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CASE REPORT

Propylthiouracil-induced ANCA-negative cutaneous small vessel vasculitis

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ABSTRACT

Propylthiouracil (PTU) is a commonly used medication for the treatment of hyperthyroidism. PTU is known to cause different adverse reactions including autoimmune syndromes. PTU-induced autoimmune syndromes can be classified into drug-induced lupus or drug-induced vasculitis. Differential diagnoses could be very challenging. PTU-induced vasculitis is more common than PTU-induced lupus, and has a higher risk of morbidity and mortality. Usually it is limited to the skin in a form of cutaneous leukocytoclastic vasculitis, but may also affect organs including kidneys and lungs. Discontinuation of PTU should be a first step in the treatment and could lead to complete resolution of symptoms. Typically, lesions resolve spontaneously within 2–4 weeks, but chronic or recurrent disease may occur in up to 10% of patients. In cases without improvement after drug discontinuation, cases refractory to glucocorticosteroids, with necrotizing skin lesions or extracutaneous organ involvement referral to rheumatologist for more aggressive immunosuppressive treatment is indicated. Optimal duration of immunosuppressive therapy is unknown, but it is reasonable to gradually taper mediations and monitor clinical response. Frequent monitoring for side effects is mandatory for patients on PTU therapy. Treatment should be stopped immediately, if patient develops any of autoimmune syndromes. An accurate and prompt diagnosis is essential, because it determines further management. We report a rare case of antineutrophil cytoplasm antibody-negative cutaneous small vessel vasculitis as a result of longstanding exposure to PTU.

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1. Introduction

Propylthiouracil (PTU) is a commonly used medication for the treatment of hyperthyroidism. PTU is known to cause different adverse reactions including fever, skin lesions, arthralgia, myalgia, blood dyscrasia, hepatotoxicity, and autoimmune syndromes [1,2]. Patients with thyroid disease may be prone to develop drug-induced autoimmune diseases [3]. PTU-induced autoimmune syndromes can be classified into drug-induced lupus (DIL) or drug-induced vasculitis (DIV) based on definitions, clinical features, and serological features [4]. Many of autoimmune diseases including systemic lupus erythematosus (SLE), DIL, DIV, and idiopathic antineutrophil cytoplasm antibody (ANCA) vasculitis share similar clinical features and laboratory markers [5]. An accurate diagnosis is essential, because it determines further management. We report a rare case of ANCA-negative cutaneous small vessel vasculitis (CSVV) as a result of longstanding exposure to PTU.

2. Case report

A 66-year-old Caucasian female with past medical history of Graves' disease had been receiving PTU for 4 years. She presented with 6 months of multiple painless non-blanching purple patches with surrounding erythema involving her arms, legs, and anterior trunk (Figure 1). Her rash was persistent, progressive, and occupied up to 15% of her body surface area at the time of our evaluation. In the preceding time, patient was treated with topical and oral glucocorticosteroids without improvement in her lesions by different providers. Eventually, she had a skin biopsy performed by dermatologist which revealed superficial, deep perivascular and interstitial dermatitis associated with small vessel vasculitis and thrombi with extensive degeneration of collagen. Direct immunofluorescence was negative for deposition of immune reactants and complement. During our evaluation, the patient also complained of fatigue, anorexia, xerostomia, and joint stiffness. The patient denied pruritus, arthralgia, and mucosal ulcers. There was no family history of autoimmune disease. She denied alcohol, tobacco, and illicit drug abuse. She denied a history of arterial or venous thrombosis, miscarriages, or estrogen use. Review of system was negative for fever, chills, dyspnea, lymphadenopathy, dysuria or hematuria, weight loss, diarrhea. Physical examination and vital signs were unremarkable besides described cutaneous lesions. Laboratory

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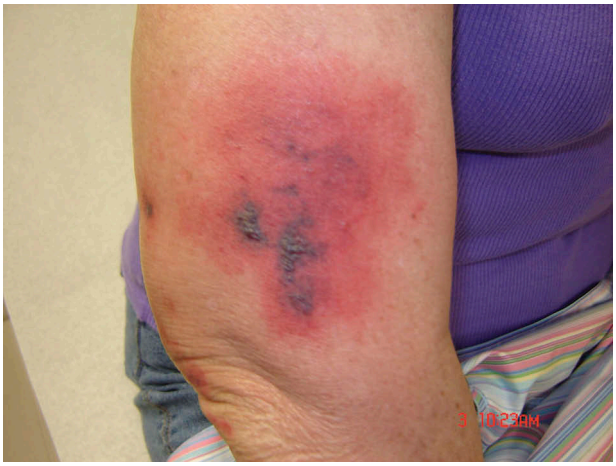

Figure 1. Image showing painless non-blanching purple patches with surrounding erythema on the arm in our patient. It was later confirmed to be propylthiouracil-induced ANCA-negative cutaneous small vessel vasculitis.

studies revealed elevated inflammatory markers – ESR of 33 mm/h, CRP of 4.79 mg/dL, positive ANA with antichromatin antibodies of 1.2 AI, elevated proteinase-3 of 11.9 U/ml with normal c-ANCA and p-ANCA, and elevated IgG and IgM anticardiolipin antibody levels – 20 and 25 units, respectively. Urinalysis showed trace protein and no blood or casts. Hepatitis B and C tests were negative. We suspected ANCA-negative CSVV as a result of long-standing exposure to PTU. PTU was discontinued. Due to extent and chronicity of her disease, as well as failure of glucocorticosteroids, she was treated with oral cyclophosphamide for a short period of time. Her skin lesions totally disappeared within the following 3 months without scarring. Her inflammatory markers and anticardiolipin antibodies returned to normal. We have been following the patient for 6 years and she remains asymptomatic.

