Leukocytoclastic Vasculitis: A Rare Manifestation of Propylthiouracil Hypersensitivity

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Introduction

The thionamide group of drugs such as propylthiouracil (PTU) and methimazole (MMI) are generally first-line drugs in the therapy of hyperthyroidism. When used these drugs may cause mild and severe side effects. The most common mild side effects are transient granulocytopenia, pruritus, urticaria, generalized maculopapular and papular purpuric rashes, arthralgia, myalgia, and drug-induced fever. Skin eruptions occur in 3–5% of adults treated with PTU.

Rarely do these drugs cause agranulocytosis and even more rarely do they cause other severe adverse effects such as aplastic anemia, thrombocytopenia, hypoprothrombinemia, hepatitis, cholestatic jaundice, splenomegaly, lupus-like syndrome, polyarteritis nodosa, disseminated intravascular coagulation, vasculitis, and nephrotic syndrome [1–4]. We hereby report a rare case of leukocytoclastic vasculitis as a manifestation of PTU hypersensitivity.

Case Report

A 66-year-old woman with toxic adenoma treated with PTU 150 mg daily for 6 years presented with a 3-month history of purpuric rashes on her buttocks, legs and feet bilaterally (fig. 1). She was diagnosed to have thyrotoxicosis, grade 3 multinodular goiter,
red nonpalpable purpura in the lower extremities and proximal myopathy. Her endocrinological and other laboratory analyses were as follows: free triiodothyronine: 16.4 pmol/l (normal: 4.26–8.1); free thyroxine: 49.4 pmol/l (normal: 10–28.2); sensitive thyroid-stimulating hormone: 0.004 μU/ml; p-ANCA (–), c-ANCA (–), ANA (–), anti-ds DNA (–), LE cell (–), C3, C4, and RF (–). Immunoglobulins were polyclonally increased: IgG 1,760 mg/dl (normal: 800–1,700), IgA 514 mg/dl (normal: 100–490) and IgM 288 mg/dl (normal: 50–360). WBC 4,090 mm$^3$ (55.1% neutrophils), ESR 40 mm/h, anti-TPO (–), anti-Tg (–). Urine analysis was normal. Thyroid scintigraphy showed a hot nodule, with central necrosis, in the left thyroid lobe (fig. 2). Cervical MR scan revealed a hyperintense nodule, 6.5 × 5 cm in the left thyroid lobe which was pressing on the trachea, and extending to upper mediastinum, as well as an isointense nodule, 2.5 × 1.2 cm in the right thyroid lobe (fig. 3). Skin biopsy from lower extremity showed leukocytoclastic vasculitis with characteristic findings of a mononuclear cell infiltration. There was leukocytoclasis in the dermis and around damaged capillary vessel with abundant nuclear dust and endothelial swelling (fig. 4). Propylthiouracil therapy was discontinued but β-blocker (propranolol 40 mg/day) and MMI (20 mg/day) were started due to her hyperthyroidism. Approximately 15 days later, the purpuric rash had resolved and subtotal thyroidectomy was performed to restore euthyroidism. At 6-month follow-up, the patient was asymptomatic and the skin was normal.

Discussion

The most frequently encountered skin findings during the administration of antithyroid drugs are generalized maculopapular and papular purpuric rashes, with an incidence of 3–5% [5]. However, vasculitis is an uncommon side effect, reported to occur more frequently in patients treated with PTU than with MMI. It appears to occur not only during the first few weeks of treatment but also after months or even years (13 years) of treatment [6].

In our case, vasculitis appeared during the 6th year of treatment. We assumed that the vasculitis was due to PTU because the lesions rapidly regressed when the drug was discontinued and equally important the patient was not taking any other drug.

Propylthiouracil vasculitis has no apparent association with patient age. Its possible predilection for women and girls [7] may merely be a reflection of the greater prevalence of thyroid disease in female patients [4]. Although the skin may be the organ system most commonly affected [6] there are few reports describing this condition in the endocrinological and dermatological literature. In some cases, the clinical features of PTU hypersensitivity vasculitis may be limited almost entirely to the skin [8], as observed in our patient. Conversely, there are many reports of PTU hypersensitivity vasculitis with multisystem involvement. This form usually pre-
presents as a Wegener’s granulomatosis-like or polyarteritis nodosa-like [9] process affecting the skin, joints, kidneys, lungs, and other organ systems. Previously reported cases have been characterized on presentation by the classic tetrad of fever, sore throat, arthralgias, and skin rash. Many patients have also presented with myalgias, fatigue and weight loss [10]. Our patient had none of these signs and symptoms.

Drug-induced hypersensitivity may be an immune-mediated reaction with multiorgan involvement in which a combination of polyarteritis, cutaneous vasculitis, and fever is common [8], but the cause of PTU-induced vas-
Propylthiouracil-induced cutaneous vasculitis is unknown [1, 5]. Although immune complex deposition is widely considered to be the pathogenetic mechanism of hypersensitive vasculitis such as in systemic lupus erythematosus or rheumatoid arthritis, not all cases have had immune complexes demonstrated [11].

We treated our patient with MMI for the persistent hyperthyroidism. Several adult patients have also been treated with MMI as a substitution for PTU with no untoward effects [6]. However, because vasculitis has also been reported with the use of MMI [12], careful attention should be paid to the possibility of a recurrence of vasculitis.

The histological hallmark of the hypersensitivity vasculitis is a leukocytoclastic venulitis involving the superficial and deep dermal vessels, endothelial swelling, red blood cell extravasation, and nuclear dust are common findings [11]. The vessels are often occluded by fibrin thrombi [5] and are frankly necrotic [10]. When biopsies are obtained in the acute phase of active disease, the typical pattern of neutrophil infiltration is readily observed. In the subacute or chronic stages, biopsies often reveal mononuclear cell or eosinophilic infiltration [11]. In our patient, skin biopsy showed leukocytoclastic vasculitis with the histological hallmark of a chronic stage.

**Conclusion**

This report indicates that leukocytoclastic vasculitis should be considered in the differential diagnosis of patients with a vasculitic rash. The discontinuation of PTU was associated with disappearance of the lesions. Treatment with MMI as a substitute for PTU may be useful in reaching euthyroidism.