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RESEARCH ARTICLE

Cutaneous arteritis: Clinicopathological study of 21 cases

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Abstract

Objectives: We conducted this study to clarify the progress of cutaneous arteritis.

Methods: We examined 21 cases of cutaneous arteritis that were diagnosed at our hospital between 2005 and 2020. The male-to-female ratio was 1:6 with a mean age of 52.2 years.

Results: The lower legs were involved in all cases, and the upper extremities or trunk was also involved in some cases. Cutaneous manifestations presented as indurated erythema ($n = 15$), subcutaneous induration (11), edema (7), livedo (6), and ulcer (3). In addition, extracutaneous conditions including numbness (10), arthritis (8), fever (2), and myalgia (1) were observed. Laboratory tests showed an increase of inflammatory markers in most cases (14). Histopathological features showed necrotizing vasculitis of small-sized arteries at the dermo-subcutaneous junction, and the inflammatory stages of arteritis were histopathologically divided into acute stage (5), subacute stage (5), reparative stage (7), and healed stage (1). The therapies administered were oral prednisolone (11), antiplatelet drug (14), warfarin (1), non-steroidal anti-inflammatory drugs (6), biological drug (1), and other drugs (14). There were no cases showing progression to systemic polyarteritis nodosa during follow-up period. All three patients with ulceration complained of numbness, and one was revealed to have mononeuropathy multiplex. They were treated with low-dose oral prednisolone. Three ulceration cases were histopathologically classified into the acute and subacute stages.

Conclusions: In conclusion, all 21 patients followed a chronic course with recurrent skin lesions without systemic complications. Cases with ulceration seem to reveal neurological symptoms and need systemic steroid treatment.

KEYWORDS
cutaneous polyarteritis nodosa, numbness, therapy, ulcer

1 | INTRODUCTION

Cutaneous arteritis (cutaneous polyarteritis nodosa – cPAN) was originally described by Lindberg,[1] who reported a pediatric female case involving the lower legs. Although the pathogenesis of cutaneous arteritis remains unclear, the majority of cutaneous arteritis cases are not associated with systemic polyarteritis nodosa. Histopathology of cutaneous arteritis at the acute stage exhibits small arteritis with fibrinoid necrosis and infiltration of neutrophils with nuclear dusts in and around the vessel walls located at the junction of the dermis and subcutis. The arteries located in the dermis are usually not affected.

Cutaneous arteritis predominantly affects small arteries in the panniculus and at the dermal-subcutaneous junction.[2] The clinical features of cutaneous arteritis are livedo, small macules, or subcutaneous nodules, with or without ulceration.[3–5] To date, there have been several reports of a large or small number of case series of cutaneous arteritis.[6–12] Nevertheless, questions about whether cutaneous arteritis progresses into systemic polyarteritis nodosa still remain unsettled because this skin-limited arteritis disorder occasionally associates with underlying peripheral nerve or muscle involvement. We herein describe our experience of 21 cases of cutaneous arteritis at our hospital between 2005 and 2020 to reevaluate this unique chronic cutaneous arteritis disorder clinically and histopathologically.

2 | METHODS

Our study was approved by the institutional review board of Fukushima Medical University. We enrolled 21 patients with histopathologically proven cutaneous arteritis, and excluded those with positive anti-neutrophil cytoplasmic antibody (ANCA), cryoglobulinemia, and connective tissue diseases from database of vasculitis registered at the Department of Dermatology at Fukushima Medical University between 2005 and 2020. Vasculitis associated with possible causes, such as infection, drugs, and cancer, was also excluded. Clinical charts were retrospectively examined and patients' data, such as age, gender, involved sites, extracutaneous organ involvement, associated diseases, and symptoms such as fever, arthralgia, and myalgia, were also evaluated.

