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Leukocytoclastic vasculitis in an adolescent with ulcerative colitis: Report of a case and review of the literature

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Abstract

An adolescent female with long-standing, difficult-to-control ulcerative colitis developed leukocytoclastic vasculitis, a rare cutaneous extra-intestinal manifestation of the inflammatory bowel disease. The authors provide a literature review on leukocytoclastic vasculitis complicating ulcerative colitis. Furthermore, the clinical features of leukocytoclastic vasculitis are compared and contrasted with the more common cutaneous extra-intestinal manifestations of inflammatory bowel disease, erythema nodosum, and pyoderma gangrenosum.

Keywords

Leukocytoclastic vasculitis, ulcerative colitis, extra-intestinal manifestations

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Introduction

Overall, extra-intestinal manifestations (EIMs) of the inflammatory bowel disease (IBD) are common, being present more frequently in Crohn's disease (CD) (20%–40%) than in ulcerative colitis (UC) (15%–20%).[1–3] EIMs may affect the skeletal system (peripheral and axial arthritis), eyes (uveitis, episcleritis, and iridocyclitis), liver (sclerosing cholangitis and autoimmune hepatitis), and skin. The most common cutaneous manifestations of IBD are erythema nodosum (EN) and pyoderma gangrenosum (PG), although other less common skin manifestations have been reported, including psoriasis, Sweet's syndrome (*acute febrile neutrophilic dermatosis*), dermatitis herpetiformis, epidermolysis bullosa acquisita, necrotizing vasculitis, and leukocytoclastic vasculitis (LV). We present a case of LV complicating severe UC and review the literature on this rare association.

Written consent and assent for the case report were given by the mother and the patient, respectively. At our institution, a single case report does not require institutional review board (IRB) review. However, case reports must be prepared in accordance with the requirements of privacy regulations.

Patient report

A 12-year-old girl was admitted to the hospital with exacerbation of UC manifested as abdominal pain, arthralgia, vomiting, bloody diarrhea, and tenesmus. UC had been diagnosed 3.5 years earlier and had been difficult to control. She failed treatment with mesalamine and was steroid-dependent, necessitating therapy with infliximab, which she had been receiving for 2 years at 5 mg/kg every 8 weeks. Examination on admission was significant for mild tachycardia (126 bpm), normal blood pressure, pallor, absence of oral lesions, no joint swelling or erythema, no rashes, diffuse abdominal tenderness to palpation but no hepatosplenomegaly or masses, no perianal disease, and grossly bloody stool on digital examination. Laboratory evaluation showed a microcytic anemia (hemoglobin = 9.7 g/dL; mean corpuscular volume (MCV) = 66 fl), thrombocytosis (platelet count = 698,000/mm^3), and hypoalbuminemia (3.3 g/day); liver panel, serum electrolytes, C-reactive protein, erythrocyte sedimentation rate,

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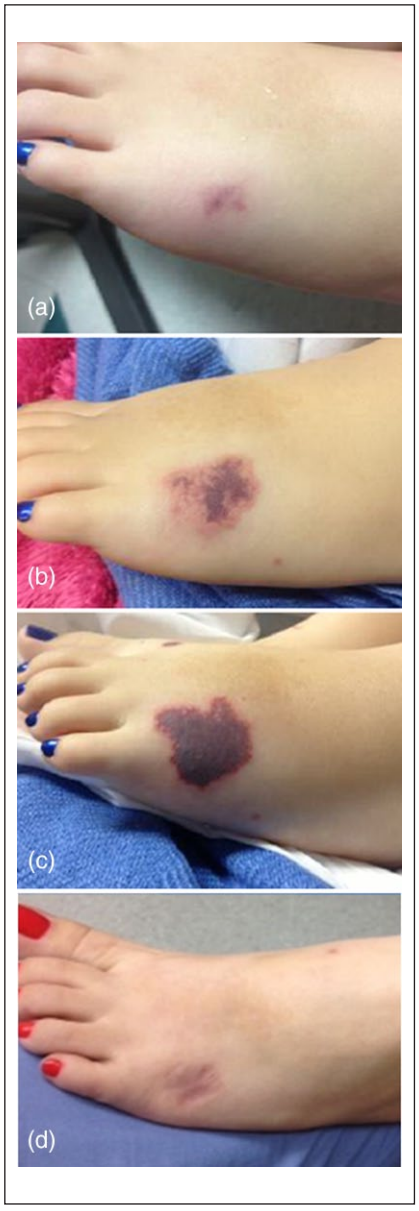

