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Use of Anti-collagenase Properties of Doxycycline in Treatment of α_1-antitrypsin Deficiency Panniculitis

PHILIPPE HUMBERT, BRIGITTE FAIVRE, ROGER GIBEY and PIERRE AGACHE

Departments of Dermatology and Biochemistry, Hôpital St Jacques, Besançon, France

Three patients (a 71-year-old man and 2 women, 73 and 50 years, respectively) with recurrent panniculitis associated with α_1-antitrypsin deficiency are presented. Because the concept of chronic and exaggerated inflammatory response in the patients with α_1-antitrypsin deficiency is based on the theory of protease–antiprotease imbalance, we suggest that tetracyclines will alleviate this condition. Indeed, tetracyclines were found to inhibit collagenase activity. The total remission of the condition in these 3 patients underlines for the first time the effects of doxycycline on a condition characterized by deficiency of the antiprotease system. A review of the 23 reported cases of panniculitis associated with α_1-antitrypsin deficiency is presented in table form.

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P. Agache, Department of Dermatology, Hôpital St Jacques, 25030 Besançon Cedex, France.

First recognized by Warter et al. (1), panniculitis with deficiency of the enzyme α_1-antitrypsin (A1AT) is a chronic, recurring and widely disseminated condition. To date, we are aware of 23 reported cases of panniculitis associated with A1AT deficiency (1–17).

Since A1AT is the principal serum protease inhibitor (18), it may attenuate the damaging effects of various neutrophil and macrophage enzymes. A genetically determined deficiency of this protein is found in about 10% of most European populations (19), and predisposes deficient subjects to inflammatory and immunologically mediated diseases. Thus, deficient patients may have a propensity for exaggerated immunologic and inflammatory responses, leading to recurrent panniculitis or to other chronic conditions (18, 20).

Because the concept of chronic and exaggerated inflammatory response in patients with A1AT deficiency is based on the theory of protease–antiprotease imbalance, it can be argued that any drug that enables one to partly re-establish protease–antiprotease homeostasis may be beneficial to these individuals. A few years ago, Golub et al. (21) reported the anticollagenase activity of tetracyclines, whose anticollagenase properties suggest a beneficial therapeutic effect in A1AT deficiency panniculitis. We present 3 patients with recurrent panniculitis associated with low levels of A1AT where doxycycline effected a total remission of the condition.

CASE REPORTS

Case 1

A 73-year-old white woman was referred to our hospital with a 15-year-history of erythematous nodules on the anterior and posterior aspects of the legs (Fig. 1), and extensor surfaces on the arms, associated with fatigue and nocturnal sweating. During the development of the condition, the lesions were painful and some nodules ulcerated, with drainage of an odorless fluid (Fig. 2). On admission, numerous atrophic, hyperpigmented scars were present on

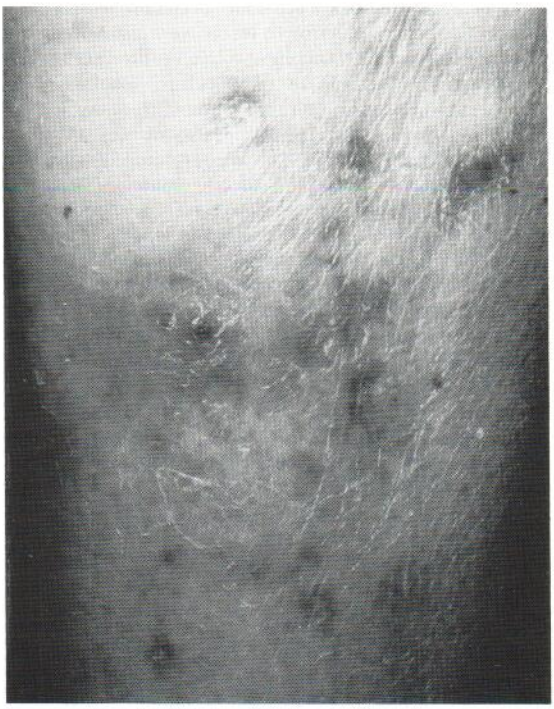

Fig. 1. Panniculitis on the anterior aspect of the leg of patient no. 1.

