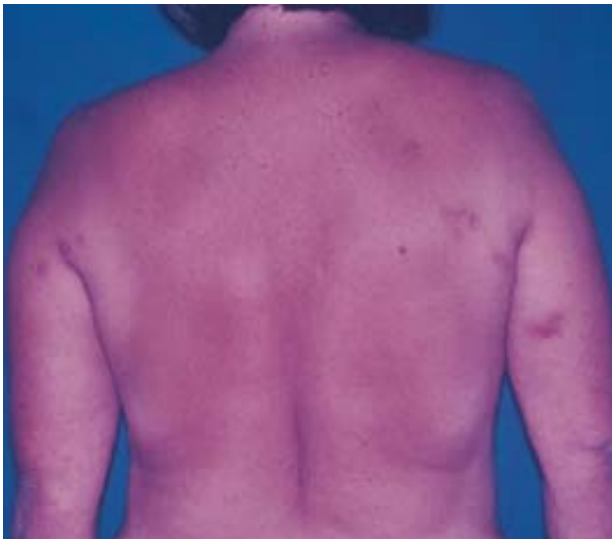

Figure 1. Lesions on the trunk and arms that left hyperpigmented residual zones.

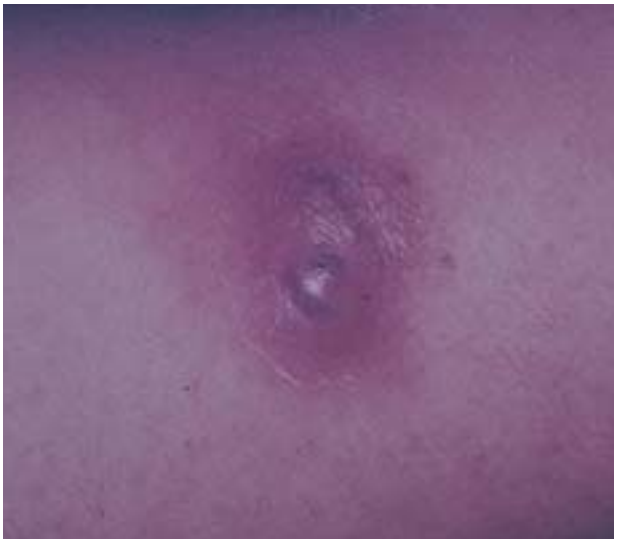

Figure 2. An ulcerated nodule.

Prednisone treatment (60 mg/d) was commenced immediately and yielded good results within 2 weeks. The prednisone dosage was then gradually reduced to 15 mg/d after 6 months. By that time, the lesions had disappeared, but the patient had a cushingoid appearance. Abdominal ultrasonography did not reveal hypo-echogenicity of the liver as detected previously. Prednisone was discontinued, and the patient was started on deflazacort at an equivalent dosage (22 mg/d). Within 2 weeks, one nodular lesion appeared on the buttock and another on the trunk. Without discontinuing deflazacort, therapy with minocycline (100 mg every 12 hours) was started. The lesions disappeared within 3 weeks. Two months later, minocycline treatment was discontinued, and the steroid (deflazacort) dose was gradually reduced.

Two months later, by which time the patient was receiving 15 mg/d of deflazacort, a lesion arose in the perineal region. Treatment with minocycline was recommenced (100 mg every 12 hours), and the lesion disappeared within 4 weeks. Seven months later, deflazacort was discontinued and the minocycline dosage was reduced to 100 mg/d. One year and 7 months later, the minocycline dosage was further reduced to 100 mg every 48 hours. Minocycline was discontinued after 5 months, and 3 months later a lesion arose on the trunk; this lesion disappeared with the reintroduction of minocycline. Two years later, minocycline was again discontinued, but a lesion arose on the patient's thigh after 3 months.

Comment

Proteases (such as collagenase and elastase) are enzymes that catalyze the degradation of proteins. Protease inhibitors play an important role in the regulation of protease activity. The most important protease inhibitor in serum (accounting for >90% of total antiprotease activity) is α_1AT, which inhibits the activity of enzymes including collagenase, neutrophil elastase, and leukocyte proteases. The normal form of α_1AT is denominated M, and its phenotype is PI MM. However, more than 30 defective variants (due to a mutation in the α_1AT gene) have been identified, of which the most frequent are those denominated Z and S. Affected persons may be homo- or heterozygous for the defect; the patient described in the present study is ZZ.

Although panniculitis is one of the most frequent conditions occurring in patients with α_1AT deficiency, it only occurs in a minority of such patients.[2,3] The reason is not known. It is typically (although not exclusively) observed in patients with a severe (homozygotic) defect of α_1AT. However, the serum levels of α_1AT are not related to the prognosis of the panniculitis.[3]

Research suggests that up to 15% of panniculitis cases may be due to α_1AT deficiency.[4] Panniculitis due to α_1AT deficit is characterized clinically by periodic outbreaks of ulcerating nodular lesions in subcutaneous fat. Fever and other systemic alterations are rare. Lesions are often triggered by trivial traumas and have a cellulitislike appearance. Useful histologic indications of α_1AT-deficiency panniculitis include edema and fragmentation of dermal collagen; destruction of elastic tissue; and, most notably, the focal, nondiffuse nature of subcutaneous lesions.[4,5]

Various drugs have been proposed for the treatment of α_1AT-deficiency panniculitis. Dapsone

(25–200 mg/d) is considered the treatment of choice but is not always effective. This drug may act by interfering with myeloperoxidase, which is known to inhibit α_1AT.[3] Steroids are generally useful, but exacerbation of clinical manifestations has been reported.[5] Intravenous infusion of α_1 proteinase inhibitor concentrate (ie, etiologic treatment) is highly effective but is currently expensive; thus it is only appropriate for cases that do not respond to other approaches or have severe systemic involvement. Other drugs used with varying degrees of success include potassium iodide, cyclophosphamide, and colchicine.[5]

The use of tetracyclines in the treatment of α_1AT-deficiency panniculitis was first reported by Humbert et al.[1] The efficacy of these drugs is probably principally due to their anticollagenase activity,[6-8] which is in turn due to their chelation of calcium and zinc. Other properties of tetracyclines that may contribute to their efficacy are the capacity to inhibit leukocyte chemotaxis[9,10] and phagocytosis.[11] In addition, tetracyclines have an anti-inflammatory effect[12] attributable to their antioxidant activity[13] and protein kinase C-inhibitory activity.[14]

In our patient's case, long-term treatment with minocycline allowed for control of the manifestations of the disorder without the negative side effects of steroids and dapsone. Because prolonged treatment with tetracyclines has no significant negative effects, we consider these types of drugs to be appropriate treatment for patients with relapsing α_1AT-deficiency panniculitis.

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