Received: 1 March 2020 | Revised: 14 April 2020 | Accepted: 20 April 2020

DOI: 10.1111/cup.13726

CASE REPORT

JOURNAL OF CUTANEOUS PATHOLOGY WILEY

Cutaneous arteriolitis: A novel cutaneous small vessel vasculitis disorder clinicopathologically different from cutaneous polyarteritis nodosa and cutaneous venulitis

Toshiyuki Yamamoto MD, PhD[1] | Ko-Ron Chen MD, PhD[2]

[1]Department of Dermatology, Fukushima Medical University, Fukushima, Japan

[2]Meguro Chen Dermatology Clinic, Tokyo, Japan

Correspondence
Toshiyuki Yamamoto, Department of Dermatology, Fukushima Medical University, Hikarigaoka 1, Fukushima 960-1295, Japan.
Email: toyamade@fmu.ac.jp

Abstract

Cutaneous vasculitis can be classified into two types based on the affected vessel size: small vessel vasculitis predominantly affecting dermal venules, and muscular vessel vasculitis as found in cutaneous arteritis predominantly affecting arteries located at the dermal-subcutaneous junction. We describe two cases with a novel small vessel vasculitis disorder, which exclusively affected arterioles in the mid-dermis, and show clinical and pathological difference distinct from cutaneous polyarteritis nodosa and cutaneous venulitis. Both patients were male, and presented with painful infiltrative plaques, involving the palms, soles, and thighs without extracutaneous involvement except for fever and arthralgia. Histopathological examination revealed vasculitis in the mid-dermis characterized by a predominant infiltration of neutrophils with vessel wall fibrinoid necrosis and leukocytoclasia identical to the features of leukocytoclastic vasculitis, except that the affected vessels were arterioles rather than venules. Serological examinations showed normal levels of serum complements, immune complexes, and antineutrophil cytoplasmic antibodies, and vasculitis disorders associated with systemic diseases were excluded in both patients. The patients showed a good response to short-term treatment with prednisolone up to 30 mg. This novel cutaneous arteriolitis clinicopathologically different from both cutaneous venulitis and cutaneous arteritis appears to be a skin-limited disorder.

KEYWORDS

cutaneous polyarteritis nodosa, cutaneous venulitis, mid-dermal arteriolitis

1 | INTRODUCTION

Based on the depth levels of vessels involved, vasculitis in the skin has been classified into dermal small vessel vasculitis and muscular vessel vasculitis, including cutaneous arteritis and phlebitis identified in the deep dermis to subcutis.[1,2] Cutaneous polyarteritis nodosa (cPAN), now renamed cutaneous arteritis,[3] is a vasculitic disorder involving muscular arteries in the skin,[1,3] and dermal small vessel vasculitis found in both skin-limited and systemic-associated disorders is almost confined to dermal venules.[4-13] Vasculitis with both dermal venulitis and muscular vessel vasculitis (cutaneous arteritis/phlebitis) could be identified in some systemic vasculitides[2] such as Behçet disease,[11,12] connective tissue diseases,[13] and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.[14] By contrast, it seems

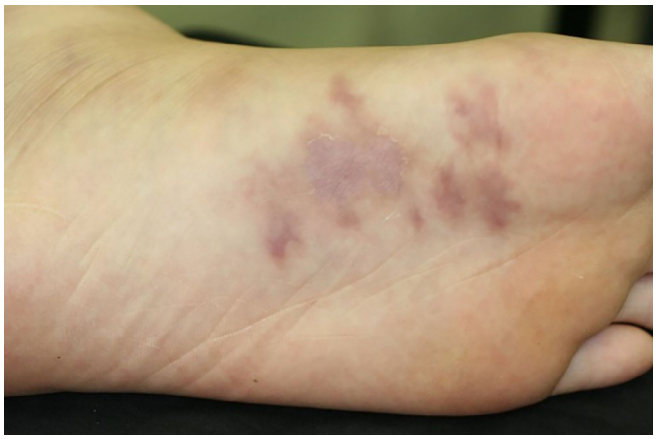

FIGURE 1 Clinical features showing a painful brownish plaque on the sole (case 1)

