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PTU-associated cutaneous vasculitis with ANCA anti-MPO and anti-PR3 antibodies

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ABSTRACT

A 36-year-old woman presented at our clinic with symmetrical, tender, palpable purpuric lesions on her lower legs and buttocks after restarting PTU therapy for relapsing Graves' disease. PTU-induced vasculitis was diagnosed with remarkable ANCA anti-MPO and anti-PR3 antibody positivity. The purpuric skin lesions resolved immediately after discontinuation of the drug and the ANCA titres lowered. In the presence of activated neutrophils, PTU could induce a high cytotoxity and injure the vessel walls. Treatment of choice is discontinuation of the drug. Sometimes more aggressive therapy as cyclophosphamide or plasmapheresis is warranted.

INTRODUCTION

Propylthiouracil (PTU) is a frequently used drug to treat hyperthyroidism. It inhibits the synthesis of thyroid hormones by competitive inhibition of the enzyme peroxidase. One of the most serious complications of this drug is PTU-induced vasculitis.
Antineutrophil cytoplasmic antibodies (ANCA) are important diagnostic markers associated with the spectrum of vasculitides that includes Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, and primary pauci-immune necrotising and crescentic glomerulonephritis.[1] Two specific types of ANCA have been shown to be useful in the diagnosis of this disease spectrum: antiproteinase 3 (anti-PR3) antibodies, which produce a cytoplasmic pattern of staining (c-ANCA) by indirect immunofluorescence, and antimyeloperoxidase (anti-MPO) antibodies, which produce a perinuclear pattern of staining (p-ANCA).[2] PTU may induce ANCA-positive vasculitis. The majority of these PTU-induced vasculitis cases are associated with anti-MPO ANCA.[1,3]
We describe a patient who presented with anti-MPO and anti-PR3 associated vasculitis while treated with PTU for Graves' disease.

CASE REPORT

A 36-year-old woman with Graves' disease was treated with methimazole for several months. Methimazole was withdrawn because of development of urticaria, and propylthiouracil (PTU) was started. The treatment was discontinued after one year of euthyreoidism. Nine years later the hyperthyroidism relapsed [free thyroxin 31 pmol/l (normal 11-25); thyroid-stimulating hormone <0.02 µ/l (normal 0.30-4.00)] and PTU treatment was restarted while waiting for I^{131} therapy. Several weeks thereafter she visited her general practitioner with symptoms compatible with sinusitis. Treatment was started with clarithromycin and loratadine. She had been treated likewise in the past without complications. A few days later the patient developed an erythematous rash. After withdrawal of the antibiotic treatment, the rash worsened and was accompanied by symmetrical, tender, palpable purpuric lesions on her lower legs and buttocks (*figures 1* and *2*). The patient was referred to our hospital. Laboratory test on admission revealed: ESR 33 mm/h (1-20), Hb 8.1 mmol/l (7.4-9.9), Ht 0.38 l/l (0.36-0.46), platelets $209*10^9$/l (150-400), white blood cells $2.9*10^9$/l (3.5-11.0). Differentiation (%): segmented cells 1 (40-75), lymphocytes 73 (20-45), monocytes 26 (1-12), no eosinophils, atypical lymphocytes ++. ANA and anti-dsDNA antibodies were negative.

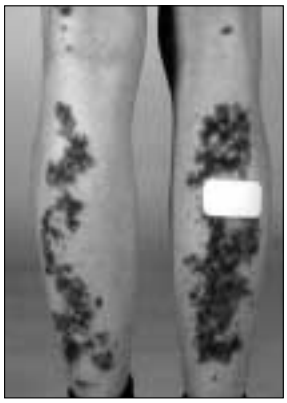

Figure 1
Cutaneous lesions of the lower legs of our patient (the plaster is there because of the biopsy taken from the lesion)