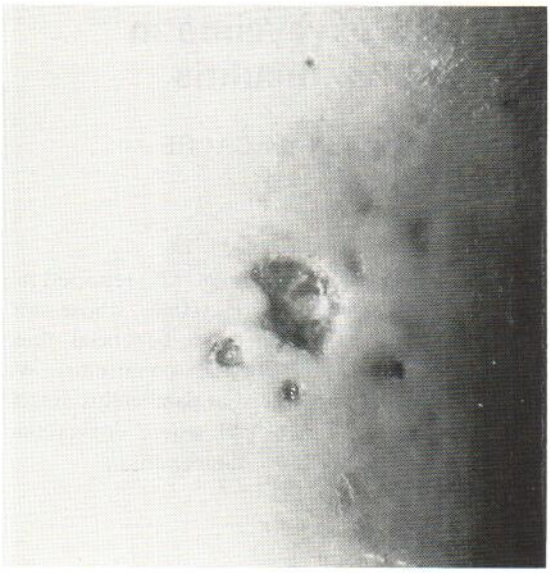

Fig. 2. Leg panniculitis with ulceration and drainage (patient no. 1).

the sites of previous lesions on the legs. Findings of heart and lung examinations were normal. There was no lymphadenopathy or hepatosplenomegaly. The panniculitis had previously been unresponsive to oral corticosteroids, nonsteroidal anti-inflammatory drugs and dapsone.

Laboratory data included: hemoglobin 12.4 g/dl, hematocrit 37.2%, white blood cell count 6100/mm^3 with normal differential count. Electrolyte levels were normal; serum glutamic-oxaloacetic transaminase 16 units/litre, serum glutamic-pyruvic transaminase 10 units/litre, alkaline phosphatase 117 units/litre, bilirubin 8 μmol/litre, amylase 115 units/litre. Angiotensin-converting enzyme was 15 nmol/ml/min (normal 12 to 25). The Westergren sedimentation rate was 30 mm/hour. Tests for rheumatoid factor and antinuclear antibody gave negative results. Complement levels were normal. The α_1-antitrypsin level was 1.20 g/l (normal 1.80 to 3.20), the phenotype was PiMS.

Biopsy specimens of the cutaneous, subcutaneous and adipose tissues demonstrated a lymphohistiocytic infiltrate in the subcutaneous fat tissue. Fat cells were replaced by acutely inflammatory cells, and giant cells were observed (Fig. 3).

Cultures and special stains for bacteria, mycobacteria, and fungi gave negative results. A dramatic improvement occurred following doxycycline medication (200 mg/day) for 3 months. Total remission was achieved using a 100 mg doxycycline regimen. There has been no recurrence of the condition for 2 years (Fig. 4).

Case 2

Over a period of 2 months, painful erythematous lesions rapidly developed on the ankle of a 50-year-old woman. There was no history of preceding trauma or infection. She was known to have suffered from Hashimoto's thyroiditis for 1 year. She was found to have α_1-antitrypsin deficiency (1.18 g/l) and the phenotype was PiMS. Serum lipase, amylase, total complement, C_1 esterase inhibitor, C_3, C_4 and antithrombin values were within the normal range. The antithyroid antibody titre was 1/100. She received L-thyroxin for a mild hypothyroidism. Skin biopsies demonstrated panniculitis, with especially areas of normal fat adjacent to necrotic areas containing neutrophils and histiocytes. She was treated empirically with doxycycline, 200 mg per day. Two months later, her condition began to improve and after 3 months of doxycycline therapy, the condition had completely disappeared. No recurrence was observed in spite of discontinuing of the therapy.