Figure 1. Leukocytoclastic vasculitis involving the foot. The photographs show the progression of the (a)–(c) vasculitis lesion and (d) the resulting scar.

stool culture, and *Clostridium difficile* toxin were all normal. Antibodies to infliximab were obtained and found to be positive. She was placed on intravenous fluids and Solu-Medrol (40 mg daily). She had improvement in abdominal pain and vomiting, but the diarrhea persisted. Colonoscopy showed severe chronic colitis involving the entire colon. On the fourth day of hospitalization, she developed frank arthritis of her left wrist and the metacarpophalangeal joint of her right index finger as well as a discrete non-blanching red plaque with surrounding edema over the metatarsophalangeal joint of her left fifth toe (Figure 1). The lesion grew rapidly over the next 3 days and became ecchymotic, with development of two smaller lesions on her left lower leg. The lesions eventually ulcerated, and a diagnosis of PG was made; scarring developed at the site of the lesion. Diarrhea improved, and she was discharged on oral steroids and adalimumab for treatment of colitis and ferrous sulfate.

She was successfully weaned from steroids over the next 6 weeks but experienced an allergic reaction to adalimumab after the third dose. Treatment was initiated with azathioprine (100 mg each evening), and therapeutic levels were attained. She remained asymptomatic for 5 months and then again developed abdominal pain and bloody diarrhea. Laboratory evaluation showed improvement in anemia (hemoglobin = 12.6 g/dL; MCV = 71 fl), persistent thrombocytosis (platelet count = 599,000/mm^3), and elevated C-reactive protein (3.9 mg/day, normal <0.5 mg/dL); liver panel, serum electrolytes, erythrocyte sedimentation rate, and stool culture were all normal. *Clostridium difficile* toxin was positive. She was admitted to the hospital for intravenous fluids; azathioprine was continued and metronidazole begun. Repeat colonoscopy showed marked worsening of the colitis, with development of diffuse pseudopolyps in the left colon (Figure 2). On the third day, she developed an ecchymotic rash at the site of her intravenous catheter (Figure 3). The catheter was removed for concerns of infiltration as the cause of the rash. The rash continued to progress, prompting a dermatology consultation. A punch biopsy was obtained and showed features of LV (Figure 4). She was started on oral prednisone for both colitis and vasculitis. The lesion

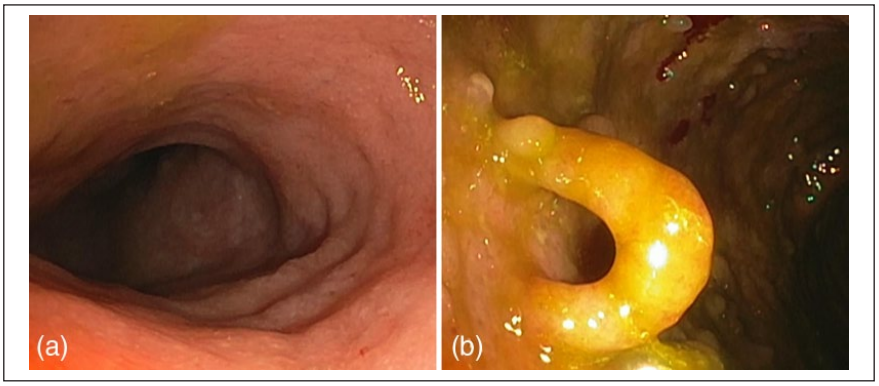

Figure 2. Colonoscopic findings: (a) Colonoscopy showed severe pancolitis with edema, loss of haustral folds, erythema, and friability. (b) There was more severe involvement of the left colon, with diffuse pseudopolyp formation and the presence of a mucosal bridge.

