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Letter to the Editor

Leukocytoclastic vasculitis with eosinophilic infiltration associated with thalidomide therapy for multiple myeloma: A case report

Dear Editor,

Thalidomide (Thal) has been shown to be effective in treating multiple myeloma (MM), erythema nodosum leprosum (ENL), and various autoimmune diseases through various mechanisms such as inhibition of growth factor secretion, activation of cytotoxic T and natural killer cells, and suppression of angiogenesis.¹ One report stated that leukocytoclastic vasculitis (LCV) associated with cryoglobulinemia was successfully treated with Thal.² In contrast, Thal has been reported to cause various adverse effects, including LCV.^{3–6} We herein describe for the first time a patient who developed LCV with eosinophilic infiltration during Thal treatment for MM.

In September 2014, a 76-year-old male having a history of hypertension and acute myocardial infarction presented with numbness in his lips and fingers. There were no neurological or physical abnormalities. Hematological and biochemical examination showed the following aberrant values: hemoglobin, 8.8 g/dL; total protein, 9.2 g/dL; immunoglobulin [Ig]A, 3000 mg/dL; and Ig light chain κ , 25.8 mg/L. The blood showed hyperviscosity. Bone-marrow aspirate analysis demonstrated that 20% of the total nucleated cells were composed of atypical plasma cells. Osteolytic changes in the spine, scapulae, clavicles, breastbone, costae, pelvic bone, and femurs were observed by ^{99m}Tc-methoxyisobutylisonitrile scintigraphy. Based on these findings, this case was diagnosed as MM (IgA/ κ type; Durie and Salmon staging system, III; International staging system, II). Treatment was started with weekly BD (bortezomib 2.2 mg/d sc, dexamethasone 20 mg/d po), followed by BCD (BD + cyclophosphamide 300–450 mg/d), and BRD (BD + revlimid 10 mg/d) chemotherapy, which caused side effects such as blepharidema and erythema, and was altered to VTD (Velcade = B + Thal 50 mg/d + D). Seven days later, Thal was administered on alternate days as drowsiness and erythema occurred. Although the erythema remained without exacerbation, the laboratory abnormalities gradually but considerably improved (e.g. IgA 3030 → 198 mg/dL). However, the cutaneous symptoms were remarkably exacerbated 140 days after starting VTD. He presented with ~10 mm macular palpable purpura without pruritus on the limbs and trunk (Fig. 1a). Blood data, including myeloperoxidase (MPO)/proteinase-3 (PR3)-anti-neutrophil cytoplasmic antibody (ANCA), the number of leukocytes and eosinophils, drug-induced lymphocyte stimulation test for Thal, and immune complexes, which were examined by C1q solid phase enzyme

immunoassay using labeled IgG, were normal. Histopathological examination of a purpura demonstrated perivascular infiltration of inflammatory cells consisting of eosinophils and neutrophils in the upper and middle dermal regions (Fig. 1b). Fibrinoid degeneration, leukocytoclasia, and erythrocyte extravasation were also observed. Thal was discontinued and treatment with external use of clobetasol propionate was started. The purpura resolved 7 days after withdrawal of Thal (Fig. 1c). When Thal was readministered, the purpura relapsed, and was immediately improved after elimination of Thal. Based on the clinical course, we diagnosed the cutaneous symptoms as the drug-induced LCV by Thal.

Vasculitis with eosinophilic infiltration can be found in eosinophilic granulomatosis with polyangiitis and recurrent cutaneous eosinophilic vasculitis. However, our case showed no characteristic clinical and laboratory findings of these diseases, such as bronchial asthma, eosinophilia, angioedema, or positive MPO-ANCA.

One report stated that cryoglobulinemia-induced LCV accompanied by MM was successfully managed with Thal.² It is possible that Thal was effective in treating MM and cryoglobulinemia, producing a concomitant response to LCV. In contrast, a few case reports have shown that LCV was induced after Thal administration to treat MM or ENL and disappeared immediately (~7 days) after discontinuation of the drug (Table 1).^{3–6} There is no description of eosinophils as infiltrating cells in these reports. Recruitment of eosinophils from the circulation requires adhesion to the endothelium, activation, and transmigration of the cells mediated by various eosinophilic and endothelial surface proteins.⁷ The cell surface expression of some of these proteins has been shown to be suppressed by Thal, probably inhibiting extravasation of inflammatory and myeloma cells.⁸ However, in this study, we have shown that considerable perivascular eosinophilic infiltration occurred during Thal administration, which was effective in suppressing the progress of MM, although peripheral eosinophilia was not observed. Eosinophils might have been attracted in and out of the dermal blood vessels through an unknown mechanism other than that associated with alteration in the expression of cell-adhesion proteins.

