CASE REPORT

Antithyroid arthritis syndrome

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Accepted 14 February 2017

SUMMARY

Antithyroid arthritis syndrome is a constellation of symptoms of myalgia, arthralgia, arthritis, fever and rash associated with the use of antithyroid medications. We report a case of a patient with severe hyperthyroidism likely secondary to Graves' disease who presented with the abovementioned symptoms after being treated with methimazole (antithyroid medication). Our aim is to increase awareness regarding this uncommon but disabling and life-threatening adverse effect of antithyroid medications among clinicians. We also discuss the proposed pathophysiology for this immunological reaction as well as management options in these patients.

BACKGROUND

Antithyroid medications like methimazole and propylthiouracil are commonly used in the treatment of hyperthyroidism. Most common adverse effects noted with these agents are skin eruptions and the most serious but well-known adverse effects are agranulocytosis and acute liver toxicity. One of the rare side effects of this class of medications is antithyroid arthritis syndrome which has been reported in the case described below.

CASE PRESENTATION

A Caucasian woman aged 50 years presented with fever, palpitations, anxiety and severe arthralgia of 5-day duration. One month prior, she was diagnosed with hyperthyroidism and was started on methimazole 20 mg three times a day along with metoprolol 25 mg two times per day. This treatment partially alleviated her symptoms until 5 days prior to the aforementioned presentation.

On arriving at the emergency room, she reported fever of 103°F, palpitations and anxiety along with severe joint pain and rash over her joints. She described sharp, constant pain in her hands, wrists, shoulders, knees and ankles that worsened with movement and touch. She had no pain relief with ibuprofen. The patient denied any personal or family history of autoimmune or thyroid disease and also denied any tobacco, alcohol or drug use. Family history was only significant for breast cancer and hypertension in her mother. Vitals signs revealed blood pressure of 163/79 mm/Hg, pulse of 120 bpm, temperature of 101.3°F and oxygen saturation of 92% on room air. She was thin, anxious appearing, diaphoretic and appeared to be in moderate distress. Extraocular movements were intact. She had mild proptosis and chemosis. Thyroid examination revealed a bilaterally enlarged firm and non-tender thyroid gland without nodules or bruit. She had a fine tremor to outstretched hands.

Cardiopulmonary examination was significant only for sinus tachycardia. Musculoskeletal examination demonstrated decreased range of motion in the bilateral upper and lower extremities with swelling, warmth, erythema and tenderness in multiple joints, including the knee, ankle, hand and wrist.

INVESTIGATIONS

Her initial labs showed thyroid-stimulating hormone <0.01 IU/mL (0.27–4.20), free T4 3.7 ng/dL (0.8–1.8) and free T3 6.4 pg/mL (2.0–4.4). Blood cultures, urinalysis and urine culture, which were ordered in the setting of mild leucocytosis and fever, were negative for infection. The patient's biochemical profile showed a normal renal function and liver function. Erythrocyte sedimentation rate was 67 mm/hour (0–20) and C reactive protein 20.16 mg/dL (<0.50). Autoimmune workup was pursued which revealed negative antinuclear antibody (ANA) screen, myeloperoxidase antibody was <1.0 (<1.0), proteinase 3 antibody <1.0 (<1.0), anticyclic citrullinated peptide (anti-CCP AB IGG) <16 arb°U (<20), antidouble-stranded DNA antibody (anti-ds DNA) 14 IU/mL (<100), antihistone antibody <1.0 U (<1.0), HLA B27 negative, rheumatoid factor (RF) negative, anti-RO antibody (SSA) <1.0 (<1.0) and anti-LA antibody (SSB) <1.0 (<1.0). Only C-ANCA (anti-neutrophil cytoplasmic antibody) was positive with a titre of 1:20 (<1:20).

Ultrasound of thyroid showed a bilaterally enlarged thyroid gland with increased blood flow throughout the gland and no discrete nodules.

TREATMENT

Owing to concern for thyroid storm on admission, she was started on dexamethasone 2 mg every 6 hours intravenously, propylthiouracil (PTU) 250 mg every 6 hours orally (methimazole was discontinued) and propranolol 60 mg every 6 hours. The following day her steroids were switched to prednisone 60 mg daily. During her hospital stay, she was noted to have migratory polyarthritis and hence steroids were continued. Over the next couple of weeks, she showed clinical as well as biochemical improvement and was discharged on prednisone 30 mg oral tablets, two times a day to be tapered over the next 10 weeks, PTU 150 mg oral tablets three times a day and propranolol 60 mg three times a day.

OUTCOME AND FOLLOW-UP

One month after hospitalisation, the patient was seen in outpatient endocrine clinic. She was symptom-free while on PTU and tapering doses of prednisone. Definitive treatment options of

To cite: Modi A, Amin H, Morgan F. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-218459

radioactive iodine ablation versus total thyroidectomy were discussed with the patient for a presumptive diagnosis of Graves' disease. Total thyroidectomy is being considered due to concern of worsening Graves' eye disease.