3 | RESULTS

Of the 21 patients, three were males and 18 females (M:F = 1:6). Their age ranged from 25 to 82 years, and the mean age was 52.2 years. All had skin lesions on the legs with lower legs limited in 10, both the upper and lower extremities in nine, and widespread involvement including the upper extremities and trunk in the remaining two cases. Clinical features were presented with indurated erythema ($n = 15$), subcutaneous nodules (11), edema (7), livedo (6), and ulcer (3) (Figure 1). Ten patients complained of numbness of the lower legs ($n = 7$) and upper extremities (3), in accordance with the involved sites, while peripheral polyneuropathy was revealed by neurological examination in two cases. Other clinical conditions were arthritis ($n = 8$), fever (2), and myalgia (1). Laboratory tests showed an increase in C-reactive protein (CRP) ($n = 13$), an elevated erythrocyte sedimentation rate (ESR) (11), and proteinuria (2). The antinuclear antibody was positive in two cases and rheumatoid factor was also positive in two cases, neither of them did not fulfill the criteria of rheumatic diseases. There were no cases that were positive for ANCA, anticardiolipin antibody, or antiphospholipid antibody. Direct immunofluorescence was performed in 13 cases, and IgG, IgA, or C3 deposition in the affected vessels was seen in six cases. The comorbidities were hypertension ($n = 3$), dyslipidemia (2), diabetes mellitus (2), thyroid dysfunction (1), autoimmune hypophysitis (1), orthopedic disease (6), and digestive system disease (5) including ulcerative colitis (1). The clinical characteristics are shown in Table 1. The histopathological features showed necrotizing vasculitis of small-sized arteries localized at the dermo-subcutaneous junction, without adjacent tissues involvement (Figure 2A). Higher

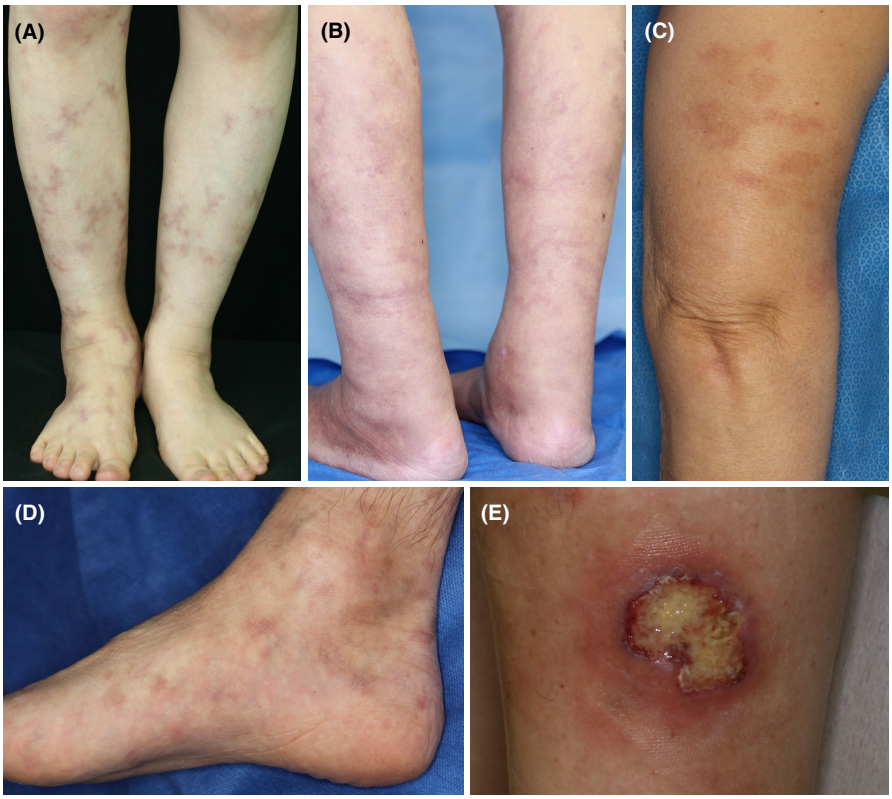

FIGURE 1 Clinical features of livedo, indurated erythema, subcutaneous nodules of the anterior and posterior aspects of the lower legs (A, B), upper extremity (C), dorsa of foot (D), and ulcer of the lower leg (E).

