Cutaneous Vasculitis After Ustekinumab Induction in Crohn's Disease

Key Words: Crohn's disease, ustekinumab, leukocytoclastic vasculitis, polyarteritis nodosa, cutaneous vasculitis

To the Editors,

Leukocytoclastic vasculitis (LCV) and cutaneous polyarteritis nodosa (cPAN) have been associated with inflammatory bowel disease (IBD).[1,2] However, it is unclear if the vasculitis in this setting is related to IBD itself or underlying therapy. Here, we present 3 cases of vasculitis in Crohn's disease (CD) after initiation of ustekinumab (UST) (Table 1).

Patient 1 is a 26-year-old woman with a 14-year history of Crohn's ileocolitis (previously treated with infliximab, mercaptopurine, and vedolizumab). She was started on UST after a hemicolectomy for a sigmoid stricture. Thirty-six days after her initial UST intravenous (IV) infusion, she presented with new palpable purpura involving both lower extremities (Fig. 1A). Skin biopsy revealed focal fibrin, neutrophils, and extravasated erythrocytes—consistent with LCV (Fig. 2A). She was started on colchicine with resolution of her rash and has been receiving UST for 1 year without further complications.

Patient 2 is a 29-year-old woman with a 6-year history of Crohn's ileocolitis with primary nonresponse to infliximab. Three months after induction with UST, she developed pink purpuric papules involving her bilateral upper and lower extremities (Fig. 1B). The appearance of the rash was consistent LCV. Prednisone resulted in complete resolution, and UST has been continued for 2 years without recurrence of her rash.

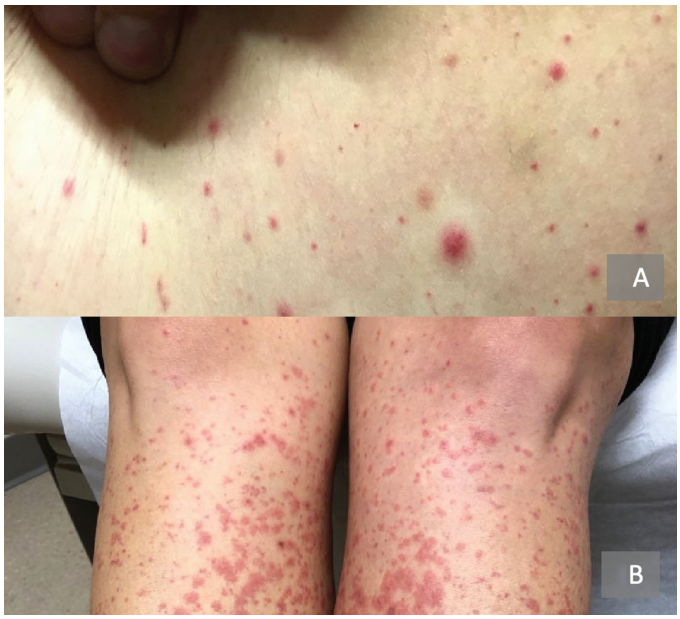

FIGURE 1. A, Rash of patient 1. Partially blanching, erythematous, nontender, nonpruritic macules, and papules over right medial thigh. B, Rash of patient 2. Pink purpuric papules and hemorrhagic vesicles involving bilateral shins. Dorsal feet, calves, and bilateral extensor forearms were also involved.

Patient 3 is an 18-year-old man with a 4-year history of small bowel CD with previous infliximab response (stopped due to paradoxical pustular psoriasis). Thirty-one days after initial UST induction dose, the patient developed new blanching red violaceous papules bilaterally on his medial insteps. Biopsy showed medium caliber vessel vasculitis with mixed neutrophilic and eosinophilic infiltrate concerning for cPAN (Fig. 2B). Ustekinumab was stopped. Two years later, he developed duodenal and jejunal strictures and was rechallenged with UST in combination with methotrexate. He has now been receiving UST for 22 months without recurrence.