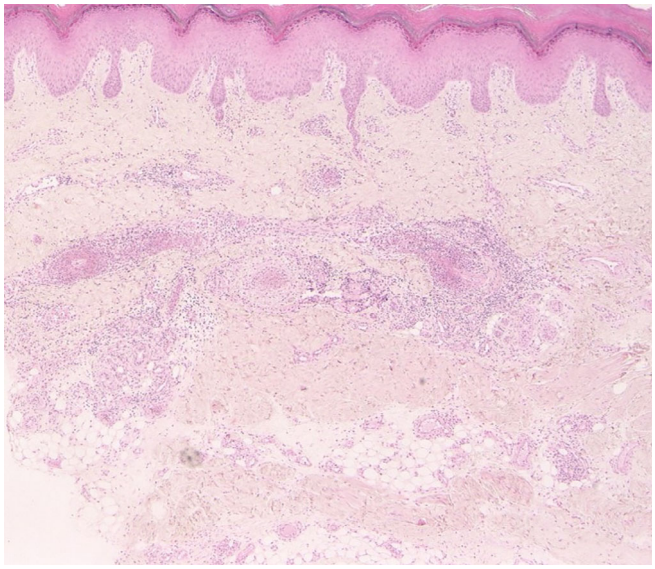

FIGURE 2 Biopsy specimen revealed vasculitis of an arteriole in the mid-dermis (hematoxylin and eosin [HE] stain, original magnification ×40)

that cutaneous vasculitis disorder predominantly involving dermal arterioles has not been mentioned previously.

Herein, we present a unique cutaneous vasculitis disorder, affecting arterioles of less than 100 μm in diameter in the mid-dermis in two male patients, and describe clinicopathological features of this novel dermal small vasculitis disorder distinct from either cPAN[1,2,15-18] or cutaneous venulitis, as seen in most vasculitides with dermal small vessel vasculitis.[1,4-13]

2 | CASE REPORT

2.1 | Case 1

A 22-year-old male developed painful erythematous lesions, joint pain of the wrist and ankle, and high fever up to 39°C following upper respiratory infection 2 months previously. He was initially treated with oral prednisolone (PSL, 15 mg/d). However, because the symptoms recurred after tapering of PSL, he was referred to our department. Physical examination showed tender erythematous plaques scattered on the bilateral palms, soles, and knees (Figure 1). Laboratory examination showed increased C-reactive protein (CRP) (14.29 mg/dL, normal<0.3) levels, white blood cell count (17 600/μL [normal range: 3800-9800], with 89% neutrophils, 4% lymphocytes, and 7% monocytes), and antistreptolysin O (ASO) (754 IU/mL; normal <166) levels. Antinuclear antibody (ANA) was 1:80, whereas neither MPO-ANCA nor PR3-ANCA was positive. Serum levels of complements, IgA, IgM, and IgG were all within normal ranges, and liver and renal functions were normal. Biopsy taken from the plantar lesion revealed leukocytoclastic vasculitis with a predominant infiltration of neutrophils and vessel wall fibrinoid necrosis at the vessels of the mid-dermis, indistinguishable from the features of leukocytoclastic vasculitis as seen in cutaneous necrotizing venulitis (Figures 2 and 3A). However, elastica van Gieson (EVG) staining revealed that a marked internal elastic lamina along the involved lumen with partial disruption indicating that the involved small vessel was an arteriole