Gender	F:M = 18:3
Age (years old)	25–82 (mean age 52.2)
Location (*n*)	Lower extremity (21), upper extremity (11), trunk (2)
Clinical features (*n*)	Indurated erythema (15), subcutaneous induration (11), edema (7), livedo (6), ulcer (3), numbness (10), arthritis (8), fever (2), myalgia (1)
Comorbidities (*n*)	Hypertension (3), thyroid dysfunction (1), dyslipidemia (2), diabetes mellitus (2), autoimmune hypophysitis (1), orthopedic disease (6), digestive system disease (5)
Laboratory test (*n*)	Increase of CRP (13), elevation of ESR (11), proteinuria (2), positive of antinuclear antibody (2), positive of rheumatoid factor (2)

TABLE 1 Clinical characteristics of the 21 patients with cutaneous arteritis.

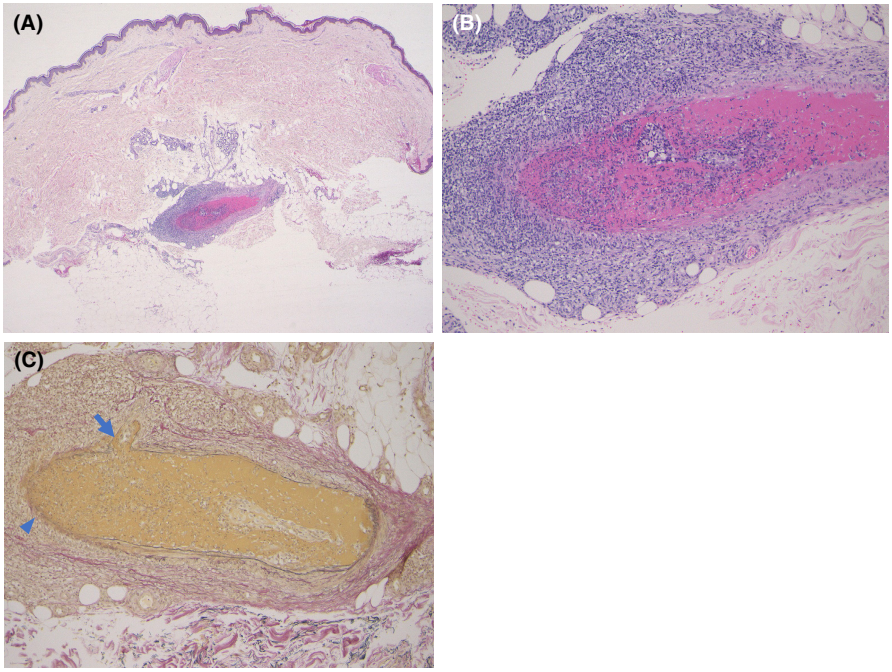

FIGURE 2 Histological features showing necrotizing arteritis of a longitudinal section of a small artery at dermo-subcutaneous junction (Hematoxylin–eosin stain, ×20) (A). Higher magnification revealed subintimal fibrinoid necrosis (Hematoxylin–eosin stain, ×100) (B). Partially disrupted internal elastic lamina (arrowhead) and the affected artery located at the site before merging into the right-angle connecting dermal small arteriole (arrow) (Elastica van Gieson stain, ×100) (C).