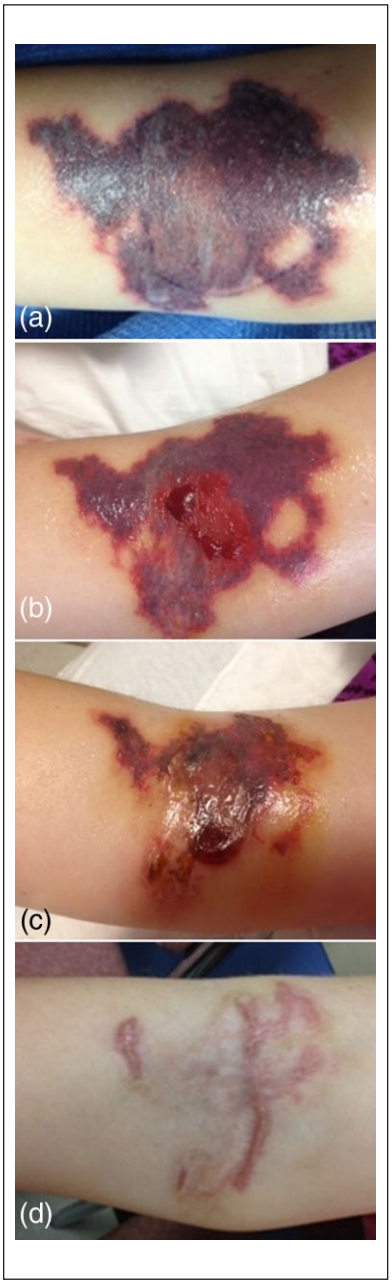

Figure 3. Leukocytoclastic vasculitis involving the arm. The photographs show the progression of the (a)–(c) vasculitis lesion and (d) the resulting scar.

eventually ulcerated and was treated with betadine, honey, and wet-to-dry dressings. The wound healed with significant linear hypertrophic scarring.

Over the next 3 months, she had repeated exacerbations of UC without recurrence of vasculitic lesions. She subsequently underwent total colectomy and creation of a J-pouch.

Discussion

Although IBD primarily affects the intestinal tract, EIMs are commonly seen involving the skeletal system, eyes, liver, and skin. The most common cutaneous EIMs seen in IBD are EN and PG. EN is more common than PG, affecting 10%–15% of patients with CD and 3%–10% of patients with UC. PG is found in 1%–2% of patients with IBD, regardless of the type.[1–7] Rare cutaneous EIMs of IBD include psoriasis, Sweet's syndrome (*acute febrile neutrophilic dermatosis*), dermatitis herpetiformis,[8] epidermolysis bullosa acquisita,[9] necrotizing vasculitis,[10] and LV.[10] To date, less than 20 cases of LV have been reported in patients with UC in the English literature (Table 1).[11–19] Review of these patients shows that LV occurs mostly in older patients, with the average age of reported patients being 40 years (median, 34 years; range, 16–68 years). There is a striking male predominance of nearly 5:1, a finding in contrast to EN (more common in women) and PG (no gender predisposition).[20,21]

The rash of LV has been variably described as erythematous papules or macules, annular purpuric macules, and multi-form purpuric target-like patches. These initial lesions may progress to hemorrhagic lesions with bullae or frank ulceration. Scarring or hyperpigmentation may develop with resolution of the rash. When LV presents as a purpuric rash, it must be distinguished from other purpuric lesions such as immune thrombocytopenia, thrombotic thrombocytopenia, and Henoch–Schönlein purpura.

Review of reported cases shows that rash may occur in multiple areas (58%) or at a single site (42%), with the most commonly involved sites being the lower extremities (83%), followed by upper extremities (42%), buttocks (25%), and trunk (25%).[11–19] Of interest, both EN and PG more commonly involve the lower extremities.[20,22,23] The patient described herein developed lesions at sites of trauma (feet and intravenous site) indicating pathergy, which has not been

