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CLINICAL LETTER

Cutaneous-limited, initially strongly unilateral microscopic polyangiitis

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Dear Editors,

A 44-year-old female patient presented in good general health, but with obesity. Strictly limited to the left half of the body, up to 20 painful, reddish, roundish macules with a hemorrhagic appearance were found. The lesions were particularly prominent on the upper body, including the left half of the face and the left arm. In the dependent areas, especially on the lower legs, the macules developed into infiltrated, hemorrhagic plaques and ultimately to hemorrhagic necroses and ulcerations (Figure 1). The symptoms had initially started one month before with a single painful ulcer on the left lower leg. Chills and other signs of infection were denied. The patient reported joint pain and episodes of abdominal pain and nausea.

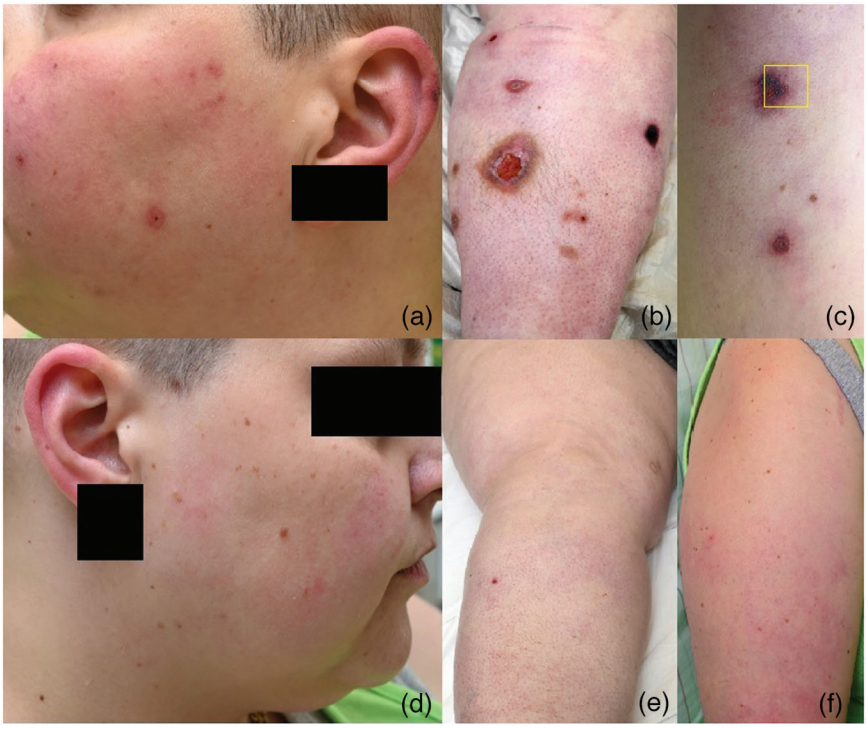

FIGURE 1 Clinical finding at initial presentation. Restricted to the left half of the body hemorrhagic round maculae and plaques with transition to hemorrhagical necrosis and ulcerations in dependent parts. (a–c) Left half of the face, left lower leg and left upper arm. The biopsy site is marked with a yellow frame. (d–f) For comparison, the right, inconspicuous half of the body: right half of the face; right lower leg, right upper arm.