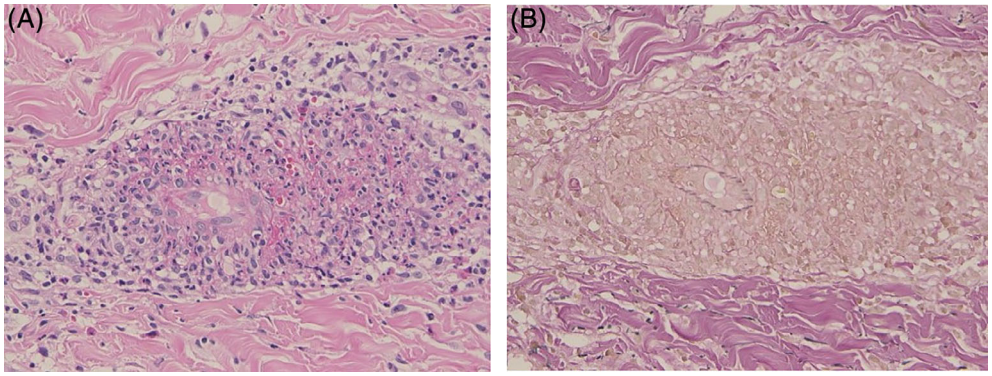

FIGURE 3 A, Higher magnification revealed leukocytoclastic vasculitis with a predominant infiltration of neutrophils and vessel wall fibrinoid necrosis at the vessels of the mid-dermis, indistinguishable from the features of leukocytoclastic vasculitis as seen in cutaneous necrotizing venulitis [HE stain, ×400]). B, Elastica van Gieson staining revealed a marked internal elastic lamina along the involved lumen, indicating that the involved small vessel was an arteriole rather than a venule (×400). HE, hematoxylin and eosin

