Unclassified vasculitis with acral ischemic lesions: "forme fruste" or idiopathic vasculitis?

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ABSTRACT

Background and objectives. *While acral ischemia and necrosis represent a common problem in connective tissue diseases and other disorders, acral ischemic lesions are also occasionally encountered in primary and secondary systemic vasculitides. Here we report on the course of 4 patients with acral ischemic lesions as a hallmark of unclassified vasculitis. We compare these cases with 4 additional cases of acral ischemia complicating classified vasculitis.*

Objectives. *To report on our experience with cases of unclassified vasculitis and acral ischemic lesions during the past 5 years and review the literature on vasculitis and acral ischemic lesions.*

Methods. *The case history of one of the patients with unclassified vasculitis and acral ischemic lesions is reported in detail. The medical history of another 3 patients presenting with vasculitic acral ischemic lesions and unclassified vasculitis during the past 5 years in our department (Lübeck/Bad Bramstedt) is summarized and compared to the course of patients with acral ischemic lesions complicating classified vasculitides. A PubMed database review of reports on acral ischemic lesions and vasculitis from 1985 to August 2006 was performed using the following combination of keywords: "Vasculitis"[MeSH] AND ("Necrosis"[MeSH] OR "Ischemia" [MeSH] OR "Infarction" [MeSH]) AND ("Extremities"[MeSH] OR "Fingers" [MeSH] OR "Toes"[MeSH] OR "limb"), yielding 1328 entries. This search was subsequently limited to "Humans, All Adult (19+ years)", yielding 904 entries and to the 1985-August 2006 period, yielding 453 entries. Only three (0.7%) of these entries described one (one paper) or more (n=28) patients (two papers) with idiopathic vasculitis characterized by digit necrosis in the absence of systemic manifestations (except in some cases for arthralgia) or laboratory parameters pointing to a diagnosis of an established type of vasculitis.*

Results. *A 37-year-old female presented with acral ischemic lesions of the left forefoot, fingers and toes, and Raynaud's phenomenon. Angiography showed multiple stenoses of ulnar and digital arteries, anterior and posterior tibialis arteries, and occlusions of radial artery and occlusion of the plantar artery in the absence of large vessel abnormalities. Histological analysis of an amputation disclosed giant cell arteritis of small vessels. The patient achieved remission with immunosuppressive treatment (cyclophosphamide and prednisolone). Three other patients with acral ischemic lesions and unclassified vasculitis also lacking other manifestations and defining laboratory and technical features during initial presentation and follow-up of 4 months to 5 years are presented. Necrotizing and leukocytoclastic vasculitis were present in two other patients, respectively. In contrast, acral ischemic lesions could be attributed to rheumatoid vasculitis and essential cryoglobulinemic vasculitis in two other cases each based on the patient's history and laboratory findings at the time of presentation of acral ischemic lesions.*

Conclusions. *While acral ischemic lesions could represent initial or isolated (forme fruste) manifestations of a defined vasculitis, acral ischemic lesions may rarely be encountered as the predominant manifestation of an as yet unclassified vasculitis. The histological findings seem to differ. Our report includes a peculiar case of giant cell arteritis of small arteries not classifiable as giant cell arteritis of large arteries or Takayasu disease.*

Introduction

The differential diagnosis of acral ischemic lesions includes common causes such as non-diabetic peripheral

arterial occlusive disease, coagulation disorders including antiphospholipid syndrome, arterial thromboembolism, malignancy, infections, drug-induced vasospasm or coagulation defects, and Winiwarter-Buerger's disease. Digital ulcers are also seen in connective tissue diseases – most frequently in systemic sclerosis - and as a complication of severe Raynaud's phenomenon. In general, angiopathy with vessel obstruction, vasospasm, endothelial cell changes, and hemorrheologic alterations constitute the pathophysiological basis of these disorders (1). Digital necrosis may also be seen in primary and secondary systemic vasculitides affecting large, medium-sized and small vessels such as giant cell arteritis, polyarteritis nodosa, rheumatoid vasculitis, cryoglobulinemic vasculitis, and ANCA-associated vasculitides (2-8). While acral ischemic lesions are usually encountered during severe disease courses with involvement of multiple organs, digital ulcers and gangrene may represent either the initial or an isolated manifestation of a defined vasculitis (so-called "*forme fruste*") in rare patients (5, 7).

Here we report on 4 patients with acral ischemic lesions and unclassified vasculitis. We compared them to 4 additional patients with acral ischemic lesions complicating classified vasculitides (rheumatoid vasculitis, essential cryoglobulinemic vasculitis) and performed a literature review.

