

Single Case

# Methimazole-Induced Leukocytoclastic Vasculitis: A Case Report

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## Keywords

Methimazole · Cutaneous · Leukocytoclastic vasculitis · Graves' disease · Thyrotoxicosis

## Abstract

Major identifiable causes of leukocytoclastic vasculitis include certain infections and medications. Amongst antithyroid drugs, methimazole (MMI) is rarely implicated as a culprit drug. We report the first case, in Thailand, of MMI-induced leukocytoclastic vasculitis in a 41-year-old Thai female who had received MMI for relapsed Graves' disease. MMI was discontinued and cholestyramine at a dose of 4 g four times daily was given instead. Her rashes on both legs resolved dramatically at 1-week follow-up. However, thyroid function test revealed unimproved thyrotoxicosis. She subsequently underwent radioiodine ablation as a definitive treatment. There were neither recurrent skin lesions nor other systemic involvements during the 3-month follow-up period. Notably, the most crucial step in the management of drug-induced leukocytoclastic vasculitis is the discontinuation of the offending drug in order to avoid further progression of the disease. The administration of immunosuppressive agents may not be necessary in patients with mild severity and non-vital organ involvement.

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## Introduction

Cutaneous small vessel vasculitis, also called leukocytoclastic vasculitis, develops mainly after certain infections or medications. The major clinical characteristics include nonblanchable tender palpable purpura or petechiae, mostly affecting the lower extremities. In patients with thyrotoxicosis, the medications which are known to be implicated in this condition include propylthiouracil (PTU), carbimazole, and much less often methimazole (MMI) [1]. The mechanism is far from well established. We herewith report a rare case of MMI-induced leukocytoclastic vasculitis in a female patient who was being treated for thyrotoxicosis.

## Case Report

A 41-year-old Thai female visited our dermatology clinic due to acute itchy rashes on both lower legs for 4 days. Six years earlier, she was diagnosed with Graves' disease. MMI and propranolol were orally administered at doses of 15 mg once daily and 20 mg thrice daily, respectively. A good clinical response was gradually achieved before becoming euthyroid, without any sequelae. The medications were then tapered and discontinued within 17 months. She had been in her usual state of health until 3 months prior to presentation, when recurrent symptoms of thyrotoxicosis, including fatigue, palpitation, irregular menstruation, frequent bowel movement, and tremor, developed. At the time, a thyroid function test revealed a free T3 of 6.77 pg/mL (normal 1.88–3.18), free T4 of 2.26 ng/dL (normal 0.70–1.48), and TSH <0.0038  $\mu$ IU/mL (normal 0.35–4.94). MMI (10 mg once daily) together with propranolol (10 mg thrice daily) was again initiated. Four days before presentation, she noted extensive pruritic small papules on both lower legs without other organ-specific symptoms. On examination, her body temperature was 37°C, pulse rate 90 beats per minute (regular), blood pressure 132/74 mm Hg, and the respiratory rate was 18 breaths per minute. Multiple small nonblanchable erythematous itchy macules and papules on both lower legs were noticed (Fig. 1a). A diffusely enlarged, nontender, mobile thyroid – measuring approximately 30 g – with bruits was palpated. The remainder of the general examination was normal. Investigations revealed that complete blood count, CH50, C3, C4, blood urea nitrogen, creatinine, urinalysis, and chest radiograph were all within normal limits. Erythrocyte sedimentation rate was 51.0 mm per hour (normal 4.0–20.0). Liver function test was normal except for gamma-glutamyl transferase of 62.0 U/L (normal 9.0–36.0). Antinuclear antibody was negative at a serum dilution of 1:80. Myeloperoxidase antibodies and proteinase 3 antibodies were both negative. Serological tests for hepatitis B, hepatitis C, and HIV were all negative. After histopathologic and direct immunofluorescent studies confirmed leukocytoclastic vasculitis (Fig. 2a, b), MMI was discontinued and cholestyramine (4 g four times daily) was initiated. Propranolol at 10 mg thrice daily was continued for symptomatic control of palpitations. One week after discontinuing MMI, the lesions on both legs resolved (Fig. 1b). The re-evaluated thyroid function test revealed a free T3 of 8.43 pg/mL (normal 1.88–3.18), free T4 of 2.26 ng/dL (normal 0.70–1.48), and TSH <0.0038  $\mu$ IU/mL (normal 0.35–4.94). Two weeks later, she subsequently underwent radioiodine ablation as a definitive treatment. There were neither recurrent skin lesions nor other systemic involvements during the 3-month follow-up period.