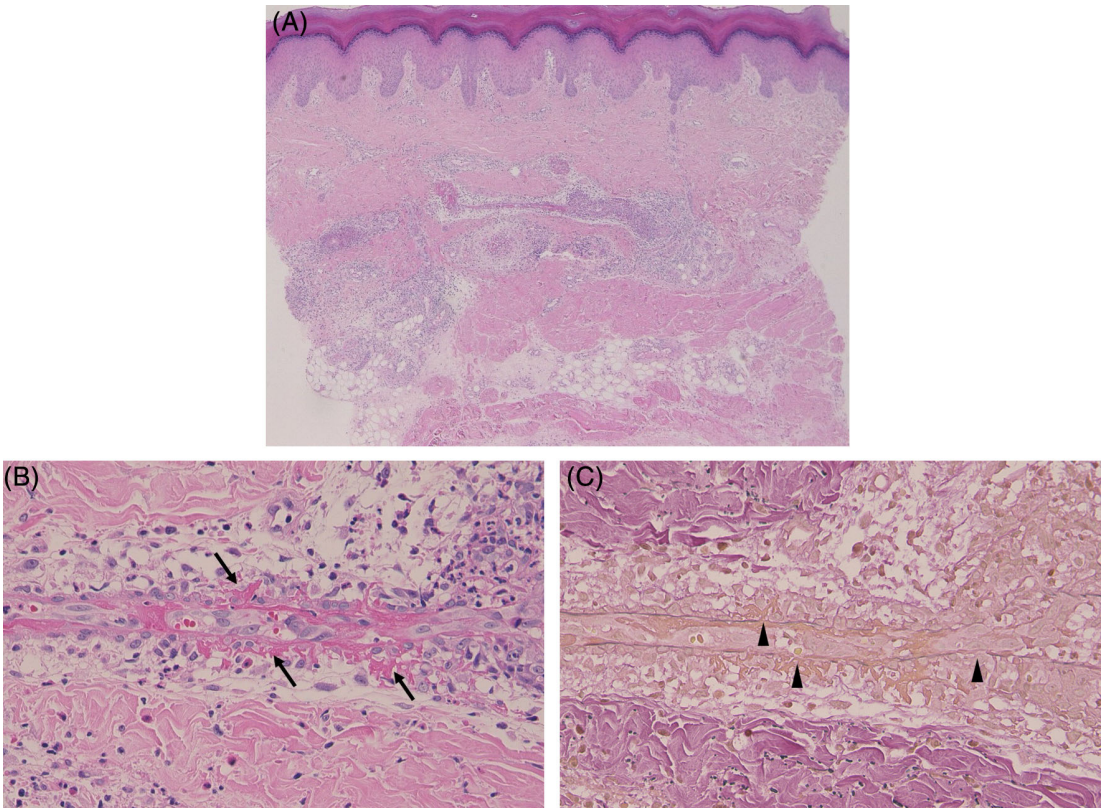

FIGURE 4 A, Serial section showed necrotizing arteriolitis in both longitudinal section and transverse section from the same affected arteriole (HE stain, ×400). B, Higher magnification showed longitudinal section of the affected arteriole having one to two muscular vessel layers and partial fibrinoid necrosis along the longitudinal arterial wall with discharge of fibrinoid necrosis (arrows) across the portion of disrupted internal elastic lamina into the perivascular area (HE stain, ×400). C, Elastica van Gieson staining showed disrupted internal elastic lamina (arrowheads) (×400). HE, hematoxylin and eosin. [Correction added on 10 August 2020, after first online publication: Figure 4C was incorrect and has been replaced in this current version.]

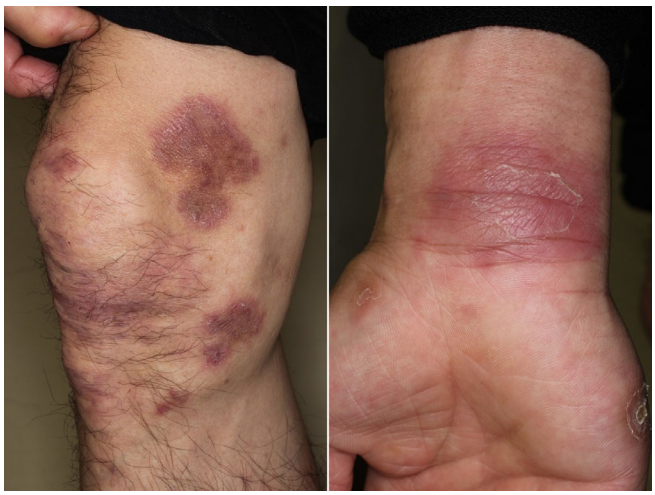

FIGURE 5 Clinical features showing dark reddish to brownish plaques on the thigh, knee, and wrist (case 2)

rather than a venule (Figure 3B). The longitudinal section showed the affected arterioles in the mid-dermis with one to two muscular vessel layers and partial fibrinoid necrosis along the longitudinal vessel wall (Figure 4A). Higher magnification showed discharge of fibrinoid necrosis through the portion of disrupted internal elastic lamina into the perivascular area in the mid-dermal arteriolitis (Figure 4B,C). A mild to moderate perivascular infiltration of mononuclear cells was also observed in both dermis and subcutis, but none of the deeper arteries located at the dermal-subcutaneous junction or subcutis were affected. On admission, detailed

