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Cutaneous leukocytoclastic vasculitis induced by thiamazole

Short title: cLCV by Thiamazole

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Dear Editor,

Thiamazole (1-methy-2-mercaptoimidazole: MMI), antithyroid-drug (ATD) for Graves' disease, can cause side effects like antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis including nephritis.¹ We report a rare case of MMI-induced ANCA-negative cutaneous leukocytoclastic vasculitis (cLCV) and review five cases of ANCA-negative cLCV or nephritis induced by MMI, propylthiouracil (PTU), and carbimazole.¹⁻³

An 82-year-old woman had been on MMI for 2 years for Graves' ophthalmopathy. Four days before first visit, diffuse erythema appeared on her cheeks and all medications except MMI and levothyroxine sodium hydrate were discontinued. She presented with eyelid swelling and erythema with purpura on trunk and lower limbs (Figure 1a,b). Oral betamethasone (3 mg/day) and intravenous immunoglobulin (0.4 g/kg/day, 4 days) were administered. However, purpura spread to both lower legs (Figure 1c). Drug-induced lymphocyte stimulation test (DLST) was positive for MMI (294%). Myeloperoxidase-ANCA and proteinase-3-ANCA were normal. The skin biopsy of erythematous lesion revealed epidermis liquefaction degeneration. The skin biopsy of purpuric lesion confirmed LCV and epidermis liquefaction degeneration (Figure 1d). Direct immunofluorescence (DIF) test was negative. Two days after first

visit, MMI was discontinued and oral betamethasone was increased (5 mg/day). Skin lesions improved within a few days.

Drug-induced vasculitis is diagnosed by clinical symptoms and timing of therapy initiation and symptom appearance.¹ Re-exposure to the suspected drug is not recommended for associated risks. Because of an association between the timing of onset of vasculitis and administration of MMI, rapid resolution after MMI withdrawal and no infection, collagen disease, or cancer, our patient was diagnosed with MMI-induced ANCA-negative cLCV.

Mean age for the five reviewed cases of ATD-induced ANCA-negative cLCV or nephritis was 55.4 years. The duration from therapy initiation to development of these conditions ranged from 1 week to 6 years (mean: 1.8 years). (Supplementary table1)¹⁻³

The effect of ANCA on ATD-induced vasculitis is unclear. Recent studies on ANCA-positive and ANCA-negative eosinophilic granulomatosis with polyangiitis suggest the effects of genetic factors on ANCA and differences in organ lesions.⁴ ATD-induced cLCV can affect multiple organ systems;³ some ANCA-positive cases were reported to be fatal.³ However, our review could not find predictors of prognosis or early diagnosis. Moreover, PTU-induced ANCA-associated vasculitis revealed that

PTU-induced abnormalities in the conformation and impaired degradation of neutrophil extracellular traps are involved in myeloperoxidase-ANCA production and ANCA-associated vasculitis.⁵ In ANCA-associated vasculitis induced by direct activation of neutrophils by ANCA, immunoglobulin and complement components are undetected. Herein, DIF of one case revealed C3 deposition on the vessel walls (Supplementary table1). DLST, a test for delayed-type hypersensitivity (allergy type IV), of our case was positive. To confirm the involvement of allergy type III or IV in ATD-induced ANCA-negative cLCV, accumulation of similar cases is needed.

Tawanwongsri et al.² suggested cross-reactivity occurs between PTU and MMI owing to structural similarities with thionamide group.² However, some reports reported that a patient previously exposed to PTU developed MMI-induced cLCV and was then readministered PTU without side effects.^{1,2} MMI-induced cLCV may be specific to MMI; however, further investigations are needed.

Long-term ATD treatment can cause vasculitis. MMI therapy should be promptly discontinued, if cLCV occurs.

Conflict of Interest: None declared.

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Figure legend

Figure 1. Clinical and histopathological features of the patient.

(a) Conjunctival inflammation, swelling of the eyelid and bilateral symmetrical diffuse erythema on the face.