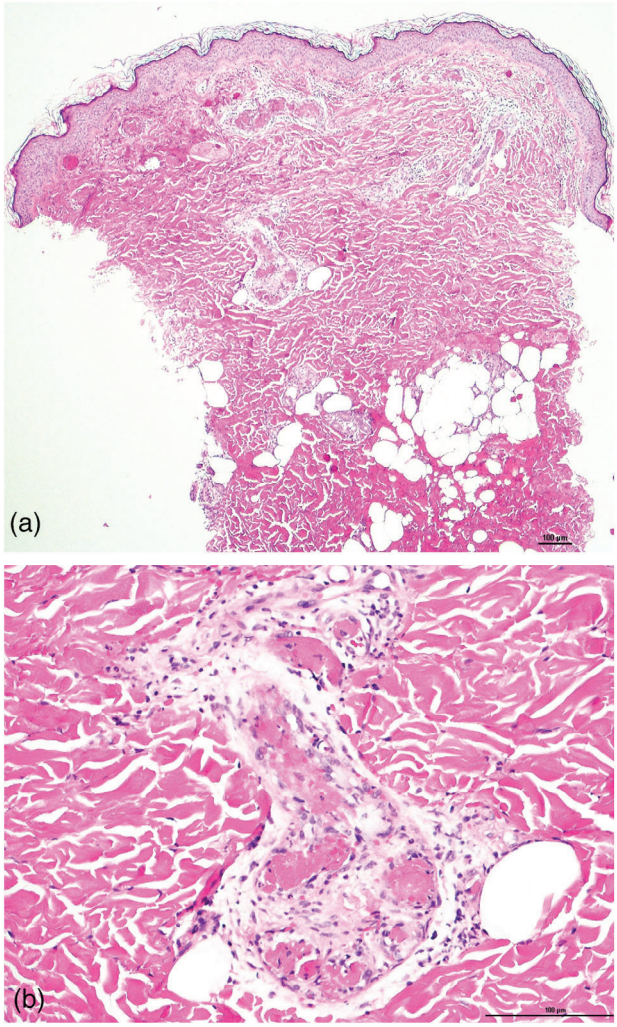

FIGURE 2 Neutrophilic vasculitis of the small dermal vessels with variable leukocytoclasia, accompanied by erythrocyte extravasation and fibrinoid degeneration and occlusion of the vessels without granuloma formation (hematoxylin-eosin stain, original magnification (a) x 40, (b) x 200).

The physical status, including the neurological status, was unremarkable.

In an external clinic, treatment with ciclosporin was initiated on suspicion of pyoderma gangraenosum after peripheral arterial occlusive disease (PAOD) had been ruled out by duplex sonography. Nevertheless, the patient continued to develop new, painful, hemorrhagic macules that progressed to hemorrhagic necrosis and ulcers.

Initial laboratory results revealed a slight increase in CRP of 6.4 mg/l (norm < 5.0 mg/l), a slight thrombocytopenia of 126×10^9/l (norm 140–400 $\times 10^9$/l) and a mild increase in liver enzymes. Coagulation values were normal. Anti-MPO (p-ANCA) was significantly elevated at 9.3 IU/ml (norm < 3.5 IU/ml). A total of four anti-MPO controls were carried out, in each of which elevated values were detected. In one control, the value rose to 21.0 IU/ml. Antinuclear antibodies (ANA) and cryoglobulins were not detected. In addition, neither blood eosinophilia nor viral hepatitis were present. The creatinine value of 0.68 mg/dl was within the normal range (0.50-0.90 mg/dl). Urine status was unremarkable. Histopathological examination of a skin biopsy of a lesion on the left upper arm revealed neutrophilic vasculitis of the small dermal vessels with variable leukocytoclasia, accompanied by erythrocyte extravasation, fibrinoid degeneration and vascular occlusion without granuloma formation (Figure 2). No IgM, IgG, IgA, fibrinogen, C3c or C1q deposits were found in follow-up direct immunofluorescence assays. Further laboratory tests, including DKK3 with urine status, as well as renal sonography, chest X-ray and cranial computed tomography with imaging of the paranasal sinuses showed unremarkable findings. High-resolution computed tomography of the lungs showed a slightly pronounced pulmonary mosaic and distinct air trapping in the expiratory images, particularly in the lower lobes. This was interpreted most likely in the context of bronchiolitis obliterans. There was therefore no internal evidence of systemic vasculitis. We made the diagnosis of unilateral cutaneous microscopic polyangiitis (MPA). Six points were achieved according to the diagnostic criteria of Suppiah et al., which supports the diagnosis of MPA (Table 1).[1] A renal biopsy was postponed, as the above-mentioned nephrological examinations showed no evidence of renal involvement.

With intravenous administration of methylprednisolone at an initial dose of 96 mg per day, the lesions healed with improvement of the local pain. The joint pain and abdominal symptoms also resolved quickly under therapy, so that additional endoscopy was postponed. No new skin lesions developed during treatment, allowing the methylprednisolone dose to be gradually reduced. Methotrexate (MTX) 5 mg per week was started by rheumatologists to maintain remission. This led to the patient developing persistent fatigue and renewed unilateral skin lesions in the form of hemorrhagic plaques on erythema, so that after four doses of MTX, treatment was switched to azathioprine 50 mg per day. The fatigue regressed after discontinuation of MTX. After six months, there was a significant exacerbation with involvement of the contralateral half of the body for the first time, leading to plans to switch therapy to rituximab and Avacopan. There are still no indications of systemic involvement.

