Clin Exp Nephrol (2013) 17:676–682
DOI 10.1007/s10157-012-0736-x

REVIEW ARTICLE

The Asia Pacific Meeting of Vasculitis and ANCA Workshop 2012

Skin involvement in ANCA-associated vasculitis

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Received: 26 August 2012 / Accepted: 4 November 2012 / Published online: 28 November 2012

Abstract The skin is a common target organ in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Skin lesions may present as the initial manifestation or as the associated cutaneous manifestations in ANCA-associated vasculitis. Visually assessing the cutaneous manifestations and performing a biopsy of skin lesions to facilitate histopathologic confirmation are highly valuable diagnostically. Vasculitis (which affects dermal small vessels and subcutaneous muscular vessels) and nonvasculitic inflammation cause various types of skin lesions. The coexistence of different levels of vasculitis and nonvasculitis can occur in one or in several lesions or on different occasions. These puzzling clinical and histopathologic features may be closely related to the disease activity. Understanding the complicated clinical and histopathologic spectrum of skin lesions will contribute to the early diagnosis of ANCA-associated vasculitis with cutaneous complications.

Keywords Cutaneous vasculitis · Nonvasculitis · Diverse cutaneous manifestations · Dermal small-vessel vasculitis · Palpable purpura · Subcutaneous arteritis · Livedo racemosa

Introduction

Skin lesions, a common manifestation in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, occur in 60 % of patients with Churg–Strauss syndrome (CSS) [1–3], 40 % of patients with microscopic polyangiitis (MPA) [2, 4], and 20 % of patients with granulomatosis with polyangiitis (GPA) [5]. Coexistence of different levels of cutaneous vasculitis and nonvasculitis can occur in one or several lesions or on different occasions, which accounts for the diverse cutaneous manifestations appearing in patients with ANCA-associated vasculitis during the clinical course of the disease. [1]. Understanding the complicated histopathological features and related cutaneous manifestations is not easy but is necessary for handling patients with ANCA-associated vasculitis.

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Cutaneous vasculitis in ANCA-associated vasculitis

Cutaneous vasculitis in MPA, GPA, or CSS is generally described as dermal small-vessel vasculitis affecting dermal venules and (less commonly) arterioles; it most often presents clinically as palpable purpura in the legs [1–5] (Figs. 1a, 2a, 3b, 4a, 5c). Vasculitis of muscular vessels is relatively uncommon and presents clinically as livedo racemosa (Figs. 7a, 8a), as nodular erythema (Fig. 3d), or as subcutaneous nodules [1, 6]. Muscular vessels involved in subcutaneous arteritis are identical to the vessels involved in cutaneous polyarteritis nodosa. The coexistence of dermal small-vessel vasculitis and subcutaneous arteritis or phlebitis can occur in the same or different skin lesionsor on different occasions [7] (Figs. 1, 3, 9).

Dermal small-vessel vasculitis (i.e., venulitis and arteriolitis)

Neutrophilic vasculitis (i.e., leukocytoclastic vasculitis, characterized by a predominant infiltrate of neutrophils mixed with nuclear dust) is the most common histopathologic