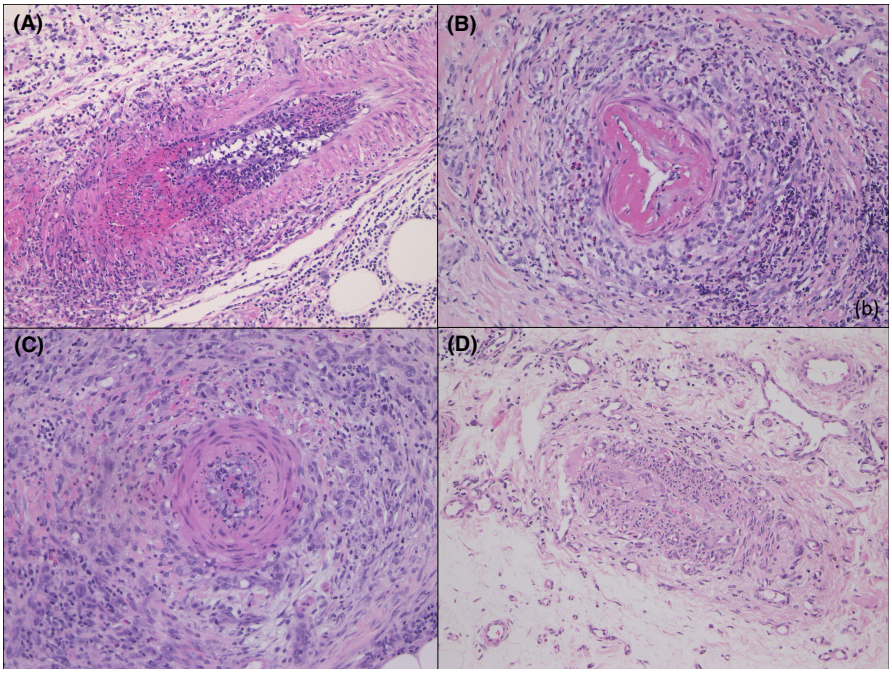

FIGURE 3 Histopathological features showing necrotizing vasculitis of small-sized arteries at the dermo-subcutaneous junction. Acute stage (A), subacute stage (B), reparative stage (C), and healed stage (D) (Hematoxylin–eosin stain, ×200).

magnification revealed fibrinoid deposition in the vessel walls infiltrated by neutrophils and lymphocytes, surrounded by a number of mononuclear cells (Figure 2B). Elastica van Gieson stain revealed partially disrupted internal elastic lamina (Figure 2C). Inflammatory evolution in cutaneous arteritis has been histopathologically divided into four stages (acute, subacute, reparative, and healed stages).[7] Our cases were five at the acute stage, five at the subacute stage, seven at the reparative stage, and the remaining one at the healed stage (Figure 3A–D). In one of the acute phase sections, infiltration of neutrophils with nuclear dusts, thrombus beneath the disrupted internal elastic lamina, and subendothelial fibrinoid necrosis were observed (Figure 3A). The affected artery located at the site before merging into the right-angle connecting dermal small arteriole (arrow in Figure 2C) is the most commonly affected site for cutaneous arteritis. The features of two different stages were seen in three cases (subacute and reparative stages in two cases and reparative and healed stage in one case). Therapy included oral prednisolone ($n=11$), antiplatelet drugs (14), warfarin (1), non-steroidal anti-inflammatory drugs (NSAIDs) (6), biological drugs (1), and other drugs such as oral vitamin E or prostaglandin E1 derivatives (14) (Table 2). The clinical symptoms were completely or partially improved in 15 cases, whereas obvious improvement was not observed in the remaining six cases. There were no cases with worsened symptoms or progression to systemic polyarteritis nodosa.

Three patients with ulceration were treated with oral prednisolone (10–40 mg/day) and continued taking prednisolone during the follow-up period. Numbness of the affected extremities was observed in all three cases with ulcers, and all were histopathologically classified into the acute ($n=2$) and subacute stages (1). We divided our patients into two groups with and without ulcers and evaluated the presence of numbness, use of oral prednisolone treatment, and histopathological stages; however, there was no significant difference between the two groups (Table 3).

TABLE 2 Therapies given to 21 patients with cutaneous arteritis.

	N	%
With treatment	19	90.5
Oral prednisolone	11	52.4
Antiplatelet drug	14	66.7
Warfarin	1	4.8
NSAIDs	6	28.6
Biological drug	1	4.8
Other drugs	14	66.7
Without treatment	1	4.8
Unknown	1	4.8

4 | COMMENT

Cutaneous arteritis presents with livedo, infiltrative small plaques, and subcutaneous nodules with or without ulceration, usually involving the lower extremities.[3–5] The name of cutaneous arteritis was coined by the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC2012) nomenclature.[2] Histopathologically, the affected arteries in cutaneous arteritis are small-sized arteries (diameter 200–400 μm) at the dermal-subcutaneous tissue junction. In a previous report of the largest series by Daoud et al.,[5] who collected 79 cases of cutaneous arteritis, painful nodules on the lower extremities with edema and swelling were the most common clinical findings, followed by livedo reticularis. Tender, infiltrative plaques were also observed. To date, several case series of cutaneous arteritis have been reported from Japan.[6–11] All studies have shown a female predominance, with varying male-to-female ratios of 1:2 to 1:13.[7–12] In the present study, we described 21 cases of cutaneous arteritis over a 16-year period. There were six times more female patients than male patients. The clinical features were presented with tender/non-tender erythematous nodules or infiltrative erythema on the lower extremities, occasionally in association with livedo racemose (Figure 1A–D). Ulcers were observed in three cases (Figure 1E), and we examined whether the presence of ulcers is associated with poor response to therapy or sequelae such as numbness; however, there were no significant differences between the groups with and without ulcers.