Vasculitides have been associated with CD as extraintestinal manifestations and as side effects of therapy, particularly with antitumor necrosis factor agents.[3,4] There is only 1 previous case in the literature relating LCV to UST in an IBD patient.[5] Although it is possible to develop both LCV and cPAN in association with CD alone, our patients all had longstanding disease with their rash occurring only after receiving UST. We further demonstrate that the development of a vasculitic rash after UST therapy may be managed with targeted treatment of the vasculitis and continuing UST.

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TABLE 1. Detailed Patient Characteristics

	Patient 1	Patient 2	Patient 3
Age	26	29	18
Sex	Female	Female	Male
IBD type	Crohn's Disease	Crohn's Disease	Crohn's Disease
Area of IBD involvement	Ileum and colon	Ileum and colon	Duodenum and jejunum
Medications tried prior to UST	6-MP monotherapy, infliximab, and combination therapy with 6-MP and vedolizumab	Budesonide, mesalamine, and infliximab	Prednisone, mesalamine, infliximab
Time from first dose of UST to rash appearance	36 days	90 days	31 days
Diagnosis	Pathology from biopsy	Visual appearance	Pathology from biopsy
Lab results			
WBC count	8800 cells/μL	6600 cells/μL	18,000 cells/μL
CRP	41.5 mg/L	13.2 mg/L	112.28 mg/L
ANCA	Positive	Negative	Negative
ANA	Positive with titer of 1:80	Positive with titer of 1:80	Negative
Management of vasculitis	Colchicine	Prednisone	Discontinuation of UST
UST therapy	Continued without interruption	Continued without interruption	Restarted 1 year later
Recurrence of rash after restarting/continuing UST	No	No	No

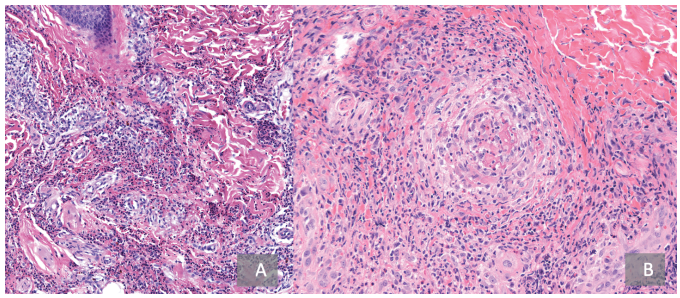

FIGURE 2. Pathology images. A, Patient 1 histology; 200x original magnification of hematoxylin and eosin–stained slide. Local fibrin, neutrophils, occasional eosinophils, and neutrophil fragments near vessels, in addition to extravasated erythrocytes and a mixed cellular infiltrate, consistent with leukocytoclastic vasculitis. B, Patient 3 histology; 200x original magnification of hematoxylin and eosin–stained slide. Left instep medium caliber vessel vasculitis with mixed neutrophilic and eosinophilic infiltrate and focal micropustule formation.

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Abbreviations: LCV, leukocytoclastic vasculitis; cPAN, cutaneous polyarteritis nodosa; IBD, inflammatory bowel disease; CD, Crohn's disease; IV, intravenous; UST, ustekinumab

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REFERENCES

1. Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatol.* 1997;136:706–713.
2. Ko JS, Uberti G, Napekoski K, et al. Cutaneous manifestations in inflammatory bowel disease: a single institutional study of non-neoplastic biopsies over 13 years. *J Cutan Pathol.* 2016;43:946–955.
3. Hagen JW, Swoger JM, Grandinetti LM. Cutaneous manifestations of Crohn disease. *Dermatol Clin.* 2015;33:417–431.
4. Cury DB, de Souza AW, Vianna GA, et al. Cutaneous vasculitis in a patient with Crohn's disease treated with adalimumab. *Inflamm Bowel Dis.* 2017;23:E1–E2.
5. Costa-Moreira P, Lopes S, Santos AL, et al. Leukocytoclastic vasculitis related to ustekinumab in a Crohn's disease patient: first case report and literature review. *J Crohns Colitis.* 2020;14:274–276.