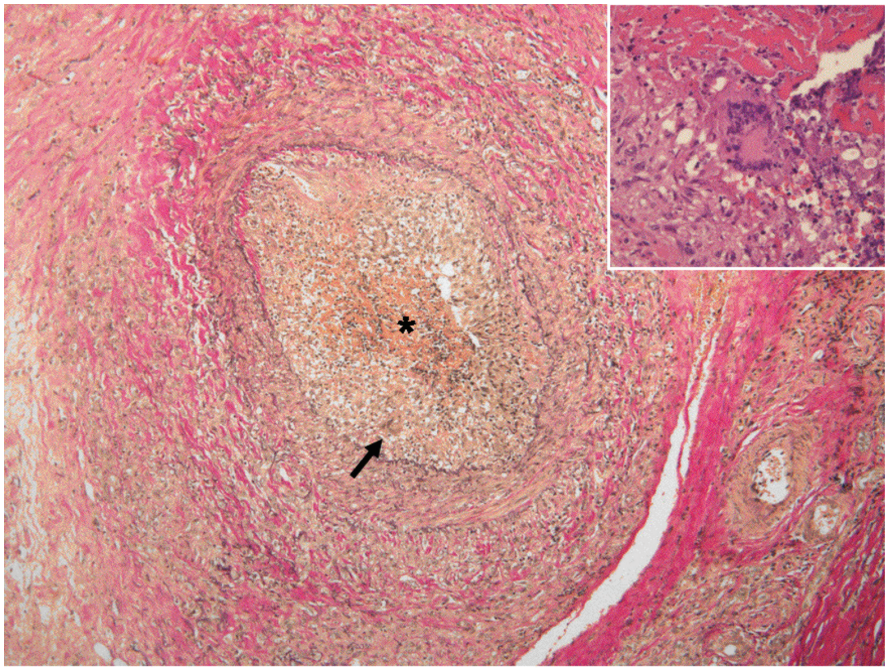

Fig. 1. *Digital artery showing typical granulomatous vasculitis*. Arterial wall with onion-skin splitting and partial destruction of elastic fibres, transmural inflammatory infiltrates including numerous epithelioid cells and giant cells (arrow and inset) as well as complete occlusion of lumen (*) by organized thrombotic material.

Methods

A patient with unclassified necrotizing vasculitis and acral ischemic lesions due to a peculiar giant cell arteritis of small vessels is described. The medical story of another 3 patients presenting with acral ischemic lesions and unclassified vasculitis during the past 5 years in our department (Lübeck/Bad Bramstedt) is summarized and compared to patients with acral ischemic lesions complicating classified vasculitides (rheumatoid vasculitis, essential cryoglobulinemic vasculitis). Further, a PubMed database review of reports on acral ischemic lesions and vasculitis from 1985 to August 2006 was conducted. The search strategy was based on the following combination of index terms: "Vasculitis"[MeSH] AND ("Necrosis"[MeSH] OR "Ischemia"[MeSH] OR "Infarction"[MeSH]) AND ("Extremities"[MeSH] OR "Fingers" [MeSH] OR "Toes"[MeSH] OR "limb"), yielding 1328 entries. This search was subsequently limited to "Humans, All Adult (19+ years)", yielding 904 entries and then further narrowed down to the papers published in the 1985-August 2006 period, yielding 453 entries. Only three (0.7%) of these entries described one (one paper) or more patients (two papers) with idio-pathic vasculitis characterized by digit necrosis in the absence of systemic manifestations (except in some cases for arthralgia) or laboratory parameters pointing to a diagnosis of an established type of vasculitis.

Results

Case report

Patient 1, female, developed Raynaud's phenomenon and acral ischemic lesions with necrosis of the left forefoot, requiring amputation in 1996 at the age of 34. Pelvic angiography was unremarkable. Over the next year, the patient developed sequentially necrosis of the third left finger, and of the first and second right toes, requiring resection of the latter. In July 2003, the fourth left finger became acutely necrotic and had to be amputated. Histological examination revealed giant cell arteritis of the small arteries (Fig. 1). Her condition deteriorated further, and in October 2003 she was admitted to our center. On examination, she looked cachectic (height 170 cm, weight 50 kg). Abnormal findings included acral necrosis of the second and third right fingers in addition to the known resections, and funnel chest. Foot pulses could not be felt. A laboratory screening showed raised ESR (46 mm/1st h) and borderline positive ANA (1:64, fine-speckled pattern) with normal or negative CRP, complete blood count (CBC), creatinine, liver function tests (LFT) (except for γ-GT raised at 61 U/l), serum protein electrophoresis, electrolytes, coagulation profile, negative rheumatoid factor and anti-CCP (anti-citrullinated cyclic peptide), normal C3 and C4 complement levels and CH50, negative ENA and antiphospholipid antibodies, normal thyroid stimulating hormone (TSH), and normal urinalysis including 24-h protein excretion. ECG, echocardiog-