## Discussion

MMI is a preferred drug in the treatment of hyperthyroidism, except in particular conditions such as pregnancy, thyroid storm, and intolerance to the medication [2]. It blocks oxidation of iodine and inhibits synthesis of thyroxine and triiodothyronine [3]. Compared with PTU, it has a longer duration of action and a lower incidence of adverse reactions [4]. Major adverse reactions include agranulocytosis, hepatitis, and vasculitis. Clinical and laboratory monitoring is highly recommended while administering this medication. Our patient had taken MMI for 3 months before developing multiple nonblanchable erythematous macules and papules coalescing into plaques on the lower extremities. The remainder of the symptoms and signs was unremarkable. Histology and direct immunofluorescent study confirmed leukocytoclastic vasculitis.

Causes of cutaneous small vessel vasculitis can be categorized into 2 groups: infectious causes, which occur in 9.0–36.0% of cases, and noninfectious causes, which include multiple etiologies, with the most common etiologies being drug induced (8.6–36.0%) and idiopathic (15.4–29.7%) [5, 6]. Common culprit drugs include  $\beta$ -lactam antibiotics, sulfonamides, hydralazine, thiazides, allopurinol, retinoids, nonsteroidal anti-inflammatory drugs, and antithyroid agents [5]. Of the antithyroid agents, PTU is the most common cause, being approximately 40 times as frequent as MMI [7]. Other less common noninfectious causes include connective tissue diseases (6.4–25.0%) and malignancies (2.3–8.0%) [5, 6].

In our patient, a comprehensive workup was performed which ruled out infections, malignancy, and other systemic diseases. A possible alternative explanation is that thyroid disease itself can cause leukocytoclastic vasculitis via certain autoimmune processes as reported by Lionaki et al. [8]. In our patient, however, we believe that MMI is the most likely culprit as there was a strong temporal association between the timing of development of vasculitis and the administration of MMI as well as rapid resolution after MMI withdrawal. In addition, by the time the vasculitis resolved, thyrotoxicosis and an abnormal thyroid function test still persisted, making thyroid disease less likely to be the culprit.

In reviewing the literature, we found a total of 8 cases with MMI-induced leukocytoclastic vasculitis. Compared with PTU-induced vasculitis, this condition is exceedingly rare [9]. Its pathogenesis remains far from fully understood. Kawachi et al. [10] reported the first case of MMI-induced antineutrophil cytoplasmic antibodies (ANCA)-associated cutaneous vasculitis in 1995. The following cases confirmed the validity of the proposed pathogenesis which is related to the stimulation of a particular immune processes, leading to the production of ANCA [11–16]. However, Kanat et al. [17] reported a case with recurrent hyperthyroidism who developed ANCA-negative cutaneous small-vessel vasculitis after taking MMI (20 mg daily) for 1 week. Likewise, in our case, we could detect neither myeloperoxidase antibodies nor proteinase 3 antibodies. Due to the low molecular weight of MMI [18], the mechanism implicated in these ANCA-negative cases is more likely to be related to an immune complex-mediated process. Although previous studies have shed some light on the pathogenesis of drug-induced vasculitis [19], further studies are still needed for a deeper understanding of the mechanisms.

It is also interesting to note that most cases with MMI-induced leukocytoclastic vasculitis took many months to develop after the initiation of the medication. However, this is only true in individuals with no history of PTU exposure [12, 13]. In contrast, 4 reported cases [11, 14, 15, 17], who had a history of prior PTU administration, developed MMI-induced cutaneous vasculitis over a shorter period of exposure (i.e., approximately 1 week). Given their similar structures, cross-reactivity between PTU and MMI may exist to increase the risks of

leukocytoclastic vasculitis development. Therefore, it is important to rule out PTU exposure prior to diagnosing MMI-induced leukocytoclastic vasculitis.