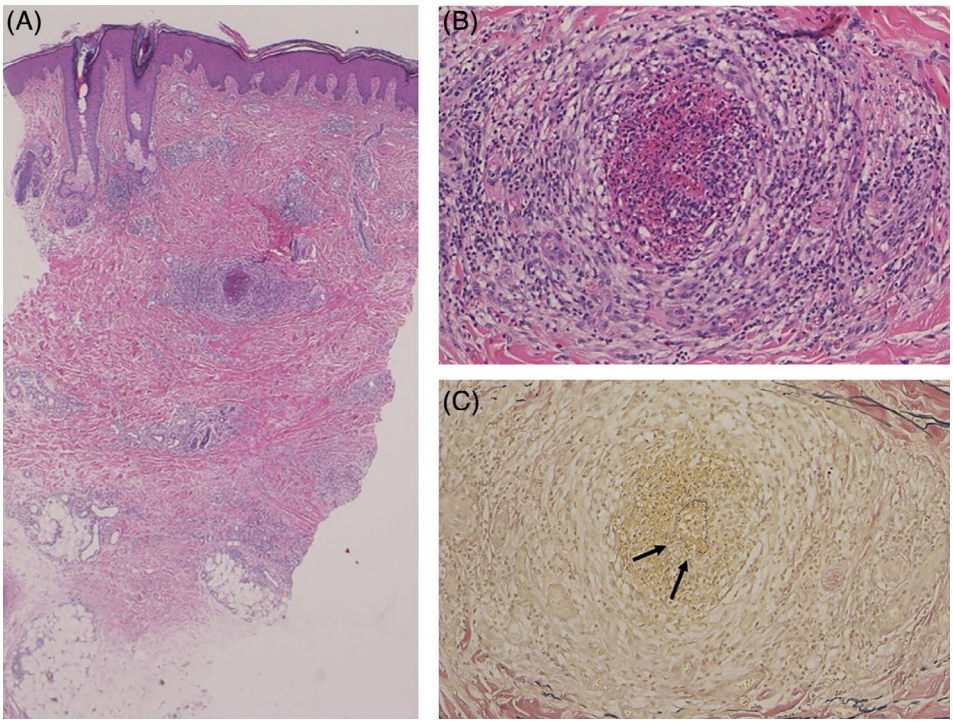

FIGURE 6 A, Histopathologic features showing small vessel vasculitis in the mid-dermis (HE stain, ×20). B, Higher magnification revealed leukocytoclastic vasculitis characterized by a marked infiltration of neutrophils with fibrinoid necrosis and nuclear dusts in and around the affected lumen mixed with peripheral infiltration of mononuclear cells (HE stain, ×400). C, Elastica van Gieson staining confirmed that the affected vessel was an arteriole and revealed partial disruption of the internal elastic lamina (arrows) (×400). HE, hematoxylin and eosin

TABLE 1 Comparison of the clinicopathological features between cutaneous arteritis and cutaneous arteriolitis

	Cutaneous arteritis (cPAN)	Cutaneous arteriolitis
Clinical features		
Age	Mean: 40s	2242 y.o.
Gender (M:F)	1:1.7 1:13 (M<F)	2:0
Site	Lower extremities	Palms, soles, wrist, thigh, and knee
Clinical features	Livedo reticularis, subcutaneous nodule, and ulcer	Tender erythematous plaque
Extracutaneous manifestation	Fever, malaise, arthralgia, myalgia, and neuropathy	Fever (1/2), arthralgia (2/2)
Histopathology		
Location of anglitis	Small-sized arteries at the dermal-subcutaneous junction	Arterioles in the mid-dermis
Diameter of vessels	200-400 μm	50-60 μm

Abbreviation: cPAN, cutaneous polyarteritis nodosa; F, female; M, male.

examination excluded internal organ involvement. The patient was successfully treated with oral PSL (30 mg/d), which was tapered and ceased within 2 weeks.

2.2 | Case 2

A 42-year-old male visited our department, complaining of painful plaques, which had appeared 1 month previously. Physical examination showed infiltrative dark reddish to brownish annular erythematous plaques on the right thigh, and wrist (Figure 5). Laboratory examination showed normal white blood cell count (9000/μL with 63% neutrophils, 27% lymphocytes, 2% eosinophils, 1% basophils, and 7% monocytes) and CRP level (0.29 mg/dL) was upper limit of normal ranges. Vasculitis-related serological examinations including ANA, MPO-ANCA, PR3-ANCA, complements, and IgA, IgM, and IgG levels were all within normal limits. Histological examination of the right knee revealed arteritis with fibrinoid necrosis in the mid-dermis (Figure 6A). A marked infiltration of neutrophils with fibrinoid necrosis and nuclear dust in and around the affected lumen mixed with peripheral infiltration of mononuclear cells was observed (Figure 6B). EVG staining revealed partial disruption of the internal elastic lamina of the affected vessel (Figure 6C). Vasculitis was not observed in either the lower dermis or the subcutis, but showed the same features as Case 1 with a mild to moderate perivascular infiltration of mononuclear cells in both dermis and subcutis. The patient was initially treated with oral PSL (15 mg/d); however, during the course, he complained of joint pain of the wrist, which was improved after escalation of the PSL dose to 30 mg/d.