colore

raphy, abdomen ultrasound (US), chest x-ray (CXR) and EMG were also unremarkable. Joint US showed no significant abnormality, while the x-rays of hands and feet were consistent with the known resections but negative for erosions. A whole-body bone scan showed no increased tracer uptake. Angiography of the aortic arch, of the supra-aortic vessels, and of the limbs showed multiple stenoses of the ulnar arteries as well as of the metacarpal and digital arteries bilaterally, a proximal occlusion of the radial artery on the left, pruning of the tibialis anterior and posterior arteries, and occlusion of the plantar artery.

A tentative diagnosis of an unclassified vasculitis was made, and in view of the worsening of the peripheral ischemia treatment with cyclophosphamide 100 mg and prednisolone 30 mg daily per os was instituted. The patient achieved remission by taking cyclophosphamide for one year and prednisolone could be tapered to 5 mg daily per os. She was switched to azathioprine for the maintenance of remission, which she has continued until now.

Review of other cases with acral ischemic lesions and unclassified and classified vasculitides

During the past 5 years another 3 patients presented with acral ischemic lesions and unclassified vasculitis (Table I). Patient 3 refused a biopsy to be taken. The biopsies disclosed a leukocytoclastic vasculitis in patient 2 and a necrotizing vasculitis of small arteries and arterioles in patient 4. The differential diagnosis included microscopic polyangiitis in patients 2 and 3 as well as polyarteritis nodosa in patient 3 and Churg-Strauss syndrome (eosinophilia only at presentation) or Winiwarter Buerger's disease (history of smoking in the past) in patient 4. However, as no other key defining organ involvement or feature in the patients' history Churg-Strauss syndrome (eosinophilia only at presentation) or Winiwarter-Buerger's disease (history of smoking in the past) in pationt 4. However, as no other key defining organ involvement or feature in the patients' history or laboratory examinations was contributing to the differential diagnoses, the diagnosis remained "unclassified vasculitis" in all four patients.

In another 4 patients, acral ischemic lesions could be attributed to a defined vasculitic entity based on the patients history and laboratory findings. Two patients each had rheumatoid vasculitis and essential cryoglobulinemic vasculitis, respectively (Table II).

Discussion

Acral ischemic lesions are an uncommon manifestation of primary and secondary systemic vasculitides, *e.g.,* giant cell arteritis, polyarteritis nodosa, rheumatoid vasculitis, cryoglobulinemic vasculitis, and ANCA-associated vasculitides (2-8). Digital necroses are usually encountered during severe disease courses of vasculitides or as a secondary complication of another active underlying disease such as rheumatoid arthritis. Two of our patients with acral

Table I. Patients with acral ischemic lesions and unclassified vasculitis.

Initials, age, gender	Manifestations	Angiography	Histology	Diagnosis	Course
Patient 1, 37 years, female	Acral ischemic lesions left forefoot, right DII and III, and left DIII and IV, and right TI and II, Raynaud's phenomenon, ANA 1:64	Multiple stenoses of ulnar and digital arteries, bilateral; occlusion of radial artery, stenoses of anterior and posterior tibialis arteries, occlusion of the plantar artery.	Giant cell arteritis of small arteries	Unclassified vasculitis	Remission (CYC 12 m.→ AZA 2 years)
Patient 2, 38 years, male	Acral ischemic lesions of left TI-V, and right TII and IV, and right and left DII and DV, distal polyneuropathy with foot and limb numbness	Microaneurysms of middle sized vessels	Leukocytoclastic vasculitis	Unclassified vasculitis (DD: Microscopic polyangiitis)	Remission (CYC since 5 m.)
Patient 3, 55 years, female	Acral ischemic lesions left DII and III, acrocyanosis, arthralgia, ANA 1:640	Segmental occlusion of right radial artery, micro-aneurysms of left segmental arteries	∅	Unclassified vasculitis (DD: microscopic polyangiitis or polyarteritis nodosa?)	Remission (CYC 6 m. → AZA 1 year), relapse after 3 years without medication, remission (CYC 3 m. → AZA since 6 m.)
Patient 4, 56 years, male	Acral ischemic lesions right DII, acrocyanosis, pruritus, arthralgia, eosinophilia (6.600/µl)	∅ (immediate amputation of right forefoot and left II, III, IV and right II, III, V digtis)	Necrotizing vasculitis of small arteries and arterioles	Unclassified vasculitis, (DD: Winiwarter Buerger`s disease, Churg-Strauss syndrome?)	Remission (CYC 6 m. → MTX since 4 years),