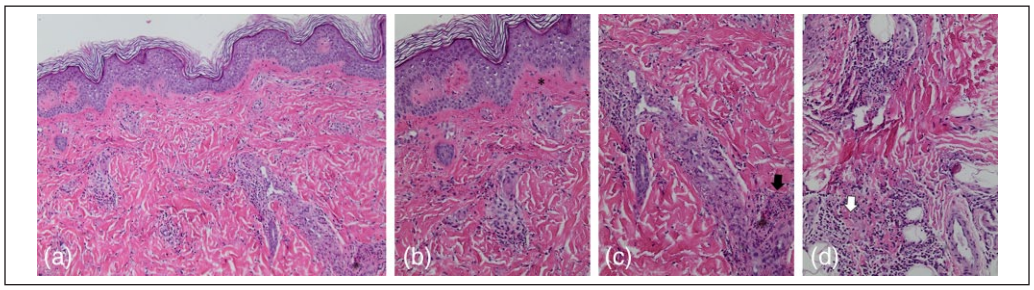

Figure 4. Histological findings of skin biopsy. (a) A punch biopsy of the lesion showed a dermal process consisting of a perivascular and intravascular infiltrate composed of polymorphonuclear leukocytes. (b) Higher magnification reveals red blood cell extravasation (asterisk), (c) the formation of nuclear dust (leukocytoclasis; black arrow), and (d) fibrinoid necrosis of vessel walls (white arrow).

Table 1. Review of demographics and clinical features of reported individuals with leukocytoclastic vasculitis complicating ulcerative colitis.

Reference (year)	Demographics		Onset of vasculitis in relation to ulcerative colitis			Other EIMs	Colonic involvement	Active disease	Location of rash			
	Gender	Age (year)	Prior[a]	Simultaneous	Following[b]				Upper extremities	Lower extremities	Buttocks	Trunk
Callen[11] (1979)	M	17			X (3 years)	None	nm	Y				X
Newton et al.[12] (1984)	M	61	X (1 month)			Sacroiliitis	Pancolitis	N/Y		X	X	
	M	68	X (6 months)			None	Pancolitis	N/Y	X	X		X
Peeters et al.[13] (1990)	M	35			X (11 years)	Sacroiliitis	s/p colectomy	N		X		
	M	50			X (20 years)	Sacroiliitis/ arthritis	"Distal"	N		X		
Cribier et al.[14] (1996)	M	60			X (12 years)	Spondyloarthritis	Rectosigmoid	Y	X	X		
Iannone et al.[15] (2003)	M	22	X (18 months)			Arthritis	Rectal	N/Y		X		
Akbulut et al.[16] (2008)	M	20	X (8 months)			Primary sclerosing cholangitis	Pancolitis	N/Y		X	X	
Tripodi Cutrì et al.[17] (2009)	M	33		X		Arthralgia	Rectosigmoid	Y	X	X	X	
Sipponen et al.[18] (2010)	M	28			X (4 months)	None	"Extensive"	Y		X		X
Hong et al.[19] (2011)	F	66			X (5 years)	None	nm	Y	X			
Present	F	16			X	Arthritis	Pancolitis	Y	X	X		

EIMs: extra-intestinal manifestations; nm: not mentioned.

[a]The time in parentheses is the time period between the initial episode of vasculitis and the diagnosis of ulcerative colitis.

[b]The time in parentheses is the time period between the initial diagnosis of ulcerative colitis and the first episode of vasculitis.

Table 2. Comparison and contrast among leukocytoclastic vasculitis, erythema nodosum, and pyoderma gangrenosum.

	Leukocytoclastic vasculitis	Erythema nodosum	Pyoderma gangrenosum
Gender predilection	Male	Female	None
Pathergy	Yes	No	Yes
Scarring	Yes	No	Yes
Primary affected location	Lower extremities	Lower extremities	Lower extremities
Colonic disease activity during rash	Active > quiescent	Active	Active ≫ quiescent
Relapsing course	Yes	Yes	Yes
Biopsy findings	Leukocytoclastic vasculitis	Panniculitis	Neutrophilic infiltrate
Proposed mechanism	Immune complex–mediated	Hypersensitivity reaction	Immune complex–mediated

described in previous reported cases associated with UC. However, this clinical finding is not surprising as pathergy is a well-described feature in LV unrelated to UC, as well as in PG; pathergy is not a feature of EN. Similarly, both LV and PG may develop scarring, while EN does not lead to scarring (Table 2). In reported cases, LV occurred alone in 33% of the patients and with another EIM in 66% of the patients. Arthritis or arthralgia was seen in 58% of the patients and sclerosing cholangitis in 8%.[11–19]

