Turkish Journal of Endocrinology and Metabolism, (2006) 2 : 45-47 **CASE REPORT**

Propylthiouracil-Induced Thrombotic Leukocytoclastic Vasculitis

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Antithyroid drug therapy with Propylthiouracil (PTU) is commonly used in Graves' disease. One of the most serious complications of this drug is PTU-induced leukocytoclastic vasculitis. We report a 23 year-old woman who developed leukocytoclastic vasculitis which is a rare and serious side effect during PTU therapy for Graves' disease. The observation of cutaneous vasculitis in this patient during administration of PTU indicates that reguler follow-up of patients on antithyroid drug regimen is mandatory.

Keywords: Propylthiouracil, leukocytoclastic vasculitis, ANCA

Introduction

Propyltliouracil (PTU) is a commonly used antithyroid drug for Graves' disease. This drug is known to have several adverse effects such as granulocytopenia, pruritus, urticaria, fever, hepatotoxicity, myalgia and arthralgia. One of the most serious complications of this drug is leukocytoclastic vasculitis (1-3), which might be associated with antineutrophil cytoplasmic antibodies (ANCA). ANCAs are important diagnostic markers for systemic vasculitic disorders such as Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome, idiopathic crescentric glomerulonephritis and drug-induced vasculitis (4-8). We here in report a patient who developed ANCA positive thrombotic leukocytoclastic vasculitis during PTU therapy for Graves' disease.

Case report

A 23-year-old woman with Graves' disease had been receiving propylthiouracil for 25 months. She developed small cutaneous nodules on her legs and ecchymotic purpura on the ears. Her history was negative for thromboembolic diseases and coagulopathies. She was hospitalized upon her referral to our clinic. She was clinically euthyroid. Physical examination revealed a grade II diffuse goitre, and bilateral exophthalmus. The results of laboratory analyses were as follows: Erythrocyte sedimentation rate (ESR) 65 mm/h (1-20), hemoglobin 11.6 gr/dl (12-16), WBC $2.6x10^9$/L (4-$11x10^9$) with a neutrophil count of $1.5x10^9$/L (2-$7x10^9$), PLT $98x10^9$/L (150-$400x10^9$), T3 1.41 ng/ml (0.8-2.0), fT4 14.8 pmol/l (12-22), TSH 1.25 mIU/L (0.27-4.25), TSH-R antibodies 68.3 U/L (9-14), antithyroglobulin antibodies (TGAbs) 435 IU/ml (0-20), antithyroperoxidase antibodies (TPOAbs): 673 IU/ml (0-50), p-ANCA positive, anti-myeloperoxidase (anti-MPO) antibodies 37.8 RU/ml (0-20), anti-proteinase-3 antibodies (anti-PR3) negative, c-ANCA negative, C3 124 mg/dl (101-186), C4 29.9 mg/dl (16-47), anti-nuclear antibodies (ANA) negative, anti-dsDNA negative, rheumatoid factor negative, LE cell negative, anticardiolipin (aCL) antibody-IgM positive (>100 MPL U/ml, n:<10 MPL U/ml) and aCL antibody-IgG negative (<10.0 GPL U/ml) and also prothrombin time, activated partial thromboplastin time and urine analysis were within normal range.

PTU was stopped with a presumptive diagnosis of vasculitis. Skin biopsy from the nodular lesion in the lower extremity showed leukocytoclastic vasculitis and intravascular thrombosis (Figure 1). The patient was administered aspirine (300 mg/day) and methylprednisone 60 mg/day.

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Vasculitic skin lesions disappeared totally within 1 month and ESR, p-ANCA, aCL antibody levels and hemogram returned to normal. The progression of the skin lesions ceased and these lesions completely disappeared. Sedimentation rate, hemogram and anticardiolipin antibody returned to normal. P-ANCA was negative. Steroid dose was tapered slowly and stopped in 3 months. She later had total thyroidectomy for Graves' disease. After thyroidectomy, she became hypothyroid and L-thyroxine was started for replacement therapy.