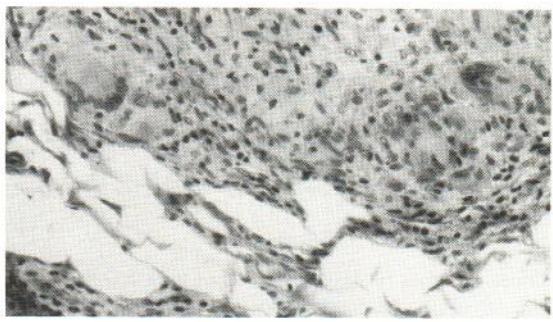

Fig. 3. Panniculitis with mononuclear inflammatory cells and giant cells (Hematoxylin eosin stain; ×250).

Case 3

Tender erythematous nodules on the left ankle developed in a 71-year-old man, following a slight trauma without any cutaneous wound. Within 2 weeks, the lesions spontane-

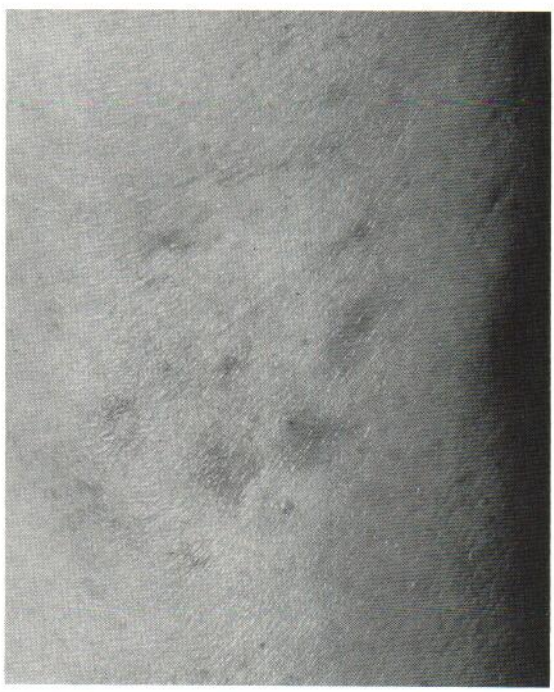

Fig. 4. Complete healing of panniculitis after doxycycline therapy (patient 1).

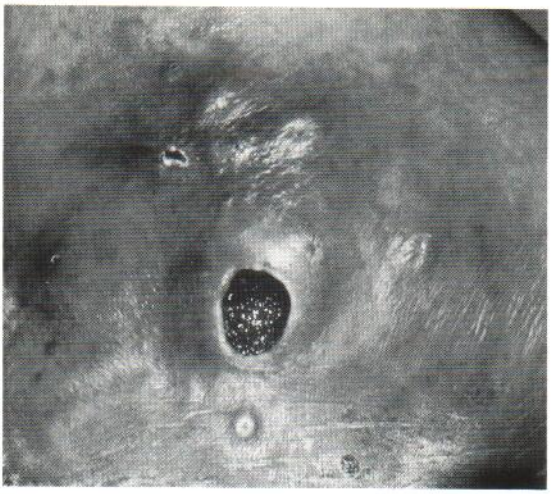

Fig. 5. Painful erythematous subcutaneous indurated nodules, progressing to deep necrotic ulcers (patient 3).

ously ulcerated, with clear fluid effusion. Progressive ulceration resulted in liquefactive necrosis (Fig. 5). Treatments, including antibiotics and indomethacin, did not alleviate the condition. Laboratory examination revealed an α_1-antitrypsin level of 1.40 g/l. Phenotyping was not performed. Routine laboratory investigations were normal. Additional normal test results included complement levels (C_3, C_4 and CH 50), C-reactive protein, serum protein electrophoresis, rheumatoid factor, antinuclear antibody, chest X-ray.

Biopsy specimens of skin and adipose tissue demonstrated panniculitis with lipophages and neutrophilic infiltrates separated the dermal collagen fibres. Special stains, cultures and serologic tests for bacteria, mycobacteria and fungi gave negative results. Doxycycline treatment was begun (200 mg/day) and within 8 weeks total wound healing occurred, with the disappearance of the painful tender nodules leaving atrophic scars (Fig. 6).