It appears that LV can occur during active colitis and during disease quiescence. The onset of LV occurred most commonly in patients with established UC (58%), with the rash occurring from 4 months to 20 years after the initial diagnosis of UC. In 33% of the patients, LV preceded clinical manifestations of UC by 1–18 months. Synchronous presentation of LV and UC occurred in one patient (8%).[11–19] Of the reported patients, LV manifested during active colitis in six patients (50%) and in the absence of colitis in two patients (17%). The other four patients (33%) initially developed LV prior to any symptoms of UC, but all developed recurrent LV with subsequent onset of active colitis.[11–19] In comparison, both EN and PG are usually related to exacerbation of colonic disease, although PG can present during quiescence of disease activity.[24,25] LV had a relapsing course in nearly half of the patients reported, similar to EN and PG.[26]

The development of LV does not appear to be related to the extent of colonic involvement with UC. In patients with LV and UC in whom the extent of colonic involvement was recorded, pancolitis was noted in 50%, distal colitis in 40%, and one patient (10%) developed LV following total colectomy.[12–17,19]

Differentiation of the different cutaneous EIMs of IBD may not be possible on clinical features and may necessitate a skin biopsy. The histological features of LV include infiltration of neutrophils and lymphocytes in and around the dermal blood vessels displaying leukocytoclasis, fibrin deposition in the vessels, fibrin thrombi, erythrocyte extravasation, and resultant epidermal necrosis. Skin biopsies in EN show a focal septal panniculitis,[23] characterized by neutrophil and lymphocyte infiltration of the subcutaneous septae.[27] PG is characterized by a dense dermal neutrophilic infiltrate, necrotizing suppurative inflammation, evidence of surface ulceration, mild perivascular infiltrate, and fibrinoid changes within blood vessels.[7,28]

The pathogenesis of LV is thought to be immune complex–mediated, similar to that of PG. In contrast, EN is thought to be due to a delayed hypersensitivity reaction.[20] It has been hypothesized that in LV associated with UC, the inflamed colonic mucosa allows fecal antigen exposure to submucosal lymphoid tissue, resulting in the formation of immune complexes.[17].The deposition of immune complexes in the vascular wall of small dermal vessels leads to complement activation, leukotaxis, release of lysosomal enzymes, and destruction of the vascular wall, resulting in erythrocyte extravasation and tissue necrosis.[29]

Treatment of LV complicating UC has included steroids, mesalamine, dapsone, colchicine, and infliximab. No single agent or combination of agents has given consistent results, and certainly none has been shown to be superior to the others. Treatment must be tailored to patients, with attention to the maintenance medications they may be receiving, as the treatment for LV and UC involves the same medications. Similar to EN and PG, treating underlying active colitis may be the key to improving the cutaneous lesions of LV.

Declaration of conflicting interests

None of the authors have any conflict of interest to report related to this article.

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References

1. Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. *World J Gastroenterol* 2003; 9: 2300–2307.
2. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011; 106: 110–119.