Legends: ∅: Not present or performed; ANA: antinuclear antibodies; AZA: Azathioprine; CYC: Oral cyclophosphamide; D: Digit; DD: Differential diagnosis; m: months; MTX: Methotrexate; T: Toe.

Table II. Patients with acral ischemic lesions and classified vasculitis.

Initials, age, gender	Manifestations	Angiography	Histology	Diagnosis	Course
Patient I, 60 years, male	Rheumatoid arthritis, acral ischemic lesions right DII and III, rheumatoid factor 857 U/ml, BPI-ANCA 50 U/ml	Stenoses of the right digital arteries of the second to the fifth finger	∅	Rheumatoid vasculitis	Remission (pCYC 3 m. → LEF since 3 years)
Patient II, 70 years, male	Acral ischemic lesions right TII and V, and left T1, type III cryoglobulin (552 mg/l), HCV and HBV negative	∅	∅	Essential cryoglobulinemic vasculitis	Remission (MTX since 3 years),
Patient III, 34 years, female	Acral ischemic lesions right DII and IV, type III cryoglobulin (838 mg/l), ANA 1:80,), HCV and HBV negative	Stenoses of middle part of the brachial artery and digital arteries	Diffuse necrosis of resected fingers	Essential cryoglobulinemic vasculitis	Remission (CYC since 6 m.)
Patient IV, 55 years, male	Rheumatoid arthritis, acral ischemic lesion right DII, acrocyanosis, dilatative cardiomyopathy, rheumatoid factor 872 U/ml	∅	∅	Rheumatoid vasculitis	Remission (pCYC 6 m. → MTX since 2 years)

Legend: ∅: Not present or performed; ANA: antinuclear antibodies; BPI-ANCA: bactericidal permeability increasing protein anti-neutrophil cytoplasmic antibodies; CYC: Oral cyclophosphamide; D: Digit; HBV: hepatitis B virus; HCV: hepatitis C virus; LEF: Leflunomide; MTX: Methotrexate; pCYC: Pulse cyclophosphamide; T: Toe.

the skin (purpura, ulcers) and nerves (polyneuropathy) as a consequence of immune-complex mediated vasculitis of small and medium-sized vessels in the presence of high rheumatoid factor. Induction of remission with cyclophosphamide is the standard treatment of rheumatoid vasculitis, but anti-TNF-α therapy may also be effective (3, 9). The underlying vasculitis in two other patients with acral ischemic lesions could be classified as essential cryoglobulinemic vasculitis. Both patients presented with digital necroses and a mixed polyclonal type III cryoglobulinemia in the absence of other clinical features. Testing for HBV and HCV infection was negative in both patients on repeated occasions. Cryoglobulinemic vasculitis usually ensues from mixed mono- and polyclonal type II cryoglobulinemia in HCV infection, in which the monoclonal IgM component as well as the polyclonal IgG fraction play distinct roles in inducing endothelial damage. Cryoglobulinemic vasculitis is less frequently a consequence of mixed polyclonal type III cryoglobulinemia, in which immune-complex mediated mechanisms play a role in inducing the vasculitis (10-12). Mono- or oligosymptomatic courses of cryoglobulinemic vasculitis may obscure the correct diagnosis and require careful evaluation of patients presenting with suspected vasculitis (12).