In terms of management, the discontinuation of the culprit drugs in cases with highly suspected drug-induced vasculitis is crucial in order to prevent disease progression, which may lead to a life-threatening condition. The administration of immunosuppressive agents may be considered in cases with extensive cutaneous involvement or vital organ damage. These agents include prednisolone, cyclophosphamide, mycophenolate mofetil, methotrexate, and azathioprine [1, 20]. Our patient's cutaneous vasculitis dramatically resolved 1 week after the offending drug was withdrawn – without using an immunosuppressive agent. This is consistent with previous reports where the lesions completely resolved within a few weeks [7, 21]. She subsequently underwent radioiodine ablation as a definitive treatment of her hyperthyroidism. There were neither recurrent skin lesions nor other systemic involvements during the 3-month follow-up period.

### Conclusion

We report the first case of MMI-induced leukocytoclastic vasculitis in Thailand which developed 3 months after exposure to the culprit drug. The diagnosis of leukocytoclastic vasculitis was confirmed by both histopathology and direct immunofluorescent studies. MMI was discontinued and the lesions resolved completely 1 week after MMI withdrawal. She subsequently underwent radioiodine ablation as a definitive treatment, and no recurrence occurred after a 3-month follow-up. MMI-induced leukocytoclastic vasculitis is exceedingly rare; however, it should be kept on the differential diagnosis as a possible culprit drug in patients who are being treated for hyperthyroidism.

### Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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## Author Contributions

W.T. collected the data and wrote the initial manuscript draft. P.C. evaluated and revised the manuscript and acted as the corresponding author. All authors read and approved the final manuscript.

## Availability of Data and Materials

Please contact the authors for data requests.

