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Case Report

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Unveiling the Uncommon: Peripheral Neuropathy and Gangrene as Early Markers of ANCA-Associated Vasculitis

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Abstract

Background: Although Peripheral nerve involvement and digital ischemia occur in many systemic vasculitic syndromes, it is exceedingly rare for them to manifest simultaneously and as the first ever presentation of vasculitis. We report a case of a middle-age male presenting with symmetric neuropathy and distal gangrene, unmasking the underlying ANCA-associated vasculitis _an atypical and seldom seen clinical occurrence.

Case presentation: A 46-year-old male presented with high-grade intermittent fever for 15 days, followed by progressive limb weakness, burning sensations and severe pain. He developed black discoloration of toes and fingers. Examination revealed dry gangrene involving toes, parts of the forefeet and patches on fingers, with absent distal pulses and warm peripheries. Neurological evaluation showed glove-and-stocking sensory loss and severe distal muscle weakness with intact proximal strength and cranial nerves. Investigations revealed elevated C-ANCA (22.84 U/mL) and arterial insufficiency on Doppler. CT angiography confirmed widespread arterial narrowing and mural thickening. Sural nerve biopsy findings confirmed vasculitic neuropathy. Despite corticosteroids and plasma exchange, amputation was required and Rituximab was initiated for ongoing treatment.

Discussion: This case highlights the rarity of peripheral nerve involvement and gangrene as initial presentations of vasculitis, particularly ANCA-associated types. Early symptoms, although subtle, must prompt comprehensive investigations, including autoimmune markers, imaging and biopsy, to confirm the diagnosis. Aggressive and Early immunosuppressive therapy, including corticosteroids, plasma exchange and biologics such as Rituximab, plays a pivotal role in halting disease progression and minimizing morbidity. Prompt initiation of therapy not only addresses current manifestations but also reduces the risk of further vascular damage and systemic involvement. However, managing vasculitis requires more than immediate intervention; close and continuous follow-up is critical and patients should be monitored meticulously to detect new complications or manifestations of the disease, such as renal or gastrointestinal involvement, which are common in ANCA associated vasculitis. A multidisciplinary approach, encompassing rheumatology, neurology, vascular surgery and rehabilitation, ensures holistic care and optimizes long-term outcomes.

Conclusion: Recognizing peripheral nerve involvement and gangrene as potential initial signs of vasculitis, especially ANCA-associated vasculitis, is vital. Early, aggressive management guided by thorough diagnostics can significantly improve outcomes. Continued research is essential to enhance therapeutic approaches for such complex cases.

Keywords: Peripheral nerve; Sural nerve; Neurological evaluation; Rituximab; Vascular surgery; Peripheral neuropathy; Gangrene; Immunosuppressive therapy; Corticosteroids; Plasma exchange; Rheumatology; Rehabilitation

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Introduction

Peripheral nerve involvement can occur in 50% to 70% of systemic vasculitic syndrome and digital ischemia and peripheral gangrene occur in a small percentage of vasculitis, however rarely do they present as a 1st manifestation [1]. Granulomatosis with polyangiitis, Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) are primary systemic vasculitic syndromes and are collectively named under the term ANCA-associated vasculitis. The relative prevalence of ANCA associated vasculitides is 24-97 cases per million for GPA and around 15 million people for eosinophilic granulomatous with polyangiitis [2,3]. ANCA-associated vasculitis has peripheral neuropathy and digital gangrene as part of their clinical symptomatology, with mononeuritis multiplex as the most common pattern of neuropathy but these occurrences are rare.

Methodology

A 46-year-old male, right-handed, with no known comorbidities and a truck driver by profession, presented with complaints of undocumented, intermittent high-grade fever associated with rigors and chills. The febrile episodes lasted for five days, during which time he received IV medications at a local clinic. There were no associated loose stools, vomiting, cough, headache, rash or sore throat. Ten days ago, he developed bilateral, symmetric lower limb weakness, which primarily affected the feet, leading to unaware slippage of slippers. This was associated with burning dysesthesias in the feet and severe pain involving the entire lower limb. One day later, he developed bilateral upper limb weakness, with the left hand more severely affected than the right. This was accompanied by burning and pins and needles sensations in both palms. Two days thereafter, the patient noted black discoloration of the toes, which was followed by similar discoloration of the fingers the next day. However, there was no subsequent progression in the extent of the discoloration. The patient denied any history of smoking or other substance use.