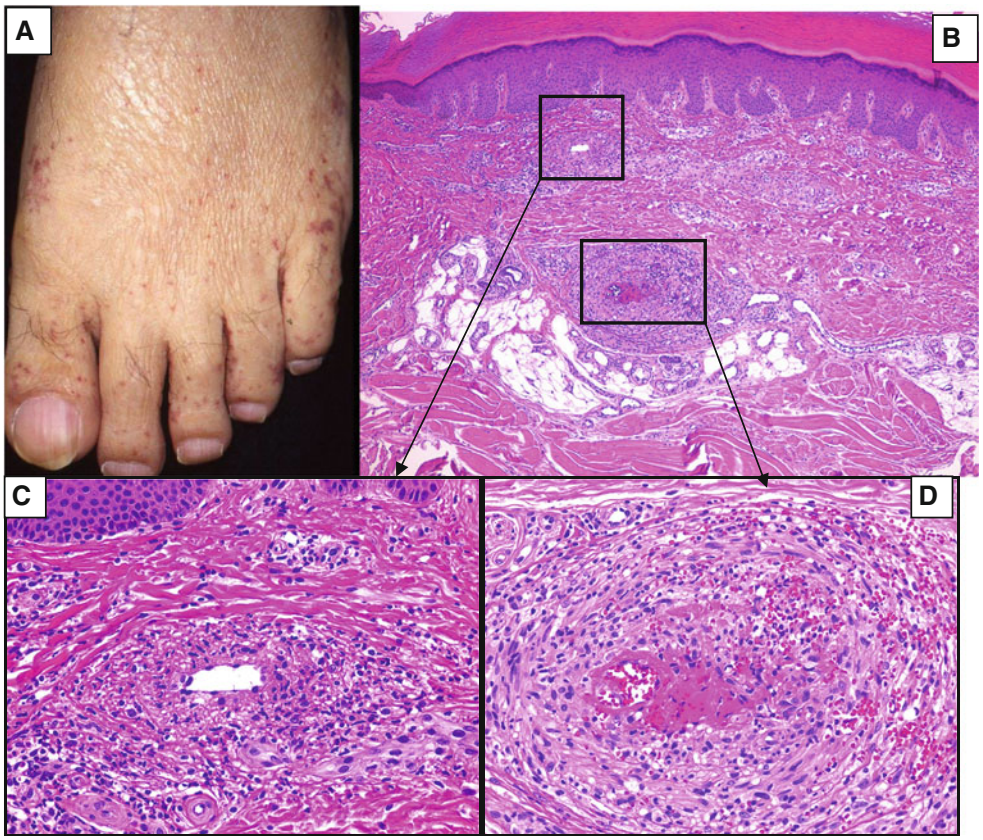

Fig. 1 **a** Microscopic polyangiitis (MPA) with palpable purpura and infiltrated erythema on the dorsal foot. **b** Coexistence of dermal leukocytoclastic vasculitis and arteritis at dermal–subcutaneous junction in the same lesion specimen. **c** Close-up view of dermal leukocytoclastic vasculitis. **d** Close-up view of arteritis

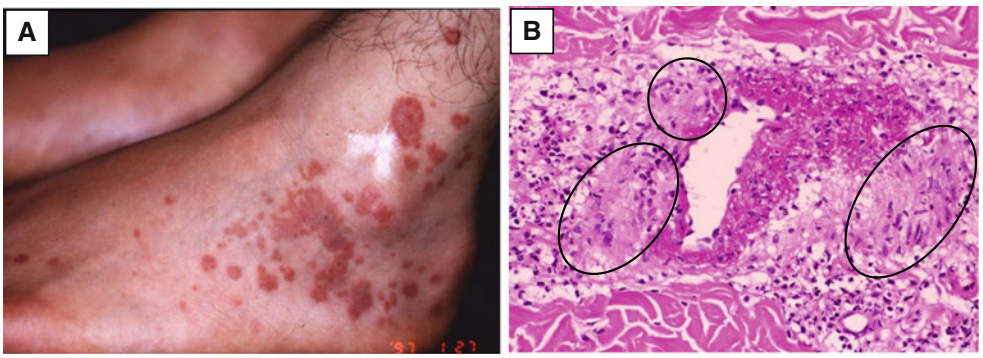

Fig. 2 **a** Granulomatosis with polyangiitis (GPA) with palpable purpura showing **b** histopathologic feature of leukocytoclastic vasculitis. Perivascular granulomas (*circles*) are a diagnostic clue for GPA

feature of both MPA (Fig. 1c) and GPA (Fig. 2b) and is an occasional feature of CSS (Figs. 3a, 5d). A unique feature of GPA is leukocytoclastic vasculitis surrounded by a granuloma or granulomatous inflammation (Fig. 2b). In CSS, two distinct types of vasculitis are present: either neutrophilic vasculitis (Fig. 3a) or eosinophilic vasculitis (Fig. 4b), based on the predominant inflammatory cells (Fig. 6). However, most cases of CSS involve a mixed infiltrate of neutrophils and eosinophils (Fig. 5d). Patients with histopathologically proven neutrophilic vasculitis are generally positive for myeloperoxidase (MPO)-ANCA [8, 9] and have renal involvement (Fig. 3), whereas patients with histopathologically proven eosinophilic vasculitis (Fig. 4) are usually negative for MPO–ANCA [8, 9] and do not have renal involvement (Fig. 6).