DISCUSSION

Transient migratory polyarthritis secondary to the use of antithyroid medications has been reported in the literature as an uncommon side effect of this therapy. The constellation of symptoms of myalgias, arthralgias and arthritis along with fever and rash is known as antithyroid arthritis syndrome.^{1,2} PTU and methimazole are thioureylenes commonly used in the management of hyperthyroidism. In a review of 500 patients managed with antithyroid drugs, rheumatic symptoms were noted in 1.6% of cases which was only second to skin eruptions.² Another review of the literature noted 53 cases of immunological side effects with the use of antithyroid drugs over a 35-year period.³ It was also noted that the reactions occurred at any age, were predominant in females, noted at any dosage and at any time during therapy.^{4–6} As per Cooper,⁷ side effects of methimazole are dose-dependent, but there is no dose relationship for PTU.

In most cases of antithyroid arthritis syndrome, the first symptom is arthralgia.^{8,9} It often develops within 2 months after initiation of antithyroid treatment but can occur at any time. It may quickly progress to a full-blown polyarthritis involving large, medium and small joints.¹⁰ The other rheumatic symptoms noted in the literature in association with antithyroid drugs include lupus-like syndrome, polymyositis, polyarteritis nodosum and life-threatening ANCA-positive vasculitis.^{11–13}

The proposed theories by which the thionamides cause immunological reactions are:

1. Thionamides and its metabolites are taken up by neutrophils where they bind to myeloperoxidase and turn it and other proteins like lactoferrin, elastase, etc, immunogenic.^{14,15}
2. Individuals with a deficit in cellular copper-binding capacity have excess free copper, which then binds to antithyroid drugs. This complex affects glutathione metabolism with resultant release of interleukins and synovial inflammation.¹⁶
3. Thiol group in antithyroid drugs binds to macromolecules and serves as haptan and induces antibody production.³
4. Metabolites of PTU may compete with thymidine triphosphatase and inhibit the DNA synthesis or be incorporated in DNA, triggering an abnormal immune function.³

It has also been suggested that patients with antithyroid arthritis may be predisposed to developing rheumatoid arthritis.¹⁷

Awareness of this syndrome is necessary for prompt diagnosis. Routine monitoring of laboratory values is not helpful. Low complement levels and elevated γ globulin suggest an immune complex mechanism. Positive ANA has been reported, but its prevalence in antithyroid medication-treated population was no greater than in the control population.¹⁸ Gao *et al*¹⁹ studied the presence of ANCA and noted that 2.9% of untreated patients with Graves' disease were ANCA-positive and 22% of patients treated with PTU were ANCA-positive. Antihistone antibody, anti-ds-DNA, anti-SSA/SSB antibodies, RF, anti-CCP AB, anti-myeloperoxidase antibody, antiproteinase 3 antibodies, anti-elastase, antilactoferrin and antikathepsin are among other antibodies shown to be associated with antithyroid therapy-induced immunological adverse effects.¹³ Creatinine phosphokinase elevation has been reported in the literature with PTU-induced polymyositis.¹² In our patient, all immunological workup was negative except C-ANCA which was only mildly elevated. It is uncertain if this is related to her underlying

Graves' disease or secondary to methimazole treatment. In the series of 500 patients studied by Shabtai *et al*,² the majority of patients who developed rheumatological symptoms had no immunological evidence on laboratory which could explain the negative immunological workup in our patient.

The first step in treatment of this syndrome is discontinuation of the antithyroid medication. For mild to moderate symptoms, non-steroidal anti-inflammatory drug can be used. The benefit of corticosteroid therapy is uncertain, but it is recommended for life-threatening or unresolving adverse effects. The suggested dose of prednisone is 0.5–1 mg/kg of prednisone.³ Our patient was started on high-dose dexamethasone due to concern for thyroid storm. This was later switched to prednisone as migratory polyarthritis was noted. Methimazole was discontinued and switched to PTU. Though, due to cross-reactivity between different thionamides in vitro,²⁰ it is advisable to consider alternative treatment if possible when side effects of thionamides occur. Our patient fortunately tolerated PTU and had no further adverse effects. In this case, thyroidectomy is being considered as a definitive treatment due to concern of worsening Graves' ophthalmopathy with radioactive iodine ablation treatment.

In conclusion, the antithyroid arthritis syndrome is a rare complication of antithyroid medications. Variability in its severity, and non-specific laboratory findings, make its diagnosis challenging. Once the diagnosis is made, it requires immediate discontinuation of the offending drug as it can rapidly progress to a life-threatening condition. Optimal management of this condition requires better understanding of the immunological process leading to antithyroid arthritis syndrome.

Learning points

- High index of suspicion for signs and symptoms of antithyroid arthritis syndrome in patients on antithyroid medications is needed for early recognition and treatment of the disease as delay in the management can lead to life-threatening complications.
- Discontinuation of the offending drug results in resolution of the symptoms.
- Cross-reactivity is noted among different antithyroid medications and hence caution is warranted in the use of alternative medications from the same thioureylenes group.

Contributors AM is the corresponding author and contributed in writing the case, literature review and writing the discussion. HA contributed in literature search and writing the manuscript. FM is the attending endocrinologist who reviewed the manuscript and made necessary changes to it.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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