The vasculitis causing acral ischemic lesions in four of our patients could not be definitely classified due to the paucity of symptoms and lack of other defining laboratory, angiographical or histological findings. Digital necrosis may represent the initial manifestation of a vasculitis (7), but in none of our patients other clinical features have developed during the observation period lasting 4 months to 5 years. Whereas one patient described in our case report also suffered from polyneuropathy, the other patients did not show any other symptoms directly attributable to the vasculitis apart from the acral ischemic lesions. Digital ischemia could represent an isolated manifestation of a vasculitis (so-called "*forme fruste*") as has been described in polyarteritis nodosa (5). The presence of microaneurysms of small arteries in angiographic pictures of one patient (patient 3) was suggestive of an isolated form of microscopic polyangiitis, which can involve medium-sized vessels in addition to small vessels, or polyarteriitis nodosa. However, the patient refused a biopsy to be taken, and no other clinical features evolved during the subsequent period of time. A relapse of her vasculits remained also confined to acral ischemic lesions as the only presentation. A history of past smoking and transient eosinophilia, which never recurred thereafter, raised the suspicion of Winiwarter-Buerger's disease or a *forme fruste* of Churg-Strauss syndrome in patient 4, but definite proof could not be obtained in the absence of other clinical or immunological features. Eosinophils were not present in biopsy specimen of his necrotizing vasculitis. Finally, a rather peculiar vasculitis was disclosed in the biopsy specimen of patient 1: she had a giant cell arteritis of small arteries. Angiography excluded stenotic involvement of larger arteries. It seemed unlikely that her vasculitis could be an initial presentation or *forme fruste* of polyarteritis nodosa (defined as necrotizing vasculitis affecting small and medium-sized arteries) or Takayasu's arteritis (confined to large arteries). Giant cell arteritis has been shown on Color-Doppler ultrasonography to affect large- to medium-sized vessels in

30% of cases (13) and to lead to limb claudication secondary to ischemia (14), but our case is peculiar because it demonstrated giant cells in a small artery. This is a very unusual finding, which does not fit with the notion of GCA as an arteritis involving large- to medium-sized arteries. In this patient, immunsuppressive treatment might have obscured the fact that her acral ischemic lesions were the prologue to other clinical features of a defined vasculitis, but the histological picture has remained elusive so far. Whether this case represents idiopathic vasculitis or a *forme-frustre* of giant cell arteritis remains an open question. The mainstay of treatment of giant cell arteritis is steroid therapy (15, 16). However, in our case, cyclosphosphamide was used because it is considered the treatment of choice for severe organ involvement or imminent organ failure (17, 18), whereas steroid therapy is of doubtful value in such cases (19). The duration of cyclosphosphamide was somehow prolonged to be on the safe side. Toxicity due to cyclophosphamide therapy, including ovarian failure, hemorrhagic cystitis, and an increased risk of developing infections or neoplasm, is a cause of serious concern, but in severe vasculitis the potential toxicity is outweighed by the clinical benefit.

We were able to identify 28 cases similar to ours in the literature (PubMed search) published in the period 1985-August 2006. Goon *et al*. (20) described one case of histologically documented vasculitis characterized by livedo reticularis and digital gangrene. A tentative diagnosis of polyarteritis nodosa and antiphospholipid antibody syndrome was made, but no visceral involvement could be demonstrated, while antiphospholipid antibodies tested repeatedly negative. Quraishy *et al*. (21) studied 57 patients that attended a District General Hospital in the UK with critical upper limb ischemia between 1980 and 1989. A diagnosis of vasculitis was made in 23 patients, which was judged to be idiopathic in 6 of them. In all patients, the diagnosis was confirmed by upper limb arteriography and by exclusion of other causes. To our knowledge, the largest series published to date is that reported by Mills *et al*. (22). The Authors evaluated prospectively 900 patients with vascular disease of the upper limbs as part of a research protocol with a Vascular Surgery Unit. 100 patients presented with severe ischemic finger ulceration progressing to skin loss or frank gangrene and were assessed more in detail. In 22 cases, a diagnosis of hypersensitivity angiitis with rapid onset of vascular occlusion was made. Systemic involvement was ruled out and all serologic test for autoimmune diseases were negative. This data suggests that idiopathic vasculitis characterized by severe digital ischemia is not uncommon and may possibly be underreported.

The presented four cases of acral ischemic lesions as the predominant manifestation of an underlying unclassified vasculitis highlight the dilemma of current classification criteria. Whereas both American College of Rheumatology (ACR) and Chapel Hill Conference (CHC) classification criteria are helpful in the study of groups of patients with vasculitis, they work less well in the evaluation of individual patients and were not designed as a substitute for diagnostic criteria of vasculitides, which we still lack. Rare vasculitic disease entities or aberrant forms of known vasculitides not fulfilling ACR and CHC criteria might be missed by applicating the criteria in trying to classify a vasculitis (23, 24). Case reports may disclose gaps in the classification (25). While we can not entirely exclude that acral ischemic lesions were only an initial or isolated manifestation of a defined vasculitis in one or two of the presented patients, lack of other manifestations and defining laboratory or other features during follow-up might point to as yet another underlying vasculitis preferentially affecting acral vessels. Polymorphic presentation of the histological picture of the vasculitis would not exclude such a designation since other primary systemic vasculitides can also present with polymorphic features (26).

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