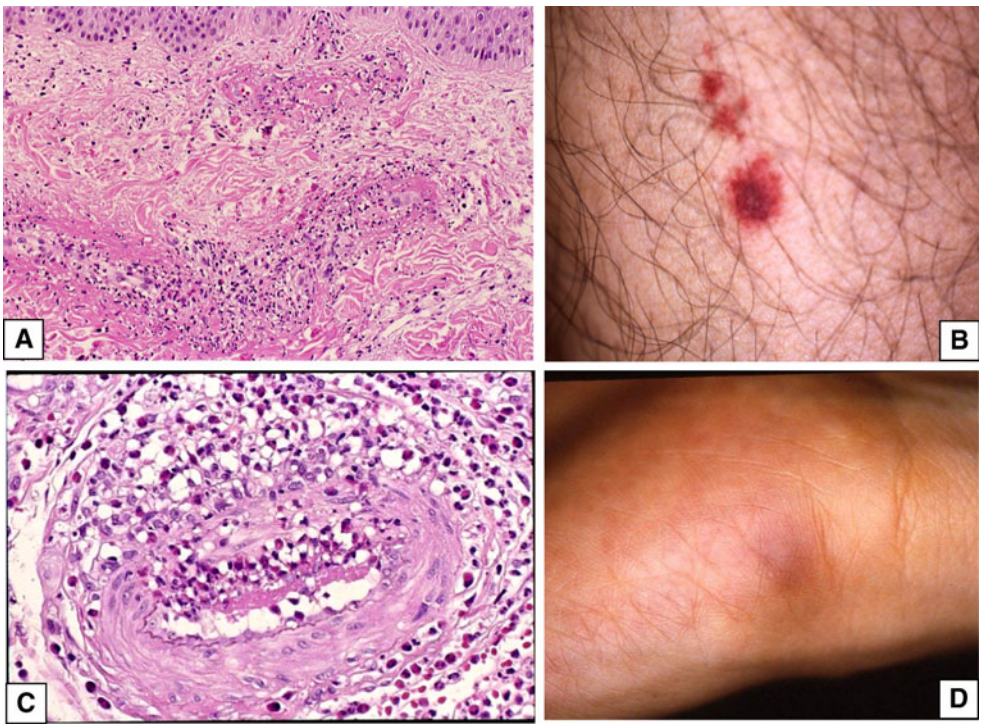

Fig. 3 Appearance of different types of vasculitis with different cutaneous manifestations appearing on different occasions in a patient with Churg–Strauss syndrome (CSS) who is positive for myeloperoxidase–antineutrophil cytoplasmic antibody (MPO–ANCA) and renal involvement. **a** Dermal small-vessel vasculitis (i.e., leukocytoclastic vasculitis). **b** Palpable purpura in dermal small-vessel vasculitis. **c** Deep dermal eosinophilic arteritis. **d** Deep dermal eosinophilic arteritis presenting as nodular erythema 18 days later

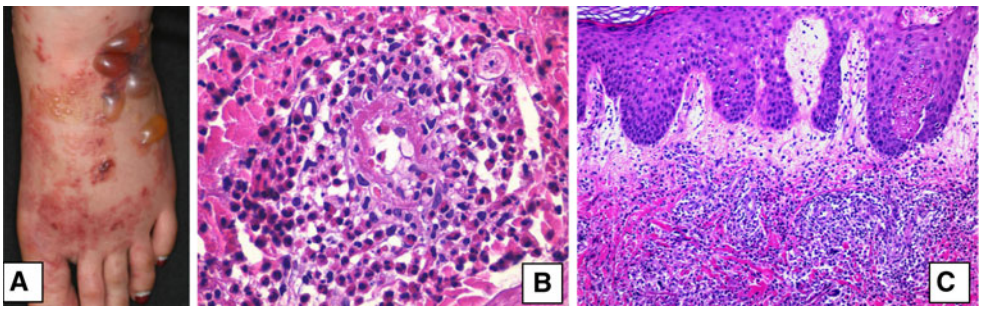

Fig. 4 **a** Coexistence of vasculitic and nonvasculitic lesions with different cutaneous manifestations on the dorsal foot of a patient with Churg–Strauss syndrome (CSS) who is negative for myeloperoxidase–antineutrophil cytoplasmic antibody (MPO–ANCA) and negative for renal involvement. **b** Histopathology of palpable purpura and hemorrhagic blisters shows dermal eosinophilic vasculitis with a predominant infiltrate of eosinophils without nuclear dust; this is distinct from leukocytoclastic vasculitis characterized by a predominant infiltrate of neutrophils with nuclear dust. **c** Histopathology of bullous lesions shows mixed dermal infiltrates of eosinophils, neutrophils, and histiocytes without evidence of vasculitis

