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Case Study

Antithyroid Arthritis Syndrome – A Rare Complication of Methimazole Therapy

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Antithyroid drugs (ATD's) commonly used as the first line treatment option for the management of hyperthyroidism. These drugs have various types of adverse effects ranging from mild to serious. Antithyroid arthritis syndrome (AAS) is one of the serious and relatively rare side effects of ATD therapy which requires immediate drug cessation. Here we report a case of 37-year-old female diagnosed as subacute thyroiditis, started on methimazole and admitted and investigated for development of severe polyarthritis. Her ANA (Antinuclear antibody), Anti Ds DNA (Deoxy ribonucleic acid antibody) and RA (Rheumatoid arthritis) factor, were negative. She was treated with injectable steroids, to which she responded well and discharged with oral steroids. Symptoms gradually subsided with oral steroids being tapered in 1 month. Antithyroid arthritis syndrome is a rare complication of antithyroid medications. This case report underlines the importance of differential diagnosis and recognition of AAS as an adverse effect of antithyroid agents and the need for prompt withdrawal of the offending drug.

Keywords: Hyperthyroidism, Thyroiditis, Antithyroid drugs, Methimazole, Arthritis.

INTRODUCTION

There are three modes of medical treatment for hyperthyroidism: Antithyroid drugs, radioactive iodine and surgical intervention. Thionamide drugs are the mainstay of hyperthyroidism treatment and include Methimazole (MMI), Carbimazole (CMI) and the Thiourea derivative- Propylthiouracil (PTU). They are highly effective, but some patients may experience serious side effects. In such cases non-thionamide drugs like iodine containing compounds can be used. Methimazole is recommended over Propylthiouracil except for pregnant women in the first trimester as per the 2016 American Thyroid Association guidelines. [1,2] The starting dose of Methimazole is usually a single dose of 15mg to 30 mg/day while that of Propylthiouracil is 300mg/day in three divided doses.

Side effects of antithyroid drugs include minor side effects like cutaneous reactions, arthralgias and gastrointestinal upset symptoms which are not life threatening and do not require discontinuation of drug. Major side effects like agranulocytosis, vasculitis, hypoglycemia, cholestasis and aplastic anemia might require immediate discontinuation of Antithyroid drug and hospitalization. [1] Arthralgias are a relatively common side effect of antithyroid drugs. In a review by Shabtai *et al*, skin reactions were the commonest side effect (1.8%) followed by polyarthralgia (1.6%) out of 500 patients with thyrotoxicosis treated with antithyroid drugs. [3] Even though development of arthralgias is classified as a "minor" reaction, it may be a precursor of a severe migratory polyarthritis called as "the antithyroid arthritis syndrome", hence it should elicit drug withdrawal. [1]

Antithyroid Arthritis Syndrome (AAS) is an uncommon but serious complication of antithyroid drugs. [2] It occurs mostly in females, who can be of any age group. It can start at any time during the therapy with Propylthiouracil and Methimazole. [4] Accompanying symptoms may include myalgia, skin

rash and high-grade fever which may progress to disabling polyarthritis involving small, medium and large joints. [2,4]

The Case:

Our patient was a 37-year-old female, who was being evaluated by gastroenterologist for sludge in common bile duct. She was planned for ERCP but during PAC (pre-anesthetic checkup), she was found to have TSH-0.1 mIU/ml and hence referred to endocrinologist. She was clinically diagnosed with Subacute Thyroiditis and started on Methimazole 10 mg once daily. After continuing for around a month, she developed pain and swelling of right elbow joint followed by similar problems in left wrist joint followed by small joints of hands, pain and swelling of left knee joint for 3 days duration. There was no history of fever, any respiratory, gastrointestinal or urinary symptoms. On clinical examinations her vitals were normal. No abnormal findings were found in systemic examination except swelling and tenderness in the above joints. All routine investigations along with arthritis panel were sent. In view of severe disabling pain 60 mg of methylprednisolone was given IV along with IV paracetamol. Next day she was better, hence was changed to oral prednisolone. Endocrinologist opinion was sought who diagnosed it as Methimazole induced inflammatory polyarthritis. There were no other side effects in the form of fever, sore throat or agranulocytosis. Methimazole was stopped and patient was discharged from ward with oral prednisolone. Patient came for follow up in OPD after 1 week, when she reported still having pain in joints of hands, other joints were better. She was advised to continue mild NSAIDs like indomethacin. Later the patient went to higher gastroenterology center for evaluation where she was finally diagnosed as Primary biliary cirrhosis.