Microscopic polyangiitis belongs to the group of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), which also include granulomatous polyangiitis (GPA, formerly Wegener's granulomatosis) and eosinophilic granulomatous polyangiitis (EGPA, formerly Churg-Strauss syndrome).[2] ANCA-associated vasculitides (AAV) are classified as small vessel vasculitides according to the current Chapel-Hill classification.[3] They include a spectrum of systemic or single-organ manifestations that can be classified on the basis of specific pathologic and clinical features as MPA, GPA or EPGA.[4,5] Microscopic polyangiitis (MPA) is defined as vasculitis of small cutaneous vessels with little or no immune deposits. Subcutaneous vessels, including arteries, are commonly involved.[5] MPA can be distinguished from granulomatous polyangiitis (GPA) and

TABLE 1 Diagnostic criteria of MPA, modified according to Suppiah et al.[1] The patient achieves 6 points, which argues for the diagnosis of MPA.

Criteria		Score	Patient's score
Clinical Criteria	Nasal involvement: bloody discharge, ulcers, crusting, congestion, blockage, or septal defect/perforation	−3	0
Laboratory, imaging and biopsy criteria	Detection of antinuclear antineutrophil cytoplasmic antibodies (pANCA) or positive antimyeloperoxidase (anti-MPO) antibodies ANCA	+6	+6
	Fibrosis or interstitial lung disease by imaging	+3	0
	Pauci-immune glomerulonephritis on kidney biopsy	+3	Not performed
	Detection of antineutrophil cytoplasmic antibodies (cANCA) or anti-proteinase 3 (anti-PR3) antibodies	−1	0
	Blood eosinophilia $\geq 1 \times 10^9$/l	−4	0
Evaluation	Five or more points are required for the diagnosis of MPA		6 points

eosinophilic granulomatous polyangiitis (EGPA) by the absence of granulomas.[4]

ANCA are IgG antibodies that are directed against autoantigenic target structures on neutrophils and monocytes.[6] Based on this target structure and a characteristic staining pattern in immunofluorescence, ANCA can be differentiated into leukocyte proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA). PR3-ANCA staining is granular and cytoplasmic (c-ANCA), whereas MPO-ANCA is predominantly perinuclear (p-ANCA).[6] In terms of pathogenesis, an initial translocation of ANCA autoantigens to the cell surface occurs in neutrophils mediated by proinflammatory cytokines.[2] ANCA binding to the corresponding autoantigens ultimately activates neutrophils, which can lead to endothelial damage and vascular destruction.[2] In MPA, antibodies against MPO can be detected in around 60% of cases, while antibodies against PR3 can only be detected in up to 30%.[2] In a meta-analysis by Guchelaar et al., the pooled sensitivity of MPO antibodies was reported to be 58.1% and the pooled specificity 95.6% in AAV diagnostics.[7]

The clinical symptoms of MPA are variable – any organ system can be affected, which complicates diagnostic workup and can lead to delays in diagnosis.[3] Patients with MPA usually show pulmonary or renal involvement.[4] Cutaneous manifestations can also occur and are usually diverse. They include purpura, livedo racemosa, splinter hemorrhages, papules and nodules, urticaria, gingival hyperplasia or oral ulceration.[4] Skin involvement may occur simultaneously with systemic involvement, but it may also follow or precede systemic involvement.[4]

The diagnosis of microscopic polyangiitis is based on a combination of ANCA detection, histology and clinical symptoms. Treatment includes the systemic administration of immunosuppressants such as glucocorticoids, MTX, azathioprine, rituximab, immunoglobulins or Avacopan (compare recommendations of the American College of Rheumatology guideline 2021 or EULAR guideline 2024).[8,9]

Our case is remarkable because the manifestation was limited to the skin and the MPA was initially strictly unilateral. Skin lesions only appeared on the opposite side about one year after diagnosis. Purely cutaneous MPA, as in our case, is rare and has been described in only a few case reports to date.[10,11] Unilateral MPA has also been described in other organ systems, for example in the form of a unilateral diffuse alveolar hemorrhage or unilateral adrenal hemorrhage.[12–14] However, one can speculate about neuroimmunological influences upon the inflammatory processes or about embryonically determined mosaicisms that affect tissue of only one half of the body.

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CONFLICT OF INTEREST STATEMENT

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