DISCUSSION

We report on 3 patients with panniculitis associated with mild heterozygous A1AT deficiency. A1AT is the major serine protease inhibitor of human plasma and is the most abundant of the anti-proteases in human serum. It is known to be synthesized in hepatocytes, but also in macrophages (22). The spectrum of inhibitory activity of A1AT is wide (Table I).

A1AT is an important regulatory protein involved in the suppression of a number of immunologic and inflammatory processes. It modulates the activation of T cells through its effects on monocytes (19), leading to abnormalities in immunoregulation, and to increased activity of a number of inflammatory pathways (18), and hence a predisposition to the development of a variety of immunologic disorders in A1AT-deficient subjects. In a recent paper, Smith

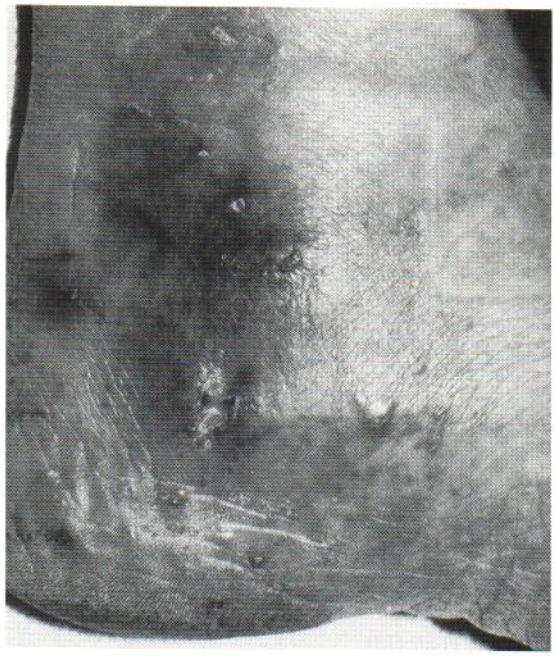

Fig. 6. Ulceration healing with atrophic scars after doxycycline therapy (patient 3).

et al. (23) identified 15 patients with A1AT deficiency among 96 patients affected by panniculitis. This estimation of the frequency of A1AT deficiency in the population of panniculitis patients may warrant a systematic screening for A1AT deficiency in

Table I. *Spectrum of inhibitory activity of α_1-antitrypsin (after Breit SN (20))*

Major importance
PMN neutral proteases
Elastase
Cathepsin G
Collagenase
Trypsin
Chymotrypsin
Factor XIa
Urokinase
Uncertain importance
Plasminogen activator
Sperm acrosin
Renin
Minor importance
Thrombin
Plasmin
Kallikrein
Hageman factor

Table II. *Summary of 26 cases of panniculitis associated with α_1-antitrypsin deficiency*

