Antithyroid arthritis syndrome caused by methimazole in a patient with Graves’ disease

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Summary
This is a report on antithyroid arthritis syndrome (AAS) which is a rare adverse effect of antithyroid agents. AAS presents with severe symptoms including myalgia, arthralgia, arthritis, fever, and skin eruption due to the use of antithyroid agents. We encountered a 55-year-old woman with severe pain in the hand and forearm and arthralgia in multiple joints, including the knee, ankle, hand, and wrist on day 23 after initiation of methimazole (MMI) for Graves’ disease. Blood tests revealed elevated inflammation markers such as C-reactive protein and interleukin-6, and magnetic resonance imaging of the hands confirmed inflammation findings. After withdrawing MMI on day 25, symptoms showed a tendency toward improvement. Afterwards, inflammation markers also dropped to an almost normal range. In addition to the above findings, the absence of anti-neutrophil cytoplasmic antibodies and most vasculitis symptoms such as nephritis, skin, or pulmonary lesions led to the diagnosis of AAS. A resolution of symptoms, except for mild arthralgia in the second to fourth fingers of the right hand, was observed 61 days after discontinuation of MMI. Although the pathogenesis is unclear, the positive drug lymphocyte stimulation test for MMI and the several weeks before the onset of AAS suggested involvement of a type IV allergic reaction. Based on a discussion of definitive treatment for Graves’ disease, radioactive iodine ablation with 131I, which was selected by the patient, was performed and improved her thyroid function. Our case demonstrates the importance of awareness regarding AAS, which is a rare and under-recognized, but life-threatening adverse effect of antithyroid agents.

Learning points
- Clinicians should be aware of the possibility of developing antithyroid arthritis syndrome (AAS) in patients treated with antithyroid medications, which can lead to severe migratory polyarthritis.
- Prompt cessation of the antithyroid agent is essential for the resolution of AAS.
- Anti-neutrophil cytoplasmic antibody (ANCA) negativity is needed to differentiate from antithyroid agent-induced ANCA-associated vasculitis, which shows arthritis similar to AAS.

Background
Graves’ disease (GD) is commonly encountered in clinical practice, and oral antithyroid agents are widely used as drug therapy. Antithyroid agents have a wide range of adverse effects from mild, such as skin eruptions, to severe such as agranulocytosis and severe hepatitis (1). The adverse effects of methimazole (MMI) are known to be dose dependent, while propylthiouracil (PTU) is not dose related. Therefore, blood tests are recommended when symptoms such as fever are observed after antithyroid drug therapy is started (2).

Antithyroid arthritis syndrome (AAS) is a rare adverse effect of antithyroid agents and can present symptoms...
that severely affect the quality of life, such as severe myalgia and arthralgia (3). In clinical practice, however, it is not as widely known as agranulocytosis and severe hepatitis. Clinicians need to recognize AAS as one of the possible severe adverse effects of antithyroid agents. The diagnosis of AAS is difficult without clinician recognition because blood tests do not show specific laboratory findings. With the aim of raising awareness of this adverse effect, we report a case of AAS in a 55-year-old woman who developed multiple arthralgia and myalgia after about 3 weeks of MMI administration for GD.

**Case presentation**

A 55-year-old woman was referred to our Department of Endocrinology and Diabetes for suspicion of GD based on clinical and biochemical evidence. She complained of excess sweating, feeling exhilarated, and hand tremors. Blood tests showed thyrotoxicosis (thyroid-stimulating hormone (TSH) < 0.01 µIU/mL (reference range (RR): 0.35–4.94 µIU/mL); free T4 (FT4): 1.83 ng/dL (RR: 0.70–1.48 ng/dL)) at the referral hospital. Her past medical history included hypertension, a previous stroke, and insomnia. There was no family history of thyroid or collagen disease. Elevated thyrotropin receptor antibody (TRAb) (32.3 IU/L (RR: 0.0–1.9 IU/L)) and thyroid stimulating antibody (TSAb) titers (659% (RR: 0–120%)) were revealed at our hospital. Ultrasonographic findings of the thyroid gland showed no enlargement and a slightly lobulated and heterogeneous low-level internal echoes with high Doppler blood flow (right lobe: 46 × 15 × 13 mm, left lobe: 41 × 15 × 14 mm, the thickness of isthmus: 4.5 mm). A diagnosis of GD was confirmed based on the above findings and 15 mg/day of MMI was started.

On day 18 after initiation of MMI, the patient noticed erythema with itching on both hands and feet. These lesions disappeared within 4–5 h (Fig. 1, panels A and B). Three days later, the patient noticed severe asymmetric arthralgia of the right wrist and left knee and bilateral stiffness of the hand and forearm. There was an improvement in these symptoms after the oral administration of celecoxib. On day 23, she presented with severe pain in the hand and forearm, and arthralgia in multiple joints, including the knee, ankle, hand, and wrist. She had no pain relief with celecoxib and could not walk on her own or open the lid of a plastic bottle. Vital signs at hospital arrival showed a temperature of 36.3°C, blood pressure of 151/81 mmHg, pulse rate of 104 bpm, and oxygen saturation of 99% on room air. A thorough examination including a CT scan was performed, but the cause of symptoms was unknown, and the patient was referred to the Department of Rheumatology and Clinical Immunology the following day. A physical examination performed by the rheumatologist revealed a swollen left knee joint, and a tender and swollen metacarpophalangeal joint of the second finger of the right hand on panel (C) was confirmed, while the fingers and hands were generally swollen. Skin lesions were not found (Fig. 1, panel C). At that time, the score on a 100 mm pain visual analog scale (pain VAS) for assessing the severity of arthralgia was 90 mm, and the health assessment questionnaire (HAQ) score was 2.50 (Fig. 2). HAQ score ranges from 0 (no incapacity) to 3 (full incapacity); a score below 0.5 is considered functional remission).

**Investigation**

Her laboratory data showed TSH < 0.01 µIU/mL (RR: 0.38–5.38), FT4 1.23 ng/dL (RR: 0.70–1.48 ng/dL), and free triiodothyronine 4.35 pg/mL (RR: 1.68–3.67 pg/mL). Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and interleukin-6 (IL-6) levels were elevated to 18 mm/h (RR: 3–15 mm/h), 4.65 mg/dL (RR: 0.00–0.14 mg/dL), and 18.4 pg/mL (RR: <7.0 pg/mL), respectively (Fig. 2). IL-1β was increased to 17.0 pg/mL (RR: <10.0

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**Figure 1**

The patient's feet (A, B) and hands (C). Numerous erythematous plaques on panels (A) and (B) were observed on her feet. The clinical pictures (A, B) were taken by the patient using a cellular phone. Swollen metacarpophalangeal joint of the second finger of the right hand on panel (C) was confirmed, while the fingers and hands were generally swollen.

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pg/mL) and tumor necrosis factor-alpha (TNF-α) levels were normal (0.81 pg/mL (RR: 0.75–1.66 pg/mL)). Autoimmune tests were performed, with negative rheumatoid factor, anti-cyclic citrullinated peptide antibodies, myeloperoxidase (MPO)-anti-neutrophil cytoplasmic antibodies (ANCAs), proteinase 3 (PR3)-ANCAs, anti-double-stranded DNA antibodies, anti-Smith antibodies, anti-ribonucleoprotein, anti-Sjögren's syndrome type A (SSA) antibodies, anti-Sjögren's syndrome type B (SSB) antibodies and anti-aminocyl-tRNA synthetase (ARS) antibodies (anti-ARS). Only the anti-nuclear antibody (ANA) screen was positive with a titer of 1:40 (<1:40).

Serum CH50, C3, and C4 titers were normal (CH50: 48.2 CH50/mL (RR: 25.0–48.0 CH50/mL), C3: 133 mg/dL (RR: 86–160 mg/dL), C4: 24 mg/dL (RR: 17–45 mg/dL)). Serum IgG, IgA, and IgM levels were also normal (IgG: 988 mg/dL (RR: 861–1747 mg/dL), IgA: 87 mg/dL (RR: 93–393 mg/dL), and IgM: 147 mg/dL (RR: 50–269 mg/dL)).

Rheumatology examinations were conducted and the radiographs of multiple joints including the ankle, foot, wrist, hand, chest, and spine revealed no specific findings except for joint space narrowing in the knee. Magnetic resonance imaging of the left hand revealed inflammation around the fourth metacarpal (Fig. 3, panels B, C and D), while a high signal intensity was also seen at the diaphysis of the third and fourth metacarpals of the right hand on the fat-suppressed T2-weighted images (Fig. 3, panel A).

**Treatment**

Although the etiology was unclear, we considered idiopathic collagen diseases and not antithyroid drug-induced ANCA-associated vasculitis (AAV) syndrome. The patient stopped taking MMI of her accord on day 25 while continuing to take non-steroidal anti-inflammatory drugs (NSAIDs). Subjective symptoms including arthralgia and myalgia showed a tendency toward improvement after the discontinuation of MMI. Therefore, as these symptoms were thought to be an adverse reaction to the MMI treatment, we substituted potassium iodide at a dose of 50 mg/day for GD. A follow-up physical evaluation 12 days after the discontinuation of MMI revealed that multiple joint swelling and tenderness resolved, while morning hand stiffness and hand pain remained. Resolution of symptoms except for mild arthralgia in the second to fourth fingers of the right hand was observed 61 days after discontinuation of MMI. We also observed that CRP, ESR, and IL-6 levels improved, respectively (CRP: 0.41 mg/dL, ESR: 6 mm/h, IL-6: 2.9 pg/mL). IL-1β levels normalized (IL-1β: < 10 pg/mL) and pain VAS and HAQ scores improved.
significantly (Fig. 2). Drug lymphocyte stimulation tests (DLSTs) for MMI using peripheral lymphocytes were positive on day 51 after initiation of MMI (stimulation index: 2.0, positive: >1.8).

**Outcome and follow-up**

We considered that an adverse effect of PTU can also occur based on cross-reactivity between antithyroid agents (4). Due to this, definitive treatments were discussed with the patient for control of GD. The patient did not have proptosis, and radioactive iodine ablation with 131I, which was selected by the patient, was performed resulting in improvement of her thyroid function.

**Discussion**

We describe a case of AAS in a 55-year-old woman who developed polyarthralgia and myalgia about three weeks after taking MMI for GD. AAS is a rare adverse effect of antithyroid medications and presents with severe symptoms including myalgia, arthralgia, arthritis, fever, and skin eruption. As polyarthralgia is known to occur in 1.6% of patients treated with antithyroid agents (3), the exact incidence of AAS has not been exactly reported.

AAS shows non-specific laboratory findings and follow-up of laboratory data is not helpful for detecting AAS. The diagnosis is difficult without knowledge of AAS, and it is an under-recognized entity caused by antithyroid agents in clinical practice. Therefore, clinicians need to recognize AAS as an adverse effect of antithyroid agents. To the best of our knowledge, MRI findings associated with AAS have not been reported previously and this is the first reported case showing inflammatory findings associated with AAS on MRI, which is helpful for diagnosing AAS.

Antithyroid drug-induced AAV and antithyroid drug-induced lupus-like syndrome also show similar symptoms such as myalgia and arthralgia, so it is important to differentiate AAS from them. ANCA measurement is necessary for differentiation, AAS is negative for ANCAs in most cases (5). In our case, we also diagnosed AAS based on the absence of ANCAs and most vasculitis symptoms such as nephritis, skin, or pulmonary lesions. ANA can be positive in patients diagnosed with AAS; Cetina et al. reported no significant difference in the rate of positive ANA between a population treated with PTU and a control population (6). Our patient was also weakly positive for ANA, but this was not considered a significant result.

One of the complications that occur after the treatment of thyrotoxicosis is thyroid acropathy. It is characterized by diffuse soft tissue edema, digit clubbing, and irregular and spiculated periosteal new bone formation, but no pain (7). In our case, the patient presented with severe pain in the hand and forearm, and arthralgia in multiple joints. In addition, the radiographs of the extremities showed no evidence of irregular and spiculated periosteal new bone formation, which is clearly different from thyroid acropathy.

The mechanisms by which antithyroid agents cause AAS are unclear. Previous reports have suggested the involvement of neutrophil MPO and copper-antithyroid drug complexes in the immunological reactions elicited by antithyroid agents (8, 9). A positive DLST for MMI has been reported in a patient who developed AAS after MMI treatment (5). Given that the DLST for MMI was positive and it took several weeks before the onset of AAS, a type IV allergic reaction may be associated with the pathogenesis of AAS. Further studies are needed to elucidate this.

Antithyroid agents should first be discontinued after the diagnosis of AAS. NSAIDs are often used for pain management, although prednisolone is occasionally used. Mancuso et al. reported that colchicine was effective in a case of AAS that was poorly responsive to NSAIDS and prednisolone (10). Colchicine has an inhibitory effect on neutrophil chemotaxis and phagocytosis. These facts suggest that neutrophils are associated with the pathogenesis of AAS. In addition, colchicine prevents IL-1β secretion which is produced by neutrophils and also elicits the activation of neutrophil function (10). In our case, IL-1β levels were elevated in the acute phase, which also indicates that neutrophil activation is involved in the pathogenesis of AAS. Pain management was possible with NSAIDS alone, and almost complete resolution of the symptoms was observed 61 days after discontinuation of MMI.

In conclusion, this case demonstrates the importance of recognizing AAS as a rare adverse effect of antithyroid treatment. Diagnosis of AAS is difficult without clinician recognition due to non-specific laboratory findings. When a diagnosis of AAS can be made, discontinuation of antithyroid agents can improve symptoms. Therefore, AAS should be considered in the differential diagnosis of polyarthritis or myalgia after antithyroid treatment.

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**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
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Patient consent
The patient provided written informed consent for the publication of her clinical details and clinical images.

Author contribution statement
M Kawasumi wrote the manuscript. All authors treated patients, discussed data, and contributed to the editing process.

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