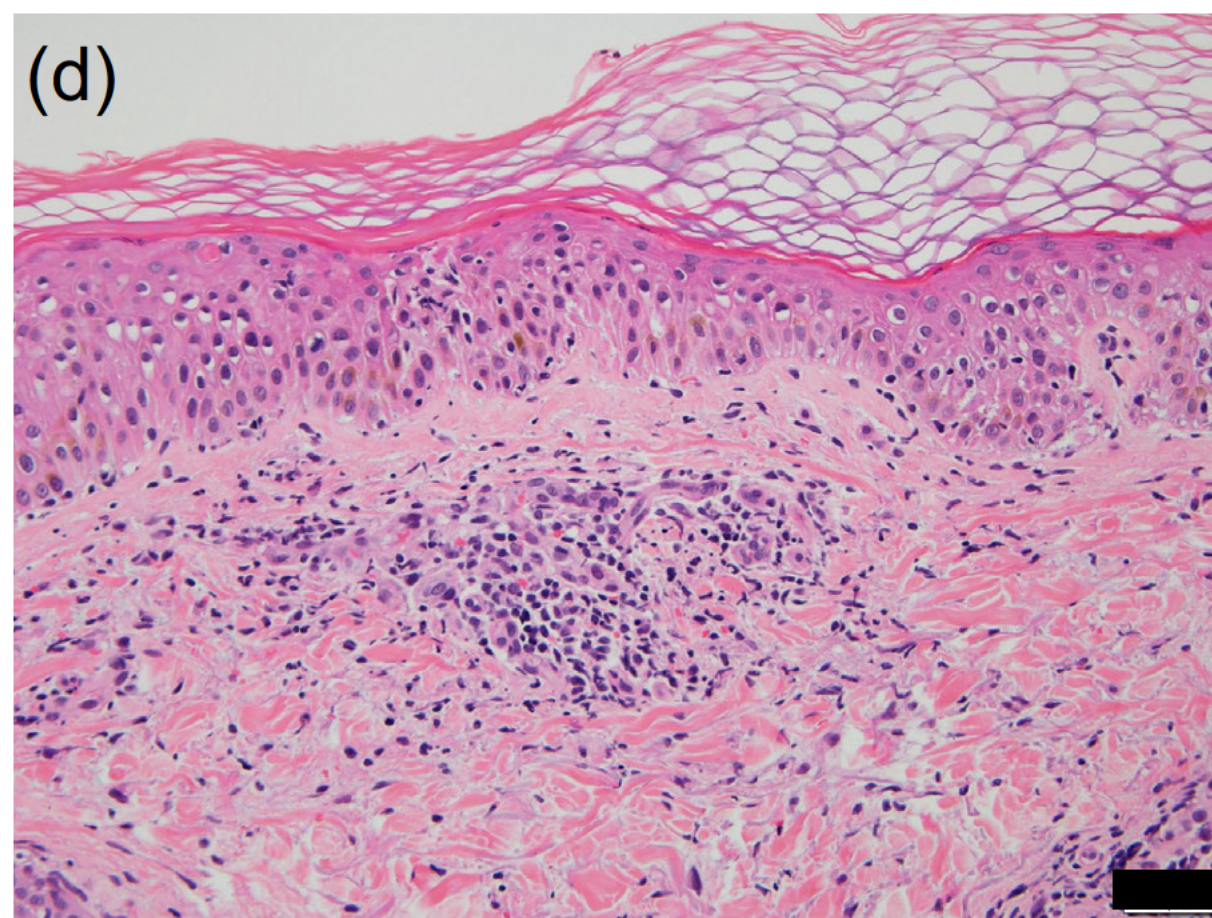
(b) Erythema with purpura surrounding normal island-shaped skin on the trunk.

(c) Erythema and palpable purpura on both legs.

(d) Histopathological analysis of leukocytoclastic vasculitis showing epidermis liquefaction degeneration, a few dyskeratotic cell in the epidermis, neutrophilic and lymphocytic perivascular infiltrates, fibrinoid necrosis, nuclear debris in the papillary dermis, and extravasation of red blood cells. (H&E staining, original magnification $\times 200$, scale bar = 50 μm).