On examination, the patient had hyperpigmented extremities. Bilateral dry gangrene was noted, with well-demarcated margins involving both the dorsal and plantar surfaces of the forefeet. Additionally, small patches of dry gangrene were present on the distal second digit of the right hand and the distal fourth digit of the left hand **(figure 1)**. The dorsalis pedis and posterior tibial pulses were non-palpable bilaterally. However, the peripheral limbs were warm to touch and there was no loss of hair. Neurological examination revealed a high-stepping gait and the patient required two-person assistance to ambulate. Motor examination showed complete loss of power (0/5) at both ankles, consistent with severe bilateral foot drop, while proximal lower limb strength was preserved (5/5). In the upper limbs, there was a left-sided wrist drop and a severely weak grip in the right hand with preserved proximal muscle strength bilaterally. These findings were accompanied by distal sensory loss of all modalities, in a glove and stocking distribution. No abnormalities were observed in the cranial nerve or cerebellar examinations.

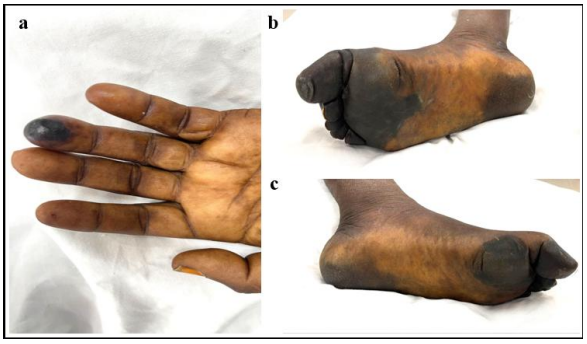


Figure 1: Small patches of dry gangrene were present on the distal second digit of the right hand and the distal fourth digit of the left hand.

Table 1: Summary of investigations.

Haemoglobin	9.6
White cell count	18
Platelets	$531x10^9$/L
Ferritin	03 ng/ml
Iron	60 µg/dl
Total iron binding capacity	109 µg/dl
Transferrin saturation	55%
Reticulocyte count	2.29%
Sodium	133 mEq/l
Potassium	3.9 mEq/l
Chloride	97mEq/l
Urea	13 mg/dL
Creatinine	0.6 mg/dL
Albumin	2.4 g/dl
SGPT	64 U/L
Calcium	8.6 mg/dL (corrected)
ESR	44 mm/hr (corrected)
CRP	9.8 mg/L
HbsAg	Non-Reactive
Anti-HCV	Non-Reactive
HIV Serology	Negative
Vitamin B12	2000 pg/mL
Thyroid stimulating hormone	4.786 uIU/L
HbA1c	6.40%
ANA	Positive (fluorescence intensity ++) Nuclear fine speckled pattern
Anti Sm	Negative
Anti dsDNA	Negative
Anti SSA/Ro	Negative
Anti SSB/La	Negative

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Anti Scl 70	Negative
Anti U1-RNP	Negative
Anti Jo-1	Negative
Anti Mi-2	Negative
Anti PM/Scl	Negative
Rheumatoid factor	206 IU/mL (++)
Serum anti-CCP	0.9 U/mL (normal)
Complement C3 C4	Normal
Cryoglobulin levels	Normal
Serum c-ANCA	22.84 U/mL
Serum P-ANCA	1.00 U/ml
Protein to creatinine ratio	1.457

Baseline investigations showed anemia of chronic disease due to low Hb counts and raised ferritin and Transferrin saturation. However, serum albumin level is 2.4 g/dL). His urine dipstick showed +1 proteins and elevated Protein to Creatinine Ratio (PCR) of 1.457 (normal range <0.2). Doppler ultrasound of the lower limbs showed monophasic waveforms in the bilateral anterior and posterior tibial arteries and Parvus Tardus waveforms in the bilateral dorsalis pedis arteries, indicating absent distal flow and severe arterial insufficiency. Nerve conduction studies revealed non-recordable CMAPs and SNAPs in all tested nerves of both upper and lower limbs, consistent with severe sensory and motor axonal polyneuropathy. Rheumatoid factor was positive at 206 IU/mL (++) and C-ANCA was markedly elevated at 22.84 U/mL (reference range <1.7 U/mL). The remainder of the autoimmune workup was negative. CT angiography of the aorta and its major branches demonstrated narrowing, irregularity and wall thickening of all three branches of the celiac artery most prominently involving the hepatic artery as well as narrowing at the origin of the mesenteric vessels, with associated branch narrowing and wall thickening. Similarly, CT angiography of the upper and lower limbs showed diffuse mural thickening, narrowing and attenuation of vessels at the level of the wrist joints, as well as the palmar and dorsal arterial arches. The common peroneal arteries and dorsalis pedis arteries appeared irregular, narrowed, thickened and attenuated bilaterally **(Figure 2)**. Sural nerve biopsy showed features consistent with vasculitic neuropathy, including intimal and transmural arteritis in medium-sized epineural vessels, with focal fibrinoid necrosis. Neurofilament immunostaining revealed a patchy distribution of axonal loss.