3. Discussion

It could be challenging to differentiate between idiopathic autoimmune diseases like SLE and ANCA vasculitis with drug-induced autoimmune syndromes. Thorough history, physical examination, tissue pathology, and knowledge of serologic markers may help. SLE rarely has an antihistone and ANCA antibodies. ANCA vasculitis is usually negative for circulating immune complexes, anti-DNA, antihistone, and antiphospholipid antibodies. Drug-induced conditions are more likely to demonstrate substantial serological overlap. Antiphospholipid and ANCA antibodies are commonly seen in DIL and DIV. Antihistone and anti-DNA antibodies are predominantly seen in DIL [5].

DIL and DIV are rare side effects of PTU therapy [6,7]. The development of PTU-induced syndromes likely depends on genetic predisposition which was shown in a study of monozygotic triplets with hyperthyroidism [8]. The proposed mechanism suggests that PTU and its metabolites create a complex with myeloperoxidase (MPO) leading to formation of cytotoxic products turning immunogenic response. The generated autoantibodies may activate neutrophils and ultimately cause vascular damage [9]. Type of autoimmune reaction (lupus or vasculitis) is likely related to spectrum of autoantibodies (anti-MPO versus ANA antigen) [10].

PTU-induced vasculitis happens more common than PTU-induced lupus. Patients with PTU-induced vasculitis tend to be older and have longer duration of treatment with PTU. Clinical and laboratory distinction between these two autoimmune conditions has been described in literature (summarized in Tables 1and 2). Patients with PTU-induced lupus have more serositis, musculoskeletal involvement, and gastrointestinal involvement. Upper airways, pulmonary, and renal involvement is prominent in PTU-induced systemic vasculitis. ANA, anti-DNA, and anti-histone antibodies are predominantly found in DIL, p-ANCA, and antiphospholipid antibodies are found in both groups; c-ANCA is detected only in patients with vasculitis [4].

PTU-induced lupus is usually self-limiting disease after discontinuation of an offending agent and rarely requires short course of steroids. PTU-induced vasculitis is often more severe disease and has a higher risk of morbidity and mortality. Usually it is limited to the skin in a form of cutaneous leukocytoclastic vasculitis, but may also affect organs including kidneys and lungs. Some fatal cases have been reported

Table 1. Clinical difference between PTU-induced lupus and PTU-induced vasculitis.

	PTU-induced lupus	PTU-induced vasculitis
Musculoskeletal symptoms	Common	Rare
Gastrointestinal involvement	Common	Rare
Serositis	Common	Rare
Mucocutaneous lesions	Common	Common
Renal involvement	Rare	Common
Pulmonary involvement	Very rare	Can be seen
Upper airway involvement	Very rare	Can be seen

Table 2. Laboratory marker differences between PTU-induced lupus and PTU-induced vasculitis.

	PTU-induced lupus	PTU-induced vasculitis
ANA	Almost universal	Common
Anti-dsDNA	Rare	Absent
Antihistone antibodies	Common	Can be seen
Antiphospholipid antibodies	Common	Common
Circulating immune complexes	Can be seen	Rare
c-ANCA	Common	Common
p-ANCA	Common	Common
Myeloperoxidase	Common	Common
Proteinase 3	Can be seen	Common

even with limited cutaneous disease [11]. Discontinuation of PTU should be a first step in the treatment and could lead to complete resolution of symptoms. Typically lesions resolve spontaneously within 2–4 weeks, but chronic or recurrent disease may occur in up to 10% of patients [12]. In cases without improvement after drug discontinuation, cases refractory to glucocorticosteroids, with necrotizing skin lesions or extracutaneous organ involvement, referral to rheumatologist for more aggressive immunosuppressive treatment is indicated. Optimal duration of immunosuppressive therapy is unknown, but it is reasonable to gradually taper mediations and monitor clinical response.

PTU should not be prescribed as a first-line drug according to the US Food and Drug Administration and American Thyroid Association. When PTU is chosen as a primary therapy for Graves' disease, the duration should be limited to 12–18 months and then discontinued if the thyroid-stimulating hormone and thyroid-stimulating antibodies are normalized [13]. In other instances, PTU could only be used temporarily to control overt hyperthyroidism prior definitive surgical or radioactive iodine ablation treatment. Frequent monitoring for side effects is mandatory for patients on PTU therapy. Treatment should be stopped immediately if patient develops any of autoimmune syndromes. PTU-induced vasculitis is a rare but potentially life-threatening disease requiring prompt diagnoses and treatment.

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Patient consent for medical photograph

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