Subcutaneous muscular-vessel vasculitis (i.e., subcutaneous arteritis or phlebitis)

Subcutaneous arteritis and phlebitis are both relatively rare. Subcutaneous arteritis in MPA has the identical clinicohistopathologic features of cutaneous polyarteritis nodosa (Fig. 7). However, the coexistence of overlying dermal venulitis can be present in the same biopsy specimen (Fig. 1). This phenomenon is not present in cutaneous polyarteritis nodosa [1, 7, 10]. The morphologic evolution of arteritis in CSS starts in the acute stage as eosinophilic arteritis (Fig. 3c). This is followed by granulomatous arteritis (Fig. 8b) and finally the healed stage [6]. Histopathologic features of eosinophilic arteritis and granulomatous arteritis

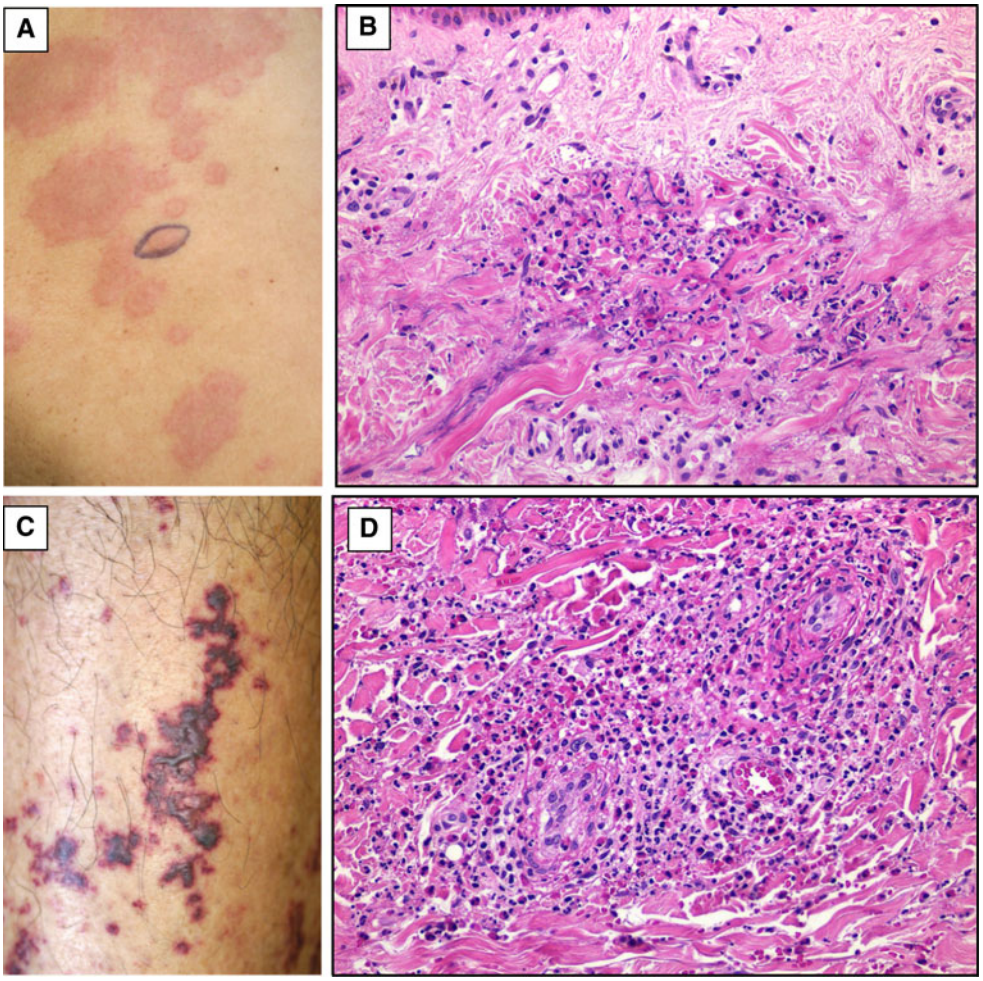

Fig. 5 Nonvasculitis and dermal small-vessel vasculitis lesions on different occasions in the same Churg–Strauss syndrome (CSS) patient. **a** Urticaria-like lesions comprise the nonvasculitis lesions. **b** Histopathology shows mixed dermal infiltrates of eosinophils, neutrophils, and histiocytes without evidence of vasculitis. **c** Palpable purpura with hemorrhagic blisters appear 8 days later in the dermal small-vessel vasculitis lesions. **d** Histopathology shows leukocytoclastic vasculitis with mixed infiltrates of neutrophils and eosinophils

