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Original Article

Arthritis Associated with Low Dose Methimazole Therapy: A Case Report

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Abstract

Here in this paper, we report a 31-year-old case admitted with symptoms of hyperthyroidism that was then diagnosed with Grave's disease (GD) and underwent treatments with a low dosage of methimazole (10 mg/day). 20 days after treatments initiations, she developed antithyroid arthritis syndrome. This patient experienced arthritis and arthralgia in at least 4 joints. All autoimmune and microbiologic evaluations were negative. She was then completely recovered without any sequelae within 4 days after drug withdrawal. Arthritis as an adverse effect of methimazole is a major and life-threatening adverse effect which requires immediate drug discontinuation and hospitalization. Contrary to what has been thought. We declare that this adverse effect might not be dose dependent as our case developed arthritis following methimazole therapy with a very low dosage (10 mg/day). The aim of the current case report is to help other physicians in order to diagnose and treat possible cases of antithyroid arthritis syndrome.

Key words: hyperthyroidism, Grave's disease, antithyroid therapy, methimazole, arthritis, case report

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1. Introduction

Grave's disease (GD) which is also known as exophthalmic goiter is the most common cause of hyperthyroidism [1]. This disease is characterized by clinical symptoms including diffuse goiter, resting tremor, fatigue, smooth and moist skin and thyroid eye disease [1].Three major modalities for treatment of GD include antithyroid drugs, radioiodine (iodine 131 [^{131}I]) therapy and surgery [2]. One of the effective modes of antithyroid therapy is the administration of oral antithyroid agents such as methimazole and propylthiouracil (PTU). Along with better-proven safety

profile of methimazole compared with PTU [3, 4], some adverse effects have been reported which range from mild to life-threatening [5-7]. Mild adverse effects include: cutaneous reaction (4-6%), arthralgia (1-5%) and gastrointestinal effects (1-5%) and on the other hand, rare life-threatening adverse effects include polyarthritis(1-2%), agranulocytosis (0.1-0.5%) and hepatitis (0.1-0.2%) which cause the discontinuation of the drug [5, 8, 9]. Arthritis is thought to be dose-dependent [10, 11] but here in this paper, we report a 31-year-old woman admitted with GD who further developed polyarthritis, 20 days after treatment with a low dosage of methimazole. As global knowledge has focused on curing and finding the etiology of chronic and life-threatening diseases such as cancers [12-14], presentation of this rare case helps us and other physicians to diagnose and treat other possible cases of antithyroid arthritis syndrome.

2. Case

Here, we present a 31-year-old woman who was referred to Al-Zahra hospital, Isfahan, Iran due to symptoms of hyperthyroidism. She was a housewife and had been married for 8 years and had 2 healthy children. The patient showed mild weight loss (about 5 kg), tachycardia, and tremor as the initial presenting symptoms. She had given birth to a full term healthy baby 3 months prior to her admission. Her course of pregnancy was associated with no disorder and her past medical and psychosocial history revealed no problems such as allergies or joint symptoms or former symptoms of thyroid or collagen-vascular diseases. Moreover, her family history revealed no issues including thyroid or collagen-vascular diseases. Her initial physical examinations indicated that the patient was afebrile with the body temperature of 37 degrees Celsius. Her heart rate was 140 beats per min. and her blood pressure was 70/100 mmHg. Her height and weight was 160 cm and 65 kg respectively. She had no exophthalmos. Physical examinations also indicated smooth and moist skin and tremor in her hands. Further examinations of her thyroid gland showed a diffusely enlarged gland. Laboratory data also indicated elevated serum T3 (650.0 ng/dl) and serum T4 (22.0 µg/dl) and a marked decreased TSH (<0.005 mIU/l). There was also a positive result for antithyroid peroxidase Ab (anti-TPO) with the result of >2000 IU/ml but anti-thyroglobulin (Tg) Ab was normal (86.02 IU/ml). Moreover, TSH receptor antibodies (TRAb) were elevated (4 IU/l) with a normal range of ≤1.75 IU/l. Other lab data are summarized in Table 1. Ultrasonography showed no mass but diffusely enlarged thyroid gland. Doppler ultrasonography also demonstrated high

Table1. Laboratory data at the presentation with GD symptoms.