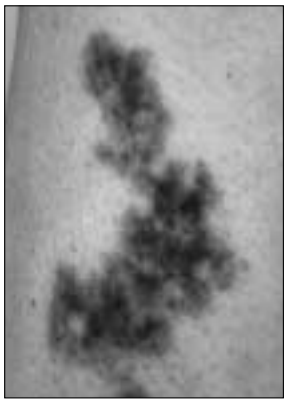

Figure 2
Detail of the cutaneous lesions

Immunofluorescence: p-ANCA positive; 1: >320. Specificity in Elisa: MPO and PR3 positive. Urine analysis showed no proteinuria, leucocyturia or erythrocyturia. Skin biopsy taken out of the rim of a palpable purpuric lesion was compatible with leucocytoclastic vasculitis (*figure 3*). Direct immunofluorescence studies were not performed. We diagnosed the patient as having PTU-induced vasculitis, and discontinued the drug. The skin lesions began to regress and resolved completely. The ESR returned to the normal range and the granulocytopenia resolved in five days. The ANCA (IFT) titre initially dropped to 1:160 after seven weeks of withdrawal although it rose again to 1:320 four months later, despite the good clinical condition of our patient.

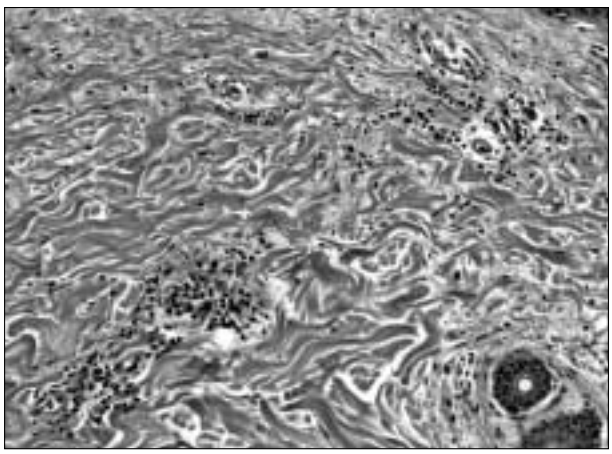

Figure 3
Detail of skin biopsy of leucocytoclastic vasculitis

DISCUSSION

Systemic complications of PTU treatment are mentioned in 1 to 5% of PTU users. The most common side effects are agranulocytosis, hepatotoxicity and drug-induced hypersensitivity.[4-7] Although PTU-induced vasculitis is well documented, it is a relatively rare side effect of PTU therapy. The association of positive ANCA with antithyroid drug therapy was first described by Dolman *et al.* in 1993.[8] In absolute amounts, more females than males are affected with PTU-induced ANCA positive vasculitis. Although in most cases the symptoms appear many months after starting the medication, some patients manifested symptoms within one month or even within two weeks after starting the drug.[4,5,8,9] Symptoms as fever, general fatigue, polyarthritis, myositis, scleritis, pleuritis, alveolar haemorrhage, pericarditis, nephritis, hepatitis and skin ulceration have been reported.[5,8,10-12] In some cases, the clinical features of PTU-induced vasculitis may be limited entirely to the skin, especially the breasts, the helices of the ears, the face and, as noted in our patient, the distal lower extremities.[5,9] After the medication is discontinued, the symptoms disappear in most cases.
Biopsy specimens of skin lesions generally show leucocytoclastic vasculitis. This is described as endothelial swelling, extravasation of erythrocytes and pronounced perivascular infiltration of neutrophils, with fragmented leucocytic nuclei in and around the vessels.[6,9] Some vessels are occluded by fibrin thrombi and some are even necrotic, as in our patient.[6,13] Most cases of PTU-induced vasculitis had negative direct immunofluorescence tests, but deposition of IgM, IgG, IgA, fibrinogen, and complement factor C3 in dermal blood vessel walls has been reported.[6,13]