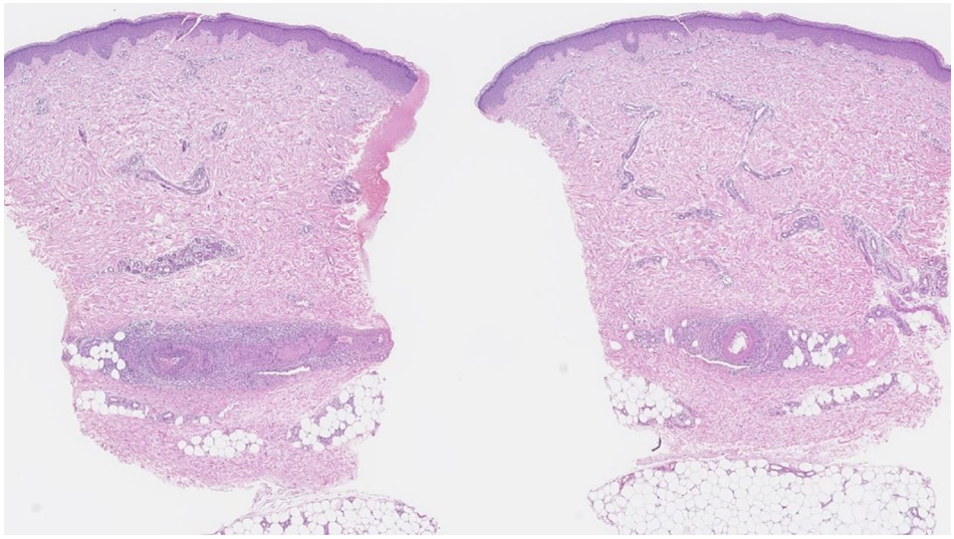

FIGURE 7 Histopathology of cPAN at dermal-subcutaneous junction. Longitudinal section (left) and transverse section (right) (×20). cPAN, cutaneous polyarteritis nodosa

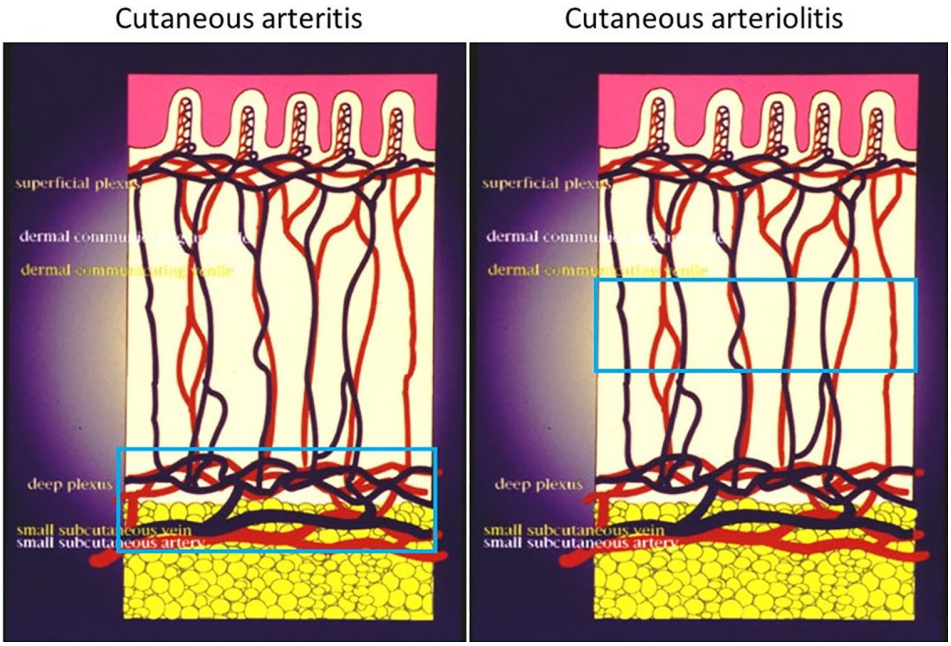

FIGURE 8 Comparison of the affected vessel levels (enclosed in a square) between cutaneous arteritis and cutaneous arteriolitis