Biochemistry	**Data**
T3 (ng/dl)	650.0
T4 (µg/dl)	22.0
TSH (mIU/l)	<0.005
anti TPO (IU/ml)	>2000
anti- Tg Ab (IU/ml)	86.02
ALP (U/l)	242
Vitamine D3 (ng/ml)	29.63
Ferritin (ng/ml)	211.80

T3: Triiodothyronine, T4: Total Thyroxine, TSH: Thyroid-stimulating hormone, anti TPO: Anti- thyroid peroxidase Antibody, Anti- Tg Ab: Anti Thyroglobulin Antibody, ALP: Alkaline phosphatase

blood flow to the thyroid gland. Due to the highly elevated T3 hormone compared with T4 amounts, along with a positive lab data for anti-TPO and ultrasonography findings, postpartum thyroiditis and other thyroiditis were ruled out and her diagnosis of GD was ascertained. Therefore, her treatment with methimazole 10mg daily was initiated.

After 20 days, she was admitted to Al-Zahra hospital with the presentation of arthritis and arthralgia. She had complained about pain in both of her wrists, left knee joint, and her right shoulder. Her physical examinations revealed swelling, tenderness and limited range of motion on her engaged joints. Other physical exams were normal. The patient was also examined by expert rheumatologists that led to the suggestion of arthritis in her both wrists. In her laboratory investigations, erythrocyte sedimentation rate (ESR) was high (45mm), her T4 level was normal (12.6 µg/dl) but her T3 level was still elevated (247 ng/dl). Her TSH level was also 0.024 mIU/l. Moreover, her lab data indicated a mild hematuria but no proteinuria or hemoglobinuria were observed. These results, along with other tests are summarized in Table 2 and Table 3. Besides, there was a suspicion upon reactive arthritis and autoimmune diseases such as ANCA associated arthritis and for that reason, urine tests for microorganisms and serological tests in search for autoimmune antibodies and also a complete ophthalmologic examination in search for possible uveitis were performed which all had normal results (Table 4). As a result, rheumatologic and autoimmune diseases including ANCA associated vasculitis syndrome and reactive arthritis were ruled out. Taken together, these signs and symptoms were suggestive of antithyroid arthritis syndrome. Methimazole was discontinued at once and one day after initiation of clinical improvements, she

Table2. Complete blood count and blood chemistry at the presentation with arthritis.

Laboratory data	**Data**
Complete Blood Count	
ESR (mm)	45
WBC (/mm^3)	10300
Neutrophils (%)	76.1
Lymphocytes (%)	18.1
Platelet (/mm^3)	147000
RBC (Mil/mm^3)	4.77
Hemoglobin (g/dl)	13.4
Hematocrit (%)	38.4
MCV (fL)	80.5
MCH (pg)	28.1
MCHC (g/dl)	34.9
RDW_CV (%)	10.8
Blood chemistry and hormones	
Albumin (g/dl)	4.3
ALT (U/l)	34
AST (U/l)	38
ALP (U/l)	355
Gamma GT (U/L)	68.2
Direct Bilirubin (mg/dl)	0.2
Total Bilirubin (mg/dl)	0.5
BUN (mg/dl)	10
Creatinine (mg/dl)	1.0
FBS (mg/dl)	127
T_3 (ng/dl)	247
T_4 (µg/dl)	12.6
TSH (mIU/l)	0.024
CRP	(++)

ESR: Erythrocyte sedimentation rate, WBC: White Blood Cell, RBC: Red Blood Cell, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin concentration, RDW: Red Cell Distribution Width, ALT: Alanine transaminase, AST: Aspartate transaminase, ALP: Alkaline phosphatase, Gamma GT: Gamma-glutamyltransferase, BUN: Blood urea nitrogen, FBS: Fasting Blood Sugar, TSH: Thyroid-stimulating hormone, CRP: C-reactive protein.

underwent treatments with proper hydration, injection of dexamethasone 4mg per 12 hours, propranolol 20 mg per 8 hours and propylthiouracil (PTU) 100 mg two times a day. The patient faced clinical improvement rapidly at the time of methimazole withdrawal and she was fully recovered in 4 days with no more signs of arthritis or arthralgia, so we discontinued dexamethasone administration. It is noteworthy to mention that our case was not a candidate for ^{131}I treatments for thyroid ablation due to lactation. Patient's follow up after 45 days demonstrated normal physical examination, CBC, Thyroid function test

(TFT) and liver function test (LFT) and she had no further complained.

Table 3. Urinalysis and microbiology for urine at the presentation with arthritis.