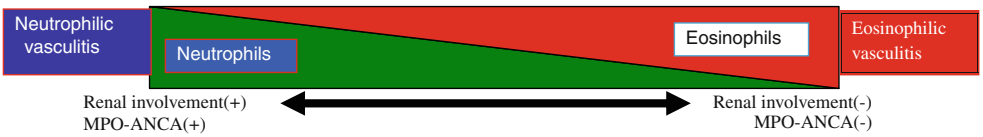

Fig. 6 Histopathologic spectrum of dermal small-vessel vasculitis and its relationship to renal involvement and myeloperoxidase–antineutrophil cytoplasmic antibody (MPO–ANCA) in Churg–Strauss syndrome (CSS)

mixed with an adjacent infiltrate of eosinophils are a diagnostic clue for CSS (Fig. 8b) [6, 7].

Coexistence of dermal small-vessel vasculitis and subcutaneous muscular-vessel vasculitis

The coexistence of dermal small-vessel vasculitis and subcutaneous arteritis or phlebitis in one or different skin lesions or on different occasions commonly occurs in skin lesions of patients with ANCA-associated vasculitis [1, 7] (Figs. 1, 3, 9).

Nonvasculitic skin lesions in ANCA-associated vasculitis

Nonvasculitic lesions show a mosaic of clinical features without the histopathologic evidence of vasculitis.

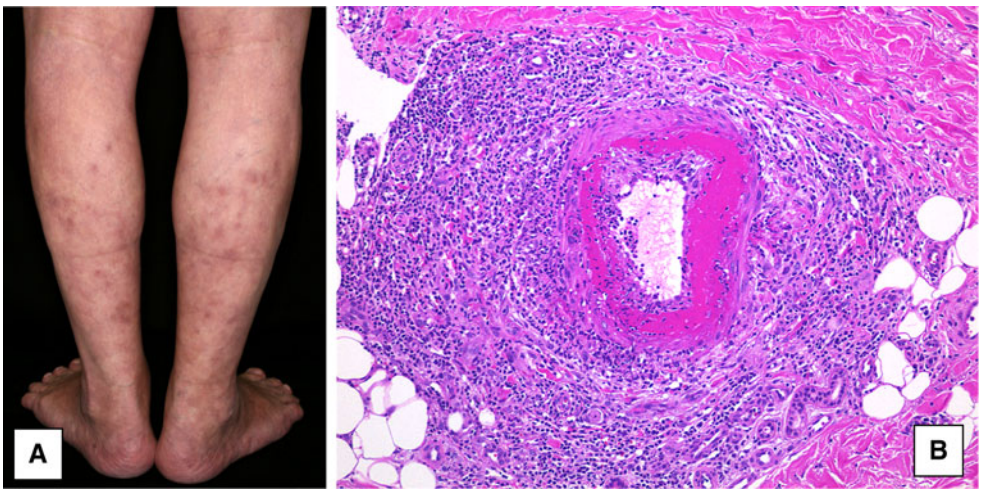

Fig. 7 **a** Infiltrated erythema with livedo racemosa in microscopic polyangiitis (MPA). **b** Histopathology shows necrotizing arteritis at the dermal–subcutaneous junction