3 | DISCUSSION

Since the first report by Lindberg[15] in 1931, cPAN is now widely accepted as a skin-limited disease involving small arteries ranging from 200 to 400 μm in diameter at the dermo-subcutaneous junction.[1,17,18] cPAN most often presents as multiple infiltrated erythema mixed with livedo racemosa and ulcerative lesions occasionally in the lower legs, and association of the underlying extracutaneous symptoms including myalgia, arthralgia, and peripheral neuropathy could be identified in areas of the affected skin lesions.[1,15-20]

Herein, we present two unique cases of a cutaneous arteritis disorder different from those with cutaneous arteritis. In both cases, the size of affected arterioles in the mid-dermis was 50 to 60 μm (less than 100 μm) in diameter, with one to two vascular smooth muscle layers (Figure 4B), which is obviously smaller than the vessels involved in cPAN ranging from 200 to 400 μm.[1,17,18] Case 1 developed infiltrative erythema on the palms and soles, and Case 2 developed painful infiltrative plaques on the thigh, knee, and wrist. The affected sites and manifestations of the skin lesions were also different from those seen in cPAN, showing multiple nodular or infiltrated erythema of 5 to 15 mm in size on the lower legs,[16-20] as shown in Table 1. Histopathological features of our cases showed that, in addition to the main lesion of necrotizing arteriolitis in mid-dermis, a mild to moderate perivascular mononuclear cell infiltration was also observed in both dermis and subcutis, which is also different from those of cPAN showing focal panniculitis around the affected artery and a mild perivascular lymphocytic infiltration in the overlying dermis.[16-20] Neither MPO-ANCA nor PR3-ANCA was positive, and neither patient had systemic

PAN, ANCA-associated vasculitis, and connective tissue diseases. Only Case 2 was under a long-term follow-up of 4 years without recurrence or development of systemic symptoms.

In comparison, histopathology of cPAN with longitudinal and transverse sections of the same involved artery at the dermal-subcutaneous junction is shown in Figure 7, which clearly shows that the affected vessels are located at the junction of the lower dermis and subcutaneous tissues, distinctly different from mid-dermal arteriolitis in the presented cases, as also shown in the schema of Figure 8.

As the two presented cases showed histopathological features of dermal leukocytoclastic vasculitis, cutaneous leukocytoclastic vasculitis, a most common form of skin-limited vasculitis disorder involving dermal venules predominantly should also be differentiated. It is indispensable to perform elastic tissue staining to confirm that the affected vessels are arterioles rather than venules, as histopathology with routine hematoxylin and eosin staining is unable to make this distinction, and shows the same morphologic changes of the affected dermal small vessels with the same features of leukocytoclastic vasculitis. The histopathological similarities between these two different cutaneous small vessel vasculitis disorders could explain why this unique cutaneous vasculitis disorder has not been previously reported.

Clinically, cutaneous necrotizing venulitis presents with erythematous to violaceous purpuric papules (palpable purpura), as well as macules, pustules, vesicles, hemorrhagic blisters, necrosis, and ulcers on the lower extremities.[2,4] In contrast, manifestations and affected sites of skin lesions in our two cases showed dark reddish to brownish infiltrated plaques with central pigmentation, as well as an annular, slightly elevated appearance arising at frictional areas such as the knees, wrist joints, and soles (Figures 1 and 5).*

In conclusion, based on the clinical and histopathological findings, the current report shows a distinct entity different from either cPAN or venulitis, the most common form of cutaneous small vessel vasculitis. This unique mid-dermal arteriolitis disorder may have previously been underreported or incorrectly diagnosed as cPAN or cutaneous venulitis. Our cases highlight the value of performing elastic fiber staining to confirm the possibility of this novel cutaneous small vessel vasculitis, when encountering cases with similar cutaneous manifestations and histopathological features of leukocytoclastic vasculitis in the mid-dermis. Further accumulation of similar cases is necessary to clarify the detailed characteristics of this new entity.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Toshiyuki Yamamoto https://orcid.org/0000-0002-8390-2573
Ko-Ron Chen https://orcid.org/0000-0001-5429-732X

*[Correction added on 10 August 2020, after first online publication: In the previous sentence, the citation of 'Figure 1 and 6' has been changed to 'Figure 1 and 5' in this current version.]

