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Case Report

Propylthiouracil induced ANCA-positive vasculitis in a patient with Graves' disease; a case report

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Abstract

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is rare, but it can be triggered by chemicals, infections, and drugs. Patients who use anti-thyroid drugs are prone to involve with ANCA-associated vasculitis. Perinuclear ANCA (p-ANCA) is almost always positive in these patients. Patients have various presentations and symptoms such as (arthritis, edema) and this disorder usually resolves with discontinuation of the drug, however, some patients require high-dose steroids, immunosuppressive or plasmapheresis. A 38-year-old woman with a history of Graves' disease was on long-term treatment with propylthiouracil (PTU), presented with severe bone pain, arthritis and edema in both feet. The patient's manifestations were resolved with discontinuation of PTU, iodine therapy, and corticosteroid administration.

Keywords: Antineutrophil cytoplasmic antibodies, Livedo reticularis, Propylthiouracil, Vasculitis

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Introduction

Graves' disease is an autoimmune disorder and the underlying cause of hyperthyroidism (1). Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is a rare autoimmune disease with an unknown cause; however, some triggers, such as infections and drugs, are recommended for the presence of this disorder (2). ANCA-associated vasculitis involves small vessels. The presentations of this type of small vessel vasculitis differ based on the organ involved (3).

Propylthiouracil (PTU) is a medication commonly used to treat hyperthyroidism over the past two decades, especially in patients with thyrotoxicosis and Graves' disease (4). The side effects of PTU are pancytopenia, cutaneous rashes, lupus-like syndrome, hepatic involvement, and vasculitis (5,6). Involvement of skin, musculoskeletal system, lungs, hematological systems, gastrointestinal systems, kidneys, and neurological systems are seen in PTU-induced vasculitis (5-7). PTU-induced ANCA-positive vasculitis is an infrequent side effect of PTU (8). In this report, we presented a woman on PTU to treat Graves' disease and referred us to severe bone and abdominal pain, arthritis, diarrhea, and livedo reticularis. After the discontinuation of PTU, the patient's complaints were resolved.

Case Presentation

A 38-year-old Iranian woman with a history of Graves' disease was treated with PTU. She was referred to an endocrinology clinic for the first time with complaints of tremors, palpitation, excessive sweating, stress, weight loss, hair loss, and heat intolerance. She mentioned that she had excessive sweating and weight-loss about 20 kg in 4 months. Physical examination revealed edema in both feet, hand tremors, hair loss, and an enlarged thyroid without lymphadenopathy. Laboratory tests were requested for her, and the tests showed TSH<0.001 with T3:7.31 microgram per deciliter with a standard range of 0.8-2.1 microgram per deciliter and T4: 27 micrograms per deciliter with a standard range of 4-12 µg/dL.

PTU 50 mg three times a day (150 mg/d) was prescribed for the patient because she was an impending thyroid storm. After three months, the patient was referred to us for follow-up since the laboratory tests revealed an increased TSH while free T4 was 1.7 µg/dL. Anti-thyroid peroxidase (anti-TPO) antibody was checked for her, and it was 237

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Implication for health policy/practice/research/medical education

Propylthiouracil is an anti-thyroid drug that is widely used for the treatment of Graves' disease. Propylthiouracil can induce ANCA-associated vasculitis. With discontinuing this drug, ANCA-associated vasculitis is resolved.

international units per millimeter with a standard range of less than 34 international units per millimeter. The dose of PTU was reduced with the following protocol; one and a half tablets of PTU 50 mg (75 mg/d) for one month and then one tablet (50 mg/d) for one next month.

In the second follow-up, after two months of PTU used with the mentioned protocol, lab tests were TSH: 0.004 mIU/L, T4: 2.32 µg/dL, T3: 7.8 µg/dL, anti-TPO antibody: 808 IU/mL, with normal CBC. In this period, the signs and symptoms of hyperthyroidism relapsed. The PTU dosage changed from one tablet to three a day (150 mg/d) again.

After four months, she was referred for flushing and vertigo. Laboratory tests were TSH: 0.03 mIU/L, T4:36 µg/dL, liver function test: normal, and FBS: 100 mg/dL. The PTU dosage was changed to three a day (150 mg) for four days and two a day (100 mg) for three days a week.

After six months, the patient was referred for severe bone pain, abdominal pain, diarrhea, arthritis, and edema in both feet. She was referred to rheumatologists, and they checked for rheumatoid arthritis factors, and all were negative. Her laboratory tests showed TSH: 0.01 mIU/L, T4: 192 µg/dL, T3: 382 µg/dL, anti-TPO antibody: 340 IU/mL, ESR: 40 mm/h (up to 20). She received iodine therapy with 6 millicuries of iodine 131 and PTU 50 mg, two tablets per day. Three months later, the laboratory tests were TSH<0.01 mIU/L, free T3: 58 µg/dL, and free T4: 14.4 µg/dL. After one month of the last follow-up, PTU was discontinued, and methimazole was started for her.