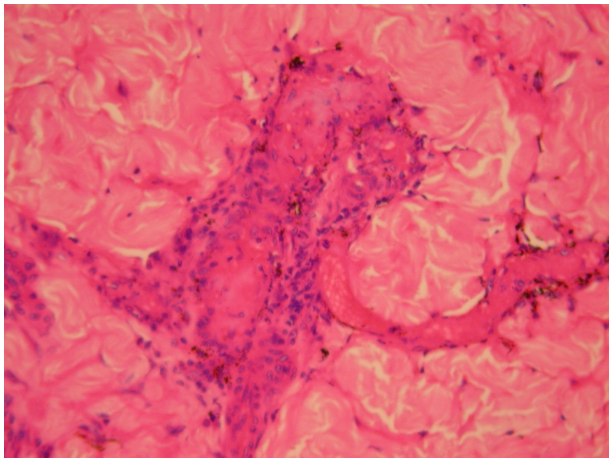

Figure 1. Skin biopsy showed leukocytoclastic vasculitis characteristic findings of heavy mononuclear cell infiltration in the dermis and intravascular

Discussion

Vasculitis is a considerably rare side effect of PTU therapy. In most cases, the symptoms appear many months after starting the medication (9-11). Sera et al. (12), reported that the proportion of patients positive for anti-MPO (p-ANCA) increased with prolongation of PTU therapy. Despite basic structural similarity, cross-sensitivity for antithyroid drugs is uncommon, however, the safety of substituting one thionamide derivate for another is unpredictable. However, anti-MPO (p-ANCA)-positive vasculitis have been reported more frequently in the patients treated with PTU compared to the patients treated with methimazol (2,9,13,14,15).

Clinical findings such as fever, fatigue, polyarthritis, myositis, scleritis, pleuritis, alveolar haemorrhage, pericarditis, nephritis, hepatitis and skin ulceration have been reported in patients with PTU induced vasculitis. In some cases, the clinical features of vasculitis may be limited entirely to the skin, especially the breasts, the helices of the ears and extremities (1,11,16). In most cases symptoms were improved by cessation of the drug or additional treatment with steroids (17).

In our patient, we observed small cutaneous nodules on both legs and ecchymotic purpura on the ears. After PTU was stopped and steroid therapy was started, the skin lesions completely disappeared. We decided that vasculitis was due to PTU because the lesions rapidly regressed when the drug was discontinued.

Two specific types of ANCA have been shown to be useful in the diagnosis of this disease spectrum: anti-PR3, which produce a cytoplasmic pattern of staining (c-ANCA) by indirect immunofluorescence, and anti-MPO antibodies, which produce a perinuclear pattern of staining (p-ANCA) (18). PTU-induced vasculitis has been associated with anti-MPO, and laboratory findings of our case was also compatible with this diagnosis.

The pathogenesis of PTU induced ANCA-associated vasculitis is not clearly understood. However, PTU has been shown to accumulate within neutrophils, binding to MPO to alter its configuration, which subsequently promotes antibody formation by polyclonal activation of B lymphocytes in susceptible individuals (19).

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 (20). The skin biopsy of our case showed leukocytoclastic vasculitis and as well as intravascular thrombosis. The pathologic findings of thrombotic vasculitis have not been documented previously. We thought that the transient positivity of aCL antibodies might be associated with these thrombotic findings, and this pathologic feature might be added to the spectrum of PTU-induced vasculitis.

Kitahara et al. described a case, which was presented with the combination of leucocytopenia and ANCA-induced vasculitis. Low neutrophil

counts might be associated with the migration of activated cells to the vasculitic lesions. However, PTU-induced bone marrow suppression has also been described in a number of reviews (21).

Our observation supports the need for regular follow-up of patients on PTU therapy, since vasculitic complications can be developed regardless of the duration of the therapy and dosage of the drug. Treatment should be stopped promptly whenever any lesion suggesting vasculitis has been observed.

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