REFERENCES

1. Sunderkötter CH, Zelger B, Chen K-R, et al. Nomenclature of cutaneous vasculitis: dermatologic addendum to the 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheumatol*. 2018;70(2):171-184.
2. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol*. 2008;9(2):71-92.
3. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.
4. Soter NA. Cutaneous necrotizing venulitis. *Fitzpatrick's Dermatology*. 9th ed. New York: McGraw Hill Education; 2019:2527-2538.
5. Lotti T, Ghersetich I, Comacchi C, Jorizzo JL. Cutaneous small-vessel vasculitis. *J Am Acad Dermatol*. 1998;39(5 Pt1):667-687.
6. Teofoli P, Lotti T. Cytokines, fibrinolysis and vasculitis. *Int Angiol*. 1995;14(2):125-129.
7. Braverman IM, Yen A. Demonstration of immune complexes in spontaneous and histamine-induced lesions and in normal skin of patients with leukocytoclastic angiitis. *J Invest Dermatol*. 1975;64(2):105-112.
8. Gammon WR. Manifestations of drug reactions urticaria and cutaneous necrotizing venulitis. *Clin Dermatol*. 1986;4(1):50-57.
9. Soter NA, Mihm MC Jr, Dvorak HF, Austen KF. Cutaneous necrotizing venulitis: a sequential analysis of the morphological alterations occurring after mast cell degranulation in a patient with a unique syndrome. *Clin Exp Immunol*. 1978;32(1):46-58.
10. Soter NA, Mihm MC Jr, Gigli I, Dvorak HF, Austen KF. Two distinct cellular patterns in cutaneous necrotizing angiitis. *J Invest Dermatol*. 1976;66(6):344-350.
11. Chen KR, Kawahara Y, Miyakawa S, Nishikawa T. Cutaneous vasculitis in Behçet's disease: a clinical and histopathologic study of 20 patients. *J Am Acad Dermatol*. 1997;36(5 Pt1):689-696.
12. Misago N, Tada Y, Koarada S, Narisawa Y. Erythema nodosum-like lesions in Behçet's disease: a clinicopathological study of 26 cases. *Acta Derm Venereol*. 2012;92(6):681-686.
13. Chen KR, Toyohara A, Suzuki A, Miyakawa S. Clinical and histopathological spectrum of cutaneous vasculitis in rheumatoid arthritis. *Br J Dermatol*. 2002;147(5):905-913.
14. Chen KR. Skin involvement in ANCA-associated vasculitis. *Clin Exp Nephrol*. 2013;17(5):676-682.
15. Lindberg K. Ein Beitrag zur Kenntnis der Periarteritis nodosa. *Acta Med Scand*. 1931;76(1-2):183-225. https://doi.org/10.1111/j.0954-6820.1931.tb18345.x.
16. Chen K-R. Cutaneous polyarteritis nodosa: a clinical and histopathological study of 20 cases. *J Dermatol*. 1989;16(6):429-442.
17. Ishibashi M, Chen KR. A morphological study of evolution of cutaneous polyarteritis nodosa. *Am J Dermatopathol*. 2008;30(4):319-326.
18. Morimoto A, Chen K-R. Reappraisal of histopathology of cutaneous polyarteritis nodosa. *J Cutan Pathol*. 2016;43(12):1131-1138.
19. Daoud MS, Hutton KP, Gibson LE. Cutaneous periarteritis nodosa: a clinicopathological study of 79 cases. *Br J Dermatol*. 1997;136(5):706-713.
20. Díaz-Pérez JL, De Lagrán ZM, Díaz-Ramón JL, Winkelmann RK. Cutaneous polyarteritis nodosa. *Semin Cutan Med Surg*. 2007;26(2):77-86.

How to cite this article: Yamamoto T, Chen K-R. Cutaneous arteriolitis: A novel cutaneous small vessel vasculitis disorder clinicopathologically different from cutaneous polyarteritis nodosa and cutaneous venulitis. *J Cutan Pathol*. 2020;47(9):854–859. https://doi.org/10.1111/cup.13726