One month later, after starting methimazole, the patient did not respond to methimazole due to an abnormal thyroid function test that was compatible with hyperthyroidism was found (TSH: 0.006 mIU/L, T3: 19 µg/dL, T4: 163 µg/dL) and PTU was started with two 50 mg tablets per day. With the use of PTU, alopecia areata and livedo reticularis in the lower extremities were presented in the patient, and bone pain, generalized arthritis, and morning stiffness were presented. The laboratory tests showed ESR: 39 mm/h (normal up to 20), TSH: 0.004 mIU/L, Ffree T4: 28 µg/dL, anti-TPO antibody: 297 IU/mL, and perinuclear ANCA (p-ANCA): 69 units/mL (normal up to 1.4).

Another time, the patient received iodine therapy, 10 millicuries, and prednisolone. After five months, laboratory tests showed p-ANCA: 0.02 U/ml, ESR: 11 mm/h, TSH: 31.7 mIU/L, free T4: 0.1 µg/dL, and free T3: 0.8 µg/dL. All complaints of the patient were cured, but these tests demonstrated the occurrence of post-tablet hypothyroidism. So, levothyroxine was started for her.

Discussion

One of the most common drugs for treating hyperthyroidism is PTU (9). PTU's most common adverse effects are hepatic toxicity, agranulocytosis, and vasculitis. PTU-induced vasculitis is manifested with arthritis, skin rashes, acute renal failure, and respiratory symptoms (10). Our case did not have changes in the liver function test, complete blood cell count, and renal function test. She also did not have any complaints of respiratory symptoms. Her manifestations were generalized arthritis and bone pain, abdominal pain, diarrhea, edema in both feet, alopecia areata, and livedo reticularis. Bensiradj et al assessed 18 case reports about benzylthiouracil (BTU)-induced ANCA-associated vasculitis. They found that about 90% of patients were female, probably due to a higher prevalence of thyrotoxicosis in the females. The mean age of involvement of BTU-induced ANCA-associated vasculitis was 38.8 years. All patients received BTU due to Graves' disease (11). Our patient had similar age and gender to Bensiradj et al'sand colleagues' report. In Bensiradj et al, the vasculitis due to use of BTU was evaluated. BTU is a type of thiouracil such as PTU, and the difference between these two drugs is in the component of benzyl or propyl attached to thiouracil (12).

Common manifestations of BTU-induced ANCA-associated vasculitis were renal involvement (83%), general symptoms including fever, anorexia, weight loss, asthenia (56%), skin involvement (39%), and arthritis or arthralgia (33%) (11). Our case had skin involvement as livedo reticularis and musculoskeletal pain. Additionally, she had abdominal pain. In the case report of Bensiradj et al (11), the case had abdominal pain; however, this presentation is not joint in patients with BTU or PTU-induced ANCA-positive vasculitis based on our knowledge.

The skin involvement of PTU-induced vasculitides, like another drug-induced vasculitis, is palpable purpura and papules on gravity-dependent areas like the buttocks and lower extremities. PTU vasculitis is presented after many months of treatment, like its presentation in our patient (13).

Livedo reticularis is a physical manifestation characterized as reddish to blue with a network-like cyanotic pattern (14). Several conditions develop livedo reticularis, and autoimmune disorders like small vessel vasculitis is one of them (15). Livedo reticularis is not mentioned as a manifestation of PTU-induced ANCA-associated vasculitis in reports based on our knowledge, and this presentation in PTU-induced ANCA-associated vasculitis is infrequent. Physicians should be aware of this presentation in patients with other presentations of PTU-induced ANCA-associated vasculitis.

Our patient did not respond to the treatment with methimazole, and this drug did not decrease thyroid

function tests. Therefore, we had to change this drug again to PTU. Although our patient did not respond to methimazole, this drug can induce ANCA-associated vasculitis, such as PTU (16).

Clinical and laboratory recovery of PTU-induced ANCA-associated vasculitis occurs after the discontinuation of PTU and corticosteroid administration (17). Our patient was treated with such treatment. We had to perform iodine therapy for the patient to treat Graves' disease.

Conclusion

Physicians should be aware of PTU-induced ANCA-associated vasculitis in patients on PTU treatment. This disorder is rare but abdominal pain, musculoskeletal pain, and skin rash, especially livedo reticularis, are uncommon in PTU-induced ANCA-associated vasculitis. If a physician doubts PTU-induced ANCA-associated vasculitis, he/she should discontinue PTU and check p-ANCA. If p-ANCA is positive and the patient has manifestation of PTU-induced ANCA-associated vasculitis, PTU should be discontinued, and the patient is treated with iodine.

Authors' contribution

Conceptualization: SK and AT.
Methodology: AT.
Validation: AT.
Formal analysis: SK and AT.
Investigation: SK and AT.
Resources: SK and AT.
Data curation: AT.
Visualization: SK and AT.
Supervision: SK and AT.
Project administration: All authors.
Funding acquisition: AT.
Writing-original draft: All authors
Writing-review and editing: All authors.

Ethical issues

This case report was conducted in accordance with the World Medical Association Declaration of Helsinki. The patient has given us written informed consent for publication as a case report. Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no competing interests.

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