Supplementary table 1

Clinical findings in published cases of antineutrophil cytoplasmic antibody -negative- cutaneous leukocytoclastic vasculitis (cLCV)/nephritis induced by antithyroid drugs, and those in the present patient.



Case	1	2	3	4	5	6
Author	Kanat et al ^{1, 2}	Day et al ¹	Trusau et al ³	Guo et al ¹	Tawanwongsri et al ²	Present patient
Age	56	72	66	27	41	82
Sex	M [¶]	M	F ^{††}	M	F	F
Underlying hyperthyroidism	Unspecified	Unspecified	Graves’ disease	Graves’ disease	Graves’ disease	Graves’ ophthalmopathy
PTU [‡] exposure history	2 years	–	–	–	–	–
Medication	MMI ^{‡‡}	Carbimazole	PTU	MMI	MMI	MMI
Duration [†]	1 week	2 weeks	4 years	6 months	6 years	2 years
Presence of rash	+	+	+	–	+	+
Findings of biopsy	cLCV ^{§ §}	1) cLCV 2) Nephritis	cLCV	Nephritis	cLCV	cLCV
DIF	N/A ^{¶¶}	–	–	N/A	Vascular wall (C3)	–
ANA [§]	–	–	+	+	–	+
C3 levels	WNL ^{†††}	WNL	N/A	Low	WNL	WNL
C4 levels	WNL	Low	N/A	WNL	WNL	WNL
Antiglomerular basement membrane positivity	N/A	–	N/A	–	N/A	N/A
Other findings	CRP ^{‡‡‡} : 2.37 mg/dl ESR ^{§ § §} : WNL	CRP: 11.4 mg/dl ESR: 25 mm/h Cre ^{¶¶¶} : 6.32 mg/dl	CRP: 4.79 mg/dl ESR: 33 mm/h	CRP: 14 mg/dl ESR: 119 mm/h Cre: 21.9 mg/dl SSA/SSB: –	ESR: 51 mm/h Cre: WNL	CRP: 9 mg/dl ESR: N/A Cre: 1.3 mg/dl
Treatment of cLCV/nephritis	① Discontinuation of MMI ② Oral prednisolone 40 mg/day	① Discontinuation of carbimazole ^{††††} ② HD ③ Oral prednisolone 30 mg/day	① Discontinuation of PTU ② Oral cyclophosphamide	① Discontinuation of MMI ② HD ③ IV dexamethasone and β-blockade	① Discontinuation of MMI ② Oral cholestyramine	① Discontinuation of MMI ② Oral betamethasone 5 mg/day ③ IVIg
Progress	Cutaneous rash improved	1) Cutaneous rash improved 2) HD dependent	Cutaneous rash improved	1) Pleural effusions resolved 2) HD dependent	Cutaneous rash improved	Cutaneous rash improved
Subsequent antithyroid therapy	Oral PTU	N/A	N/A	Total thyroidectomy and oral prednisone	Radioiodine ablation	Oral potassium iodide
Other test (i.e.,PT ^{‡‡‡‡} , DLST ^{§§§§})	PT: N/A DLST: N/A	PT: N/A DLST: N/A	PT: N/A DLST: N/A	PT: N/A DLST: N/A	PT: N/A DLST: N/A	PT: N/A DLST: MMI + (294%)

(e) Clinical findings of published cases of antineutrophil cytoplasmic antibody negative leukocytoclastic vasculitis/nephritis induced by antithyroid drugs, and those of the present patient.
†: Duration= from therapy initiation to the development of cLCV or nephritis, ‡: PTU= propylthiouracil, §: ANA= anti-nuclear antibody, ¶: M= male, ††:F= female, ‡‡ : MMI= thiamazole, §§: cLCV= cutaneous leukocytoclastic vasculitis, ¶¶: N/A= not applicable, †††: WNL= within nomal limits, ‡‡‡: CRP= C-reactive protein, §§§: ESR= erythrocyte sedimentation rate, ¶¶¶: Cre= creatinine, †††† : HD= hemodialysis, ‡‡‡‡: PT= patch test, §§§§: DLST= drug-induced lymphocyte stimulation test