3. Bernstein CN, Blanchard JF, Rawsthorne P, et al. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001; 96: 1116–1122.
4. Orchard TR, Chua CN, Ahmad T, et al. Uveitis and erythema nodosum in inflammatory bowel disease: clinical features and the role of HLA genes. *Gastroenterology* 2002; 123: 714–718.
5. Farhi D, Cosnes J, Zizi N, et al. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. *Medicine (Baltimore)* 2008; 87: 281–293.
6. Yüksel I, Başar O, Ataseven H, et al. Mucocutaneous manifestations in inflammatory bowel disease. *Inflamm Bowel Dis* 2009; 15: 546–550.
7. Campbell S, Cripps S and Jewell DP. Therapy Insight: pyoderma gangrenosum-old disease, new management. *Nat Clin Pract Gastroenterol Hepatol* 2005; 2: 587–594.
8. Lambert D, Collet E, Foucher JL, et al. Dermatitis herpetiformis associated with ulcerative colitis. *Clin Exp Dermatol* 1991; 16: 458–459.
9. Smith PK, Davidson GP, Moore L, et al. Epidermolysis bullosa and severe ulcerative colitis in an infant. *J Pediatr* 1993; 122: 600–603.
10. Lotti TM, Comacchi C and Ghersetich I. Cutaneous necrotizing vasculitis. Relation to systemic disease. *Adv Exp Med Biol* 1999; 455: 115–125.
11. Callen JP. Severe cutaneous vasculitis complicating ulcerative colitis. *Arch Dermatol* 1979; 115: 226–227.
12. Newton JA, McGibbon DH and Marsden RA. Leucocytoclastic vasculitis and angio-oedema associated with inflammatory bowel disease. *Clin Exp Dermatol* 1984; 9: 618–623.
13. Peeters AJ, van den Wall Bake AW, Daha MR, et al. Inflammatory bowel disease and ankylosing spondylitis associated with cutaneous vasculitis, glomerulonephritis, and circulating IgA immune complexes. *Ann Rheum Dis* 1990; 49: 638–640.
14. Cribier B, Cuny JF, Schubert B, et al. Recurrent annular erythema with purpura: a new variant of leucocytoclastic vasculitis responsive to dapsone. *Br J Dermatol* 1996; 135: 972–975.
15. Iannone F, Scioscia C, Musio A, et al. Leucocytoclastic vasculitis as onset symptom of ulcerative colitis. *Ann Rheum Dis* 2003; 62: 785–786.
16. Akbulut S, Ozaslan E, Topal F, et al. Ulcerative colitis presenting as leukocytoclastic vasculitis of skin. *World J Gastroenterol* 2008; 14: 2448–2450.
17. Tripodi Cutrì F, Salerno R, Lo Schiavo A, et al. Ulcerative colitis associated with leukocytoclastic vasculitis of the skin. *Dig Liver Dis* 2009; 41: e42–e44.
18. Sipponen T, Virolainen S and Arkkila P. A patient with ulcerative colitis and an unusual rash. *Gastroenterology* 2010; 139: e5–e6.
19. Hong JS, Jin SP, Choi M, et al. Annular leukocytoclastic vasculitis in a patient with ulcerative colitis. *Ann Dermatol* 2011; 23(Suppl. 3): S338–S340.
20. Timani S and Mutasim DF. Skin manifestations of inflammatory bowel disease. *Clin Dermatol* 2008; 26: 265–273.
21. Trost LB and McDonnell JK. Important cutaneous manifestations of inflammatory bowel disease. *Postgrad Med J* 2005; 81: 580–585.
22. Larsen S, Bendtzen K and Nielsen OH. Extraintestinal manifestations of inflammatory bowel disease: epidemiology, diagnosis, and management. *Ann Med* 2010; 42: 97–114.
23. Agrawal D, Rukkannagari S and Kethu S. Pathogenesis and clinical approach to extraintestinal manifestations of inflammatory bowel disease. *Minerva Gastroenterol Dietol* 2007; 53: 233–248.
24. Mir-Madjlessi SH, Taylor JS and Farmer RG. Clinical course and evolution of erythema nodosum and pyoderma gangrenosum in chronic ulcerative colitis: a study of 42 patients. *Am J Gastroenterol* 1985; 80: 615–620.
25. Levitt MD, Ritchie JK, Lennard-Jones JE, et al. Pyoderma gangrenosum in inflammatory bowel disease. *Br J Surg* 1991; 78: 676–678.
26. Lakatos PL, Lakatos L, Kiss LS, et al. Treatment of extraintestinal manifestations in inflammatory bowel disease. *Digestion* 2012; 86(Suppl. 1): 28–35.
27. López San Román A, Bermejo F, Aldanondo I, et al. Pyoderma gangrenosum associated with ulcerative colitis: response to infliximab. *Rev Esp Enferm Dig* 2004; 96: 420–422; 422–424.
28. Crowson AN, Mihm MC Jr and Magro C. Pyoderma gangrenosum: a review. *J Cutan Pathol* 2003; 30: 97–107.
29. Claudy A. Pathogenesis of leukocytoclastic vasculitis. *Eur J Dermatol* 1998; 8: 75–79.