It seems reasonable to assume that Thal (or its metabolic product), which is a low-molecular compound and does not become an antigenic target in itself, gains antigenicity as a hapten by binding to a plasma or tissue protein to form an immune complex, causing a type III allergic reaction. In our case, however, this possibility seems less likely, since such an immune complex could not be detected in the blood. Neutrophils might have been recruited to the blood vessels through an unknown cell-mediated immunological mechanism which was induced by Thal, causing LCV cooperatively with eosinophils. Further analyses are necessary to

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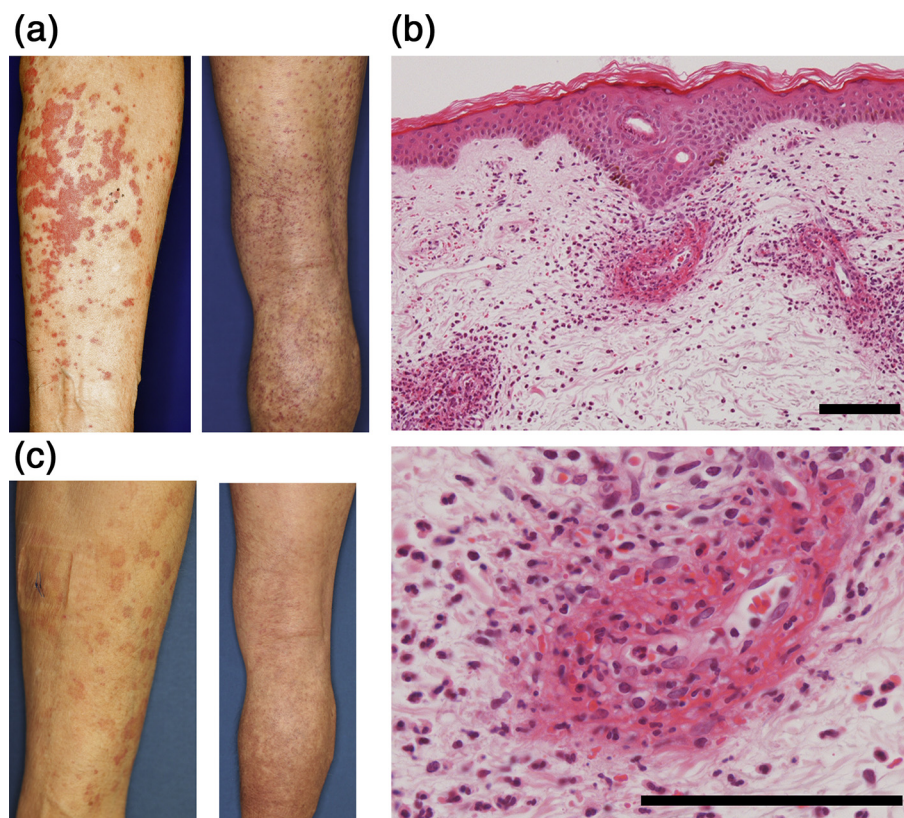


Fig. 1. (a) Clinical findings. Palpable purpura on the left forearm and right lower limb. The skin biopsy site is marked. (b) Histopathological observation of the skin biopsy, showing perivascular infiltration of eosinophils and neutrophils in the upper to middle dermal regions (hematoxylin–eosin staining, Bar = 100 μ m; original magnification, $\times 100$ (upper) and $\times 400$ (lower)). (c) Clinical findings 7 days after the withdrawal of Thal. The skin symptoms showed great improvement before suture removal.

Table 1
Cases of Thal-induced purpura.

Primary disease	Age	Sex	Time interval [†]	Infiltrating cell	Recovery period	Ref
MM	76	M	7 d	Eo, Neu	7 d	Our case
MM	62	M	4 m	nd	7 d	3
MM	48	M	4 m	nd	nd	4
MM	58	M	8 m	Neu	7 d	5
ENL	nd	nd	10 d	nd	nd	6

Abbreviations: d, day; ENL, erythema nodosum leprosum; Eo, eosinophil; M, male; MM, multiple myeloma; m, month; nd, no description; Neu, neutrophil; Ref, reference.

[†] Time interval means period before the onset of rash after Thal administration.

elucidate the underlying mechanisms of eosinophilic and neutrophilic infiltration.

To our knowledge, this is the first case showing Thal-induced LCV accompanied by eosinophilic infiltration. We should bear in mind that LCV can occur when Thal is used to treat MM, ENL and other autoimmune diseases.

Conflict of interest

The authors have no conflict of interest to declare.

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