In the literature only five patients, two with vasculitis of the skin, two with glomerulonephritis and one with arthritis, are described in whom both MPO-ANCA and PR3-ANCA were identified simultaneously.[8,11,12,14] More often the combination of MPO-ANCA and elastase-ANCA is found.[8,11] The mechanism of MPO-ANCA-associated vasculitis is still not clear. The altered state of self-tolerance present in these patients or an interaction between MPO and PTU resulting in an immunogenic compound may be responsible for development of the ANCA. Lam and co-workers found that PTU accumulation in the neutrophil seemed to be related to the oxidation of the medication, as there was an increased H_2O_2 accumulation in the cell during PTU uptake of these cells.[10] Others reported that the drug exhibited its high cytotoxicity in the presence of activated neutrophils, for instance neutrophils activated by an infection.[8,11,15] Following activation the neutrophils may release a large quantity of MPO and transform drugs to free radicals, resulting in vessel-wall injury.[15] Possibly a previous sensitisation to PTU could play a role in the

immunogenic spectrum as described by Wolf.[16] Indeed, our patient had no complications during previous use of this drug. The factors responsible for the production of anti-PR3 antibodies during PTU treatment are unclear. A puzzling fact in the case presented here is the combination of leucocytopenia and ANCA-induced vasculitis as described before by Dolman and Kitahara.[8,11] This seems to be in contradiction with the theories above describing the presence of activated neutrophils starting the vasculitis. Perhaps the neutrophilic activation is reflected in a shortage of circulating neutrophils as the neutrophils migrate to the vasculitis spots where the endothelial damage occurs. Furthermore, it has been reported that after activation the neutrophils may undergo an accelerated pattern of apoptosis, leading to cell death and further potential tissue damage secondary to necrosis.[17] But a bone marrow suppressive effect of PTU, as described by Balkin *et al.*,[18] could also be an explanation for the leucopenia, although to develop a vasculitis some neutrophilic activation, as described before, should accompany it. Caution in interpreting ANCA without knowing the medical history of a patient is mentioned by Cohen Tervaert, who described the presence of ANCA with specificity for MPO or PR3 in patients without vasculitis during treatment with antithyreoid drugs.[19] Gunton and Sera suggest alertness when using PTU in patients with ANCA as these ANCAs are usually not present at the start of the drug therapy.[20,21] Choi describes a patient who changed his ANCA pattern from c-ANCA to p-ANCA during treatment with PTU and back to a c-ANCA after the medication was discontinued.[22] Noh *et al.* investigated prospectively the development of MPO-ANCA in 73 patients treated with PTU for Graves' disease. They found development of MPO-ANCA in three of these patients. In two of them the increases were only temporary despite continuation of PTU therapy. The third patient developed oral ulcers, fever, diarrhoea and polyarthralgia after 17 months of PTU treatment. Her MPO-ANCA titre was highly increased. PTU treatment was discontinued after which the symptoms resolved and the MPO-ANCA titre decreased.[23] Whether the use of clarithromycin played a role in the development of vasculitis in our patient remains unclear. Clarithromycin itself may induce leucocytoclastic vasculitis, though very sporadically.[24-26] None of the clarithromycin-induced vasculitis cases mentioned leucocytopenia in the patients.

Although most patients (about 60% mentioned in case reports), like our patient, recover completely simply by withdrawal of PTU, some patients who have severe renal involvement or impairment of multiple organ systems may require high dosages of prednisone for several months.[4] Cyclophosphamide,[7,11,12] azathioprine,[7] naproxen,[4] or plasmapheresis[9,12,27] are other therapeutic treatments that have been used in isolated cases. Sequelae reported most often after resolving of vasculitis are scars resulting from necrosis of (sub)cutaneous tissue or arthralgia.[9] The ANCA usually returns to normal values, though sometimes ANCA titres persist for a longer time, as in this case.[7-9,12] Hyperthyroidism is treated either with radioactive iodine or with surgical treatment. Favouring the radioactive iodide treatment one should bear in mind that iodide may exaggerate symptoms of vasculitis even after withdrawal of PTU.[9] The increased movements of polymorphonuclear cells induced by the iodide into inflammatory sites are mentioned to be responsible for this reactivation of vasculitis.[28]

CONCLUSION

Propylthiouracil could be involved in inducing vasculitis. Recognition of the classic cutaneous features permits early diagnosis and may limit associated morbidity in these patients. The vasculitis is often prescribed as ANCA associated, though rarely both anti-MPO and anti-PR3 antibodies are involved. The exact mechanism by which PTU induces vasculitis remains to be resolved.

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