The cause of cutaneous arteritis remains still unknown. Hepatitis B virus (HBV) infection is suggested to be a cause of systemic polyarteritis nodosa. By contrast, the role of HBV infection in cutaneous arteritis remains unknown. There have been a few reported cases of cutaneous arteritis in patients with HBV carrier status.[13–15] It has

TABLE 3 Comparison between patients with and those without ulcers.

	With ulcer ($n=3$)	Without ulcer ($n=18$)
F:M	3:0	15:3
Numbness	3	7
Treatment with oral prednisolone	3	8
Histopathological stage (*n*)	Acute (2) Subacute (1)	Acute (3) Subacute (4) Reparative (7) Healed (1) Subacute + reparative (2) Reparative + healed (1)

also been speculated that HBs antigen-containing immune complexes induce the release of lysosomal enzymes by neutrophils and may cause vascular damage; however, HBV might have little relation to cutaneous arteritis.[3,4] In our series, HBV was detected in one case, which had a past history of HBV infection without either elevation of transaminase or reactivation of HBV.

Extra-cutaneous manifestations associated with cutaneous arteritis include edema, fever, numbness, paresthesia, neuropathy, myalgia, and arthralgia. In addition, comorbidities of cutaneous arteritis include inflammatory bowel disease, which was previously observed in 10% of 79 patients with cutaneous arteritis.[5] Only several cases of cutaneous arteritis associated with inflammatory bowel disease have been reported to date; however, in comparison with Crohn's disease,[16] cases of ulcerative colitis are rarely reported.[17] In the current study, three patients developed ulceration among 10 patients complaining of numbness, and all of them were treated with oral prednisolone.

Ishibashi and Chen[7] classified the histopathological findings of cutaneous arteritis into the acute stage, subacute stage, reparative stage, and healed stage. In their 18 specimens taken from 14 patients, the subacute stage was the most common (61%). In another study, the acute, subacute, and reparative stages were equally observed. Co-existence of different stages of arteritis has been commonly seen; however, in the present study, six cases were at the acute stage, five were at the subacute stage, seven were at the reparative stage, and two were in the healed stage. As inflammatory process of different stages of arteritis can occur at different individual skin lesions and different occasions,[8] we had performed biopsy from different sites in the same patient more frequently, coexistence of the different stages may have been observed.

Histopathological features of the acute stage show a prominent infiltration of neutrophils in and around the vessel walls with fibrin thrombi formation, partial loss of endothelial cells, and no obvious disruption of the internal elastic lamina. In one of our sections of the acute phase cutaneous arteritis, neutrophils with nuclear dusts and thrombi beneath the disrupted internal elastic lamina showed subendothelial fibrinoid necrosis (Figure 3A). Similar findings were reported by Morimoto and Chen.[8] Histopathological features of different stages, i.e., acute stage and late stage, are often observed in different biopsied sites. Macular arteritis is suggested to be a later stage of cutaneous arteritis, which lacks neutrophil infiltration within the vessel walls.

Unlike polyarteritis nodosa, cutaneous arteritis usually does not require intensive treatment. Systemic corticosteroids are usually not required, but sometimes used for neuropathy of the lower extremities. The principal treatment is the wearing of compression stockings, as well as oral NSAIDs, prostaglandin analogs, and antiplatelet agents. All our cases showed a benign course, without progression to systemic vasculitis.

There are several limitations in the current study. It was a retrospective study with a small number of cases in a single institute. Nevertheless, our case series may be useful as it consists of data from over 20 cases of cutaneous arteritis with a follow-up year up to 15 years in a single Japanese institution.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed in this study are included in this article, and not publicly available due to privacy data legislation. Further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

Approval of the research protocol: All procedures used in this research were approved by the Ethical Committee of Fukushima Medical University.

Informed Consent: N/A.

Registry and the Registration No: N/A.

Animal Studies: N/A.

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