Source	Sex/Age (year)		α_1-antitrypsin (g/l)	Phenotype (Pi)	Successful treatment
Warter et al. (1) 1972	F	47	0.44	MZ	Hydroxychloroquine (200 mg/day)
Rubinstein et al. (2) 1977	M	32	0.53	ZZ	–
	M	36	0.86	ZZ	–
Guilmot et al. (3) 1980	F	19	1.02	ND[a]	Prednisone
Olmos et al. (4) 1981	M	51	0.70	MZ	Prednisone
Balk et al. (5) 1982	M	49	0.20	ZZ	–
Breit et al. (6) 1983	M	29	0.20	ZZ	Dexaméthasone
	M	36	0.25	ZZ	Cyclophosphamide Colchicine
Pottage et al. (7) 1983	M	26	0.35	ND[a]	Kétoconazole (400 mg/day)
Bleumink et al. (8) 1984	F	25	0.28	ZZ	Dapsone (50 mg/day)
Bleumink et al. (9) 1985	F	44	0.27	ZZ	–
Lonchampt et al. (10) 1985	F	47	0.50	ZZ	Prednisone
Viraben et al. (11) 1986	M	33	0.12	ZZ	Plasma
Miller (12) 1986	M	35	0.74	ZZ	Dapsone + plasmapheresis
Pittelkow et al. (13)	F	35	0.20	ZZ	Dapsone
Smith et al. (14)	F	36	0.20	ZZ	IV α_1-proteinase
Su et al. (15) 1987	F	65	0.40	ZZ	inhibit. + Dapsone
	F	54	0.89	MZ	Fenoprofen
Pittelkow et al. (16)	M	16	1.30	MZ	–
	F	24	0.20	S. null.	Dapsone
Hendrick et al. (17) 1987	M	24	ND[a]	ZZ	Prednisone + Dapsone
	M	7	0.55	ZZ	Nafcillin
	F	33	0.72	ZZ	Dapsone
Humbert et al. 1991	F	73	1.20	MS	Doxycycline[b]
	F	50	1.18	MS	Doxycycline[b]
	M	71	1.40	ND[a]	Doxycycline[b]

[a] ND: Not Determined. [b] 200 mg/day.

this condition. Clinical and histopathologic features may suggest the possibility of A1AT deficiency associated panniculitis, in particular, spontaneous ulceration and drainage, as well as necrotic areas with neutrophils and histiocytes adjacent to normal fat (23). The diagnosis of A1AT deficiency was historically made using serum protein electrophoresis. A marked reduction in the α_1-globulin band is observed. Today, diagnosis of the A1AT deficiency states is a simple matter of measuring serum A1AT levels using a commercially available radial immunodiffusion kit (24).

The patients we report had low levels of A1AT, corresponding to a heterozygous phenotype, severe deficiency occurring most commonly in PiZ homozygotes who can also suffer from early-onset emphysema and cirrhosis. A1AT deficiency has been reported to be associated with panniculitis in 23 other previous cases (Table II). Sixteen of the 23 patients had severe A1AT deficiency with phenotype Z, 4 had intermediate deficiency with phenotype MZ, 2 had A1AT deficiency with phenotype not stated, and one had phenotype S. null. The 13 men and 13 women were in the age range 7–73 years.

Up to now, therapies that appear to provide the greatest benefit for A1AT deficiency panniculitis are Dapsone and α_1-proteinase inhibitor replacement. Several mechanisms of action have been proposed for Dapsone. Dapsone probably acts by inhibiting myeloperoxidase in polymorphonuclear leukocytes. Dapsone alone was successful in 4 cases.

Since the etiology of panniculitis associated with A1AT deficiency has not been established, therapies which may re-establish protease–antiprotease homeostasis have to be considered. Tetracyclines can inhibit the breakdown of various connective tissues

mediated by excessive collagenolytic activity. Indeed, in recent investigations, tetracyclines were found to possess a new, potentially chemotherapeutically useful property: the ability to directly inhibit the activity of collagenolytic enzymes. Since collagenase activity depends on the presence of calcium and zinc, the mechanism of action of tetracyclines is thought to act by chelation. Beneficial effects of tetracycline therapy have been observed in patients suffering with conditions characterized by an increased collagenase production, such as non-infected corneal ulcers (25) and epidermolysis bullosa dystrophica (26, 27). Doxycycline and tetracyclines may also exert an inhibitory effect on lymphocyte function (28, 29) as well as on neutrophil chemotaxis (30). Thus they may act as anti-inflammatory agents in the treatment of various inflammatory diseases.

The successful treatment with doxycycline in our patients underlines for the first time the effects of this drug on a condition characterized by deficiency of the anti-protease system. A tetracycline-related response in a case of idiopathically circumscribed panniculitis of the legs (consistent with the Rothmann-Makaï syndrome) (31) suggests to us that anti-collagenase properties of the drug have been involved in this therapeutic effect. In this regard, the beneficial effects of tetracycline therapy can be expected in other, comparable conditions.

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