Laboratory data	**Data**
Urinalysis	
Color	Brown
Appearance	semi-clear
Specific gravity	1027
PH	5
Protein	(-)
Glucose	(-)
Ketone	(-)
Amino Acid	(-)
Blood	(+)
Bilirubin	(-)
Urobilirubin	(-)
Nitrogen	(-)
RBC	many
WBC	1-2
Epithelial cell	1-2
Bacteria	(-)
Crystal	(-)
Cast	(-)
Mucus	(-)
Yeast	(-)
Dismorphic RBC (%)	20
Microbiology for Urine	No bacterial growth

(+): Present, (-): Absent, RBC: Red Blood Cell, WBC: White Blood Cell.

Table 4. Immunology and serology tests at the presentation with arthritis.

Laboratory data	**Data**
Immunology	
Anti CCP (RU/ml)	2
Anti-dsDNA (IU/ml)	14
C-ANCA (U/ml)	1
P-ANCA (U/ml)	1
ANA (U/ml)	9
Serology	
2ME	(-)
Wright	(-)
Coombs Wright	(-)
RF QL (IU/ml)	1

(-): Absent, Anti CCP: Anti–citrullinated protein antibody, Anti-dsDNA: The anti-double stranded DNA, ANA: Antinuclear Antibody, 2ME: 2-mercaptoethanol.

3. Results and Discussion

In this case report, we introduced a case of arthritis associated with methimazole therapy as a rare but serious life-threatening side effect of this drug[10]. There have been recent case reports [15, 16] of antithyroid arthritis syndrome which in turn make diagnosis and treatment of this syndrome an important issue for physicians. Antithyroid arthritis syndrome is defined as developing arthritic symptoms in one or more joints within 8 weeks of antithyroid therapy initiation [3, 17, 18]. There is still much to discover about the exact pathogenesis of the disease and as mentioned earlier. This complication is considered as a major adverse effect of antithyroid drugs such as methimazole that requires rapid discontinuation of the drug. Contrary to antithyroid arthritis syndrome, arthralgia is a minor adverse effect of methimazole which doesn't require drug discontinuation and doesn't elevate serum inflammatory markers such as CRP and ESR. But it should also be noted that arthralgia might be the first symptom in most cases [19]. Arthritis is also associated with a wide range of autoimmune and of course infectious diseases but the case which we presented, revealed no symptoms of infection and had negative test results for both autoimmune diseases and infections. Takaya and colleagues reported [16] a case of a 38-year-old woman similar to our case which developed antithyroid arthritis syndrome after thiamazole therapy. They also emphasized the importance of ruling out autoimmune diseases which can mimic antithyroid arthritis syndrome. So they had a review on some cases of Antithyroid Drug-induced Lupus-like Syndrome who had also positive results for ANCA and other autoimmune markers. Therefore, they concluded that based on the absence of autoantibodies especially ANCA and most vasculitis symptoms such as nephritis, skin lesions, and systemic symptoms, we might be able to distinguish antithyroid arthritis syndrome from vasculitis or lupus-like syndrome. This finding was in line with our case that had negative results for ANCA and other autoimmune markers.

It has also been suggested that such adverse effects may be dose-dependent meaning the higher the dose is, more frequent the adverse effects will be [10, 11]. Similarly, several case reports have reported arthritis in higher doses of the drug compared to the case presented by us. Ploegstra and colleagues [19] have also suggested that developing arthritis might be related to high doses of thiamazole. They reported a case of 15-year-old girl who had undergone treatments with thiamazole 90mg daily and developed arthritis. Furthermore, Nihei et al. [20] reported development of polyarthritis caused by methimazole in two cases who had been

under 50 and 30 mg/day therapy. There was also a report of antithyroid arthritis syndrome by Paepegaey et al [17] which occurred with 60 mg/day of carbimazole. But contrary to all these reports, we reported a case of arthritis after administration of methimazole 10 mg daily that is considered as a very low dosage therapy according to American Thyroid Association (ATA) guideline[21]. These findings demonstrate that antithyroid arthritis syndrome may not be dose-dependent as what previous studies have suggested and this issue remains a matter of dispute[10, 19].Our case was recovered completely after discontinuation of methimazole and administration of glucocorticoids along with PTU. In most cases, the next step of GD treatment is thyroid ablation by ^{131}I but in this case usage of radioiodine was contraindicated due to the lactation condition.

4. Conclusion

Taken together this scenario was a unique case of antithyroid arthritis syndrome which is a potential life-threatening adverse effect, developed following methimazole therapy with a very low dosage. Former case reports of antithyroid arthritis syndrome were mostly reported to be dose dependent but here we concluded that this particular side effect might also occur with low doses of the drug. Owing to the boost of knowledge gained from similar case reports, physicians might be able to rapidly diagnose and treat other possible cases around the world.

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