Case of Raynaud Syndrome after the Use of Methimazole

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Raynaud syndrome is a medical condition that causes pain, numbness, and changes in skin color at the distal extremities. Raynaud syndrome can be subdivided into primary Raynaud’s and secondary Raynaud’s. The former is diagnosed when the cause is unknown and the latter is caused by an underlying condition, such as connective tissue diseases, injury, smoking, or certain medications. Both cancer chemotherapy and β-blockers are relatively common causes of Raynaud syndrome but there are no reports of its association with methimazole administration. The authors encountered a 43-year-old woman with hyperthyroidism who developed digital ulcers associated with Raynaud syndrome after a methimazole treatment. Her digital ulcers and Raynaud syndrome were improved after methimazole was replaced with propylthiouracil and conventional therapy. This paper reports this case along with a review of the relevant literature. (J Rheum Dis 2018;25:203-206)

Key Words. Methimazole, Raynaud syndrome, Ulcer

INTRODUCTION

Raynaud syndrome, also known as Raynaud’s phenomenon, was first described as a medical condition by Maurice Raynaud in 1862. In Raynaud syndrome, distal blood flow is blocked by vasospasm of small arteries resulting in skin color changes, pain, and sensory disturbances in the extremities [1]. The prevalence of Raynaud syndrome varies regionally and between the sexes. It is reported that 3% ~ 19% of the total population is affected, with higher rates in women than men [2,3]. Primary Raynaud’s (also called Raynaud’s disease), which occurs without any other accompanying disease, accounts for about 80% of cases [4]. Secondary Raynaud’s (also called Raynaud’s phenomenon), occurs with many other conditions including connective tissue disorders, such as scleroderma or lupus, trauma, smoking, and certain medications [5].

Methimazole is a thionamide drug which is commonly used as a treatment for hyperthyroidism including Graves’ disease [6]. Common side effects are urticaria, rash, arthritis, and indigestion. Possible life-threatening complications of methimazole administration are agranulocytosis or toxic hepatitis [7]. In rare cases, drug-induced autoimmunity, such as vasculitis or systemic lupus erythematosus, occurs [8].

The incidence of Raynaud’s phenomenon due to the use of methimazole has not been reported. Here, we report a literature review and a case where methimazole triggered Raynaud syndrome and associated digital ulcers and small infarctions. These symptoms improved after discontinuing methimazole in this case.

CASE REPORT

A 43-year-old woman visited a tertiary hospital presenting with pain and color change in two fingers. She had a history of hyperthyroidism and had been treated with propylthiouracil for 25 years. Her medication was changed to methimazole 7 months before visiting the...
hospital. The Raynaud’s phenomenon occurred 6 months after the change in medication.

She was a kindergarten caregiver and there were no other notable findings in her social, past medical, and family histories.

She was 166 cm tall and weighed 56 kg. Her blood pressure, pulse rate, respiratory rate, and body temperature were 133/81 mmHg, 94 beats/minute, 20 breathes/minute and 36.5°C, respectively. Color changes and small digital ulcers with infarctions were observed in two fingers (Figure 1A∼C). There was no skin thickening or calcification. Laboratory findings revealed the following: normal white blood cell count 4.13×10³/μL (neutrophil 61%, lymphocyte 27.3%, monocyte 7.5%, eosinophil 3.8%, basophil 0.4%), hemoglobin 13 g/dL, hematocrit 39.8%, and platelets 184×10³/μL. C-reactive protein was 0.104 mg/dL and erythrocyte sedimentation rate was 17 mm/hour. Liver function, renal function, and urinalysis tests were normal. The thyroid function test profile indicated euthyroid function with a serum Free T4 of 0.83 ng/dL, T3 of 83.46 ng/dL, and thyroid-stimulating hormone of 1.722 μIU/mL. Antinuclear antibody, anti-double-stranded DNA antibody, anti-Smith antibody, anti-centromere antibody, anti-topoisomerase I, anti-Cardiolipin antibody, lupus anticoagulant, anti-neutrophil cytoplasmic antibodies (ANCA), and cryoglobulin were all negative. Complements were within the normal range. Chest and hand X-rays were normal.