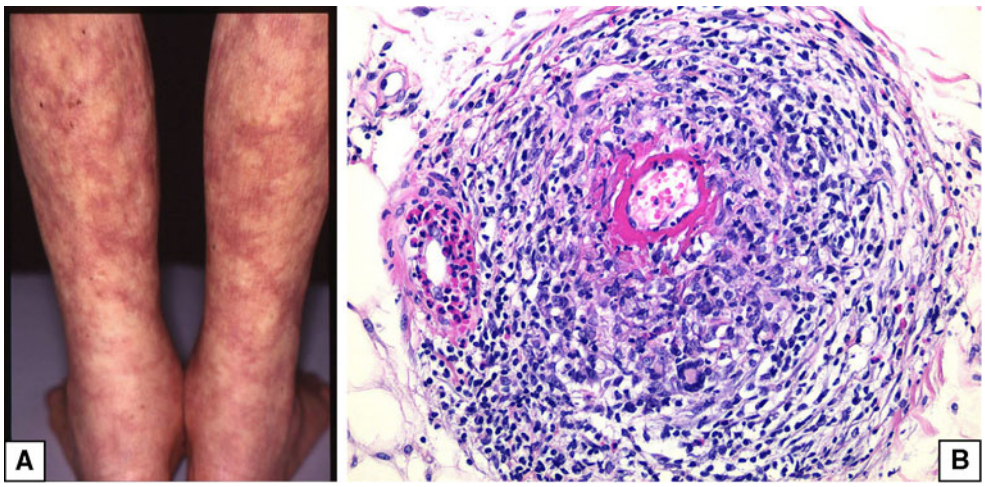

Fig. 8 **a** Livedo racemosa in a patient with Churg–Strauss syndrome (CSS). **b** Histopathology of livedo racemosa lesions shows the presence of subcutaneous granulomatous arteritis. Note the angiocentric infiltrate of histiocytes and multinucleated giant cells

Cutaneous manifestations of nonvasculitic lesions

The mosaic of cutaneous manifestations is bullae or vesicles (Fig. 4a), urticaria-like lesions (Fig. 5a), erythematous papules or plaques, erythema-multiforme-like lesions, and angioedema-like lesions (Fig. 4a) in CSS; pyoderma-gangrenosum-like lesions in GPA; and papules or nodules with an ulcerated or crusted center in GPA and in CSS. Histopathologic features of nonvasculitic lesions are the following:

Dermal perivascular infiltrate of neutrophils or eosinophils without evidence of vasculitis

Biopsies of specimens obtained from urticaria-like lesions, erythematous papule plaques, erythema-multiforme-like lesions, and angioedema-like lesions usually show infiltrates of neutrophils and eosinophils in and around the affected vessel walls; however, there is no evidence of fibrinoid necrosis, which suggests vasculitis.

Basophilic palisading granuloma (i.e., blue granuloma, Winkelmann granuloma)

Basophilic palisading granuloma most often occurs in CSS and GPA on frictional areas, such as elbows, knees, finger joints, or buttocks. It presents as papules or nodules with central crusted or ulcerated lesions (Fig. 10a). Histopathology of these lesions is characterized by a palisaded histiocytic granuloma with a central zone of basophilic (i.e., stained blue) degenerated collagen fibers mixed with nuclear dust and neutrophils (Fig. 10b). The identical

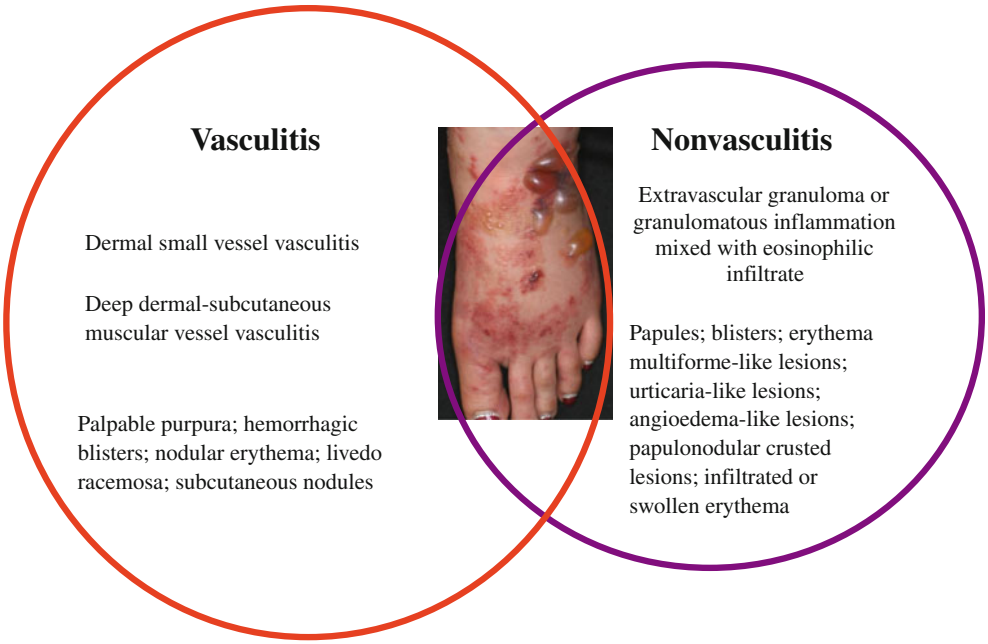

Fig. 9 Spectrum of histopathologic features in relation to the mosaic of cutaneous manifestations in Churg–Strauss syndrome (CSS). Different types of vasculitis and nonvasculitis lesions can be present on different occasions or can coexist on the same occasion during the clinical course of the disease