Name	Result	Unit	Reference range
RA test	Negative	IU/ML	
VIT B12	183.00	Ppg/mL	180-914
VIT D	64.80	Ng/mL	10-50
Blood urea	21.8	Mg/dl	15-40
Magnesium	1.97	mg/dL	1.8-2.6
Serum Calcium	8.31	mg/dL	8.6-10.3
C-Reactive protein	5.69	mg/dL	0.08-0.79
S creatinine	0.77	mg/dL	0.5-1.5
Total Bilirubin	0.54	mg/dL	0.2-1.0
AST	24.10	U/L	0-35
ALT	28.10	U/L	0-45
ALP	225.50	U/L	53-141
Anti-DNA	Negative		
ANA	negative		
Complete blood count			
Hemoglobin	10.0	Gm/dl	11.5-16.5
Total leucocyte count	8330	Per cumm	4000-11000
Neutrophil	49	%	60-70
Lymphocyte	46	%	30-40
Monocyte	4	%	2-8
Platelet count	193000	Per cumm	150000-410000
S Uric acid	5.17	Mg/dl	2.6-6.0
HBsAg by rapid card test	Negative		
HCV by rapid card test	Negative		
HIV by rapid card test	Negative		
TSH	0.01	Uiu/ml	0.3-6.0
PT (Test)	12.1	Sec	12.3-14.5
MNPT	13.4	Sec	12.3-14.5
INR	0.89		0.8-1.2

DISCUSSION:

Hyperthyroidism is primarily managed with antithyroid drugs (ATD), including methimazole (MMI) and propylthiouracil (PTU). MMI has become the main therapeutic agent due to its superior safety profile compared to PTU. However, the side effects of MMI ranges from mild manifestation like skin reaction to severe complications like hemophagocytic syndrome [5] and anti-neutrophil cytoplasmic antibody [ANCA]-associated vasculitis [AAV]). While AAV may present with polyarthritis, these articular symptoms are not pathognomonic and require differentiation from a distinct complication – antithyroid arthritis syndrome (AAS).

AAS caused by thionamides and propylthiouracil was originally described in 1946 by Williams *et al*. [6] Antithyroid drug-induced arthritis can be part of the AAS or ANCA-Associated Vasculitis (AAV). Unfortunately, its course can be unpredictable and rarely even fatal, leading to renal and respiratory failure. Most cases present initially with arthralgia. Arthritis, when compared to arthralgias are associated with synovitis, raised markers of inflammation such as leukocytosis, elevated CRP and ESR. [2] Discontinuation of therapy is warranted early as it may lead to severe transient migratory polyarthritis. An adverse reaction to any drug is based on several factors. Temporal association, clinical features, organ involvement, significant improvement of symptoms following the withdrawal of the drug (dechallenge) and reappearance of the symptoms on repeated exposure to the drug (rechallenge).[7] In our case, patient had a score of 7 on Naranjo Adverse Drug Reaction (ADR) probability scale, used for assessing adverse drug reactions suggesting high probability of relationship between Methimazole exposure and development of AAS.[8] It is important to rule out autoimmune diseases which can mimic antithyroid arthritis syndrome. In this case, the possibility of reactive arthritis and other autoimmune diseases like lupus were considered. RA factor, ANA and Anti-DNA were negative.

AAS is a rare adverse reaction caused by ATDs, characterized by fever, rash, and myalgia, with arthralgia in the joints of the lower limbs, and even in the wrists and forearms. [9] Epidemiological data is limited; 1.6% incidence has been reported in patients exhibiting polyarthralgia. [3] AAS must be distinguished from ANCA-associated vasculitis (AAV), which shares articular manifestations but requires different approach to treatment. Unlike AAV, AAS typically lacks ANCA seropositivity and systemic organ involvement. Autoimmune tests such as ANA, ANCA, and drug lymphocyte stimulation tests (DLST) can help distinguish AAS from other rheumatic condition, but the results are not definitive. [9] As with most adverse drug reactions, discontinuation of suspected medications and symptomatic treatment with NSAIDs and corticosteroids can be an effective approach to AAS, but use of colchicine was also reported as a new approach. [2]

CONCLUSION:

Antithyroid arthritis syndrome is a rare complication of antithyroid medications. It comprises of a variety of symptoms such as myalgia, arthralgia and arthritis along with fever and rash of varying severity. It has non-specific laboratory findings, making the diagnosis clinically challenging. Following diagnosis, immediate discontinuation of the responsible drug is needed for resolution of symptoms as sometimes it can rapidly progress to a life-threatening condition. Continuation of treatment without proper recognition or rechallenge with even smaller doses can prove to be dangerous. In conclusion, our case report underlines the importance of differential diagnosis and recognition of AAS as an adverse effect of antithyroid agents and the need for prompt withdrawal of the offending drug.

CONFLICT OF INTEREST: Nil

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