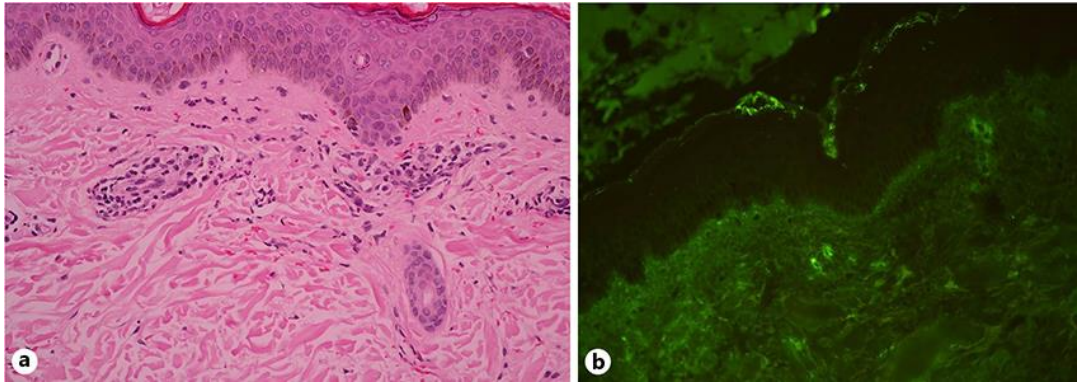
## References

- 1 Radić M, Martinović Kaliterna D, Radić J. Drug-induced vasculitis: a clinical and pathological review. *Neth J Med*. 2012 Jan;70(1):12–7.
- 2 Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid*. 2016 Oct;26(10):1343–1421.
- 3 Manna D, Roy G, Mughes G. Antithyroid drugs and their analogues: synthesis, structure, and mechanism of action. *Acc Chem Res*. 2013 Nov;46(11):2706–15.
- 4 Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. *Eur Thyroid J*. 2018 Aug;7(4):167–86.
- 5 Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol*. 2003 Mar;48(3):311–40.
- 6 Gota CE, Calabrese LH. Diagnosis and treatment of cutaneous leukocytoclastic vasculitis. *Int J Clin Rheumatol*. 2013;8(1):49–60.
- 7 Noh JY, Yasuda S, Sato S, Matsumoto M, Kunii Y, Noguchi Y, et al. Clinical characteristics of myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitis caused by antithyroid drugs. *J Clin Endocrinol Metab*. 2009 Aug;94(8):2806–11.
- 8 Lionaki S, Hogan SL, Falk RJ, Joy MS, Chin H, Jennette CE, et al. Association between thyroid disease and its treatment with ANCA small-vessel vasculitis: a case-control study. *Nephrol Dial Transplant*. 2007 Dec;22(12):3508–15.
- 9 Balavoine AS, Glinoe D, Dubucquoi S, Wemeau JL. Antineutrophil Cytoplasmic Antibody-Positive Small-Vessel Vasculitis Associated with Antithyroid Drug Therapy: How Significant Is the Clinical Problem? *Thyroid*. 2015 Dec;25(12):1273–81.
- 10 Kawachi Y, Nukaga H, Hoshino M, Iwata M, Otsuka F. ANCA-associated vasculitis and lupus-like syndrome caused by methimazole. *Clin Exp Dermatol*. 1995 Jul;20(4):345–7.
- 11 Koike KJ, Blice JP, Kylstra JA, Ralston JS, Self SE, Ruth NM, et al. Frosted branch angitis in methimazole-induced antineutrophil cytoplasmic antibody-positive vasculitis. *Retin Cases Brief Rep*. 2018;12(2):136–9.
- 12 Ribeiro CO, Magrin PF, Vilar EA, Durães SM, Estrella RR. Cutaneous leukocytoclastic vasculitis in the presence of methimazole therapy. *An Bras Dermatol*. 2013 Mar-Apr;88(2):283–6.
- 13 Shikha D, Harris J, Resta C, Park P. Antineutrophilic Cytoplasmic Antibody Positive Vasculitis Associated with Methimazole Use. *Case Rep Endocrinol*. 2015;2015:530319.
- 14 Thong HY, Chu CY, Chiu HC. Methimazole-induced antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and lupus-like syndrome with a cutaneous feature of vesiculo-bullous systemic lupus erythematosus. *Acta Derm Venereol*. 2002;82(3):206–8.
- 15 Ahmed K, Rao S, Simha V. Antineutrophil cytoplasmic antibody-positive vasculitis in a patient with Graves disease: cross-reaction between propylthiouracil and methimazole. *Endocr Pract*. 2010 May-Jun;16(3):449–51.
- 16 Tsai MH, Chang YL, Wu VC, Chang CC, Huang TS. Methimazole-induced pulmonary hemorrhage associated with antimyeloperoxidase-antineutrophil cytoplasmic antibody: a case report. *J Formos Med Assoc*. 2001 Nov;100(11):772–5.
- 17 Kanat M, Goksugur N, Parlak A. A case of methimazole induced leukocytoclastic vasculitis. *Turk J Endocrinol Metab*. 2005;4:125–7.
- 18 Kampmann JP, Hansen JM. Clinical pharmacokinetics of antithyroid drugs. *Clin Pharmacokinet*. 1981 Nov-Dec;6(6):401–28.
- 19 Grau RG. Drug-Induced Vasculitis: New Insights and a Changing Lineup of Suspects. *Curr Rheumatol Rep*. 2015 Dec;17(12):71.

- 20 Ortiz-Sanjuán F, Blanco R, Hernández JL, Pina T, González-Vela MC, Fernández-Llaca H, et al. Drug-associated cutaneous vasculitis: study of 239 patients from a single referral center. *J Rheumatol*. 2014 Nov;41(11):2201–7.
- 21 Gunton JE, Stiel J, Clifton-Bligh P, Wilmschurst E, McElduff A. Prevalence of positive anti-neutrophil cytoplasmic antibody (ANCA) in patients receiving anti-thyroid medication. *Eur J Endocrinol*. 2000 Jun;142(6):587.



**Fig. 1.** **a** Clinical features at presentation. Multiple small nonblanchable erythematous pruritic macules and papules on both lower legs. **b** Clinical improvement observed at 1-week follow-up. Resolution of skin lesions on both lower legs; remaining hyperpigmented macules.



**Fig. 2.** **a** Histology (HE,  $\times 400$ ) showing cell infiltration of vessel walls mainly composed of neutrophils and fibrinoid necrosis, nuclear dusts, as well as extravasation of red blood cells. **b** Direct immunofluorescence study ( $\times 400$ ) showing C3 deposition in superficial blood vessels.