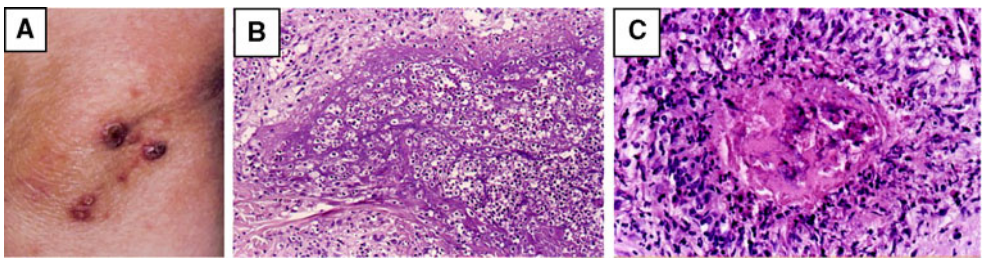

Fig. 10 **a**, **b** Basophilic palisaded granuloma (i.e., Winkelmann granuloma). **c** Eosinophilic palisaded granuloma (i.e., Churg–Strauss granuloma) in Churg–Strauss syndrome (CSS). **a** Papular and nodular lesions with a central crust on the elbow joint. **b** Histopathology of **a** shows palisading granulomas with central basophilic degeneration of collagen fibers (*stained blue*) mixed with neutrophils and nuclear dust. **c** Note that the central zone of eosinophilic degeneration of collagen fibers (*stained red*) mixed with degenerated eosinophils surrounded by an infiltrate of histiocytes in Churg–Strauss granuloma obtained from a sural nerve biopsy is distinct from the central zone of basophilic degeneration in **b** (color figure online)

clinicopathological features can be present in other systemic disorders (e.g., collagen diseases such as rheumatoid arthritis and systemic lupus erythematosus) [11].

Eosinophilic palisading granuloma (i.e., red granuloma, Churg–Strauss granuloma)

Eosinophilic palisading granuloma is a histopathologic feature that is distinct from basophilic palisading granuloma and is a diagnostic clue for CSS. Eosinophilic palisading granuloma most often occurs in extravascular lesions of internal organs in CSS; it is relatively rare in skin lesions (Fig. 10c).

Dermal granulomatous inflammation with or without granuloma formation and with no obvious evidence of collagen degeneration

The features of dermal granulomatous inflammation with or without granuloma formation and with no obvious evidence of collagen degeneration are usually present in angioedema-like lesions, papular lesions, urticaria-like lesions (Fig. 5a), or bullous or vesicular lesions (Fig. 4a) in patients with CSS. Histopathology shows mild to severe dermal eosinophilia mixed with either infiltrates of neutrophils and histiocytes (Figs. 4c, 5b) or scattered palisaded granulomas without collagen degeneration.

Pyoderma-gangrenosum-like lesions in GPA

Pyoderma-gangrenosum-like lesions are a characteristic feature of GPA and may appear on the face. This feature usually does not occur in other types of ANCA-associated vasculitis [12, 13]. Histopathology is characterized by a palisaded granuloma surrounding a large central zone of a geographic necrosis, with marked neutrophilic abscess formation and hemorrhage.

Summary

In summary, different levels of vasculitic and nonvasculitic skin lesions can be simultaneously present in the same patient or be present at different occasions in the same patient during the clinical course. This accounts for the diverse mosaic-like skin lesions in ANCA-associated vasculitis (Fig. 9). Key to the early diagnosis of ANCA-associated vasculitis with cutaneous complications are understanding the complicated clinical and histopathologic spectrum of skin lesions, and histopathologically confirming the diagnosis via a prompt and relatively noninvasive skin biopsy.

Conflict of interest The author has declared no competing interest.

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