We considered the possibility of secondary Raynaud’s associated with methimazole. We replaced methimazole with propylthiouracil and used beraprost 40 mg/day, pentoxifylline 400 mg/day and losartan 50 mg/day. There was no further deterioration after methimazole was discontinued, but the digital ulcers persisted (Figure 1D∼F). Thereafter, progressive improvement of the skin lesions was observed after 8 months of treatment (Figure

Figure 1. Change in patient’s finger lesion. (A∼C) First visit, (D∼F) after 3 months, (G∼I) after 8 months. Arrow: digital ulcer, Arrow head: small infarction.
1G~1). The patient currently takes only propylthiouracil and there has been no recurrence of her lesions.

**DISCUSSION**

Although the cause and pathophysiology of Raynaud syndrome have not yet been clearly established, it is presumed that various factors are associated with its onset. The syndrome is clinically classified into primary Raynaud's and secondary Raynaud's [9].

Primary Raynaud's follows a benign course with no damage to the blood vessels. However, in secondary Raynaud's, tissue damage due to the remodeling of capillary vessels may be accompanied by ulcers and gangrene [1,10,11]. If secondary Raynaud's is suspected, confirmation of concomitant connective tissue disease or other causes should be confirmed by testing skin sclerosis, skin calcification, antinuclear antibodies, and nail capillary microscopy [5,11].

In this case, there was digital ulceration with necrosis which is not observed in primary Raynaud's. There was no evidence of connective tissue disease in the patient's history, physical examination, or autoantibody tests. However, six months before the onset of Raynaud syndrome, the patient's anti-thyroid medication, propylthiouracil, was replaced with methimazole.

Drugs that reduce peripheral microcirculation can cause Raynaud's phenomenon. Cisplatin, bleomycin, and β-adrenoceptor blockers are known to be the most common causes of Raynaud syndrome. Others are clonidine, ergot alkaloids, dopaminergic agonists, selective serotonin re-uptake inhibitors, sympathomimetic drugs, cyclosporine, vinyl chloride, interferons, and tyrosine kinase inhibitors [12].

No case of methimazole-induced Raynaud syndrome has been previously reported, but several cases showed methimazole related Raynaud syndrome as part of other autoimmune disease it. Thong and Ajaz reported [13,14] the incidence of ANCA positive vasculitis with Raynaud syndrome in a 29-year-old woman after 3 weeks of methimazole at a dose of 10 mg and in an 18-year-old woman after 1 week of methimazole at a dose of 15 mg. Hosoi et al. [15] reported a case of cryofibrinogenemia with subsequent Raynaud syndrome, acral ulcer, and multiple arthritic joints in an 18-year-old woman who used 30 mg of methimazole.

Here, we present a case of Raynaud syndrome presenting with digital ulcers in a hyperthyroid patient treated with methimazole. Through clinical history, physical examination, and laboratory tests, including autoantibody tests, we excluded other causes and made a diagnosis of secondary Raynaud's. After discontinuation of methimazole, her digital ulcers and Raynaud syndrome gradually improved during conventional treatment with pentoxifylline, beraprost, and losartan. We did not perform a challenge test, but we determined that methimazole was the cause of the Raynaud syndrome for the following reasons: first, there were no symptoms before the use of methimazole; second, gradual improvement was observed after discontinuing methimazole; and third, there was no recurrence of Raynaud syndrome even after discontinuing the conventional treatments.

**SUMMARY**

We present the case of a patient with hyperthyroidism that developed digital ulcers associated with Raynaud syndrome induced by methimazole. The digital ulcers and Raynaud syndrome improved after methimazole was replaced with propylthiouracil. Although its exact pathophysiologic mechanism is not known, methimazole use should be included in the differential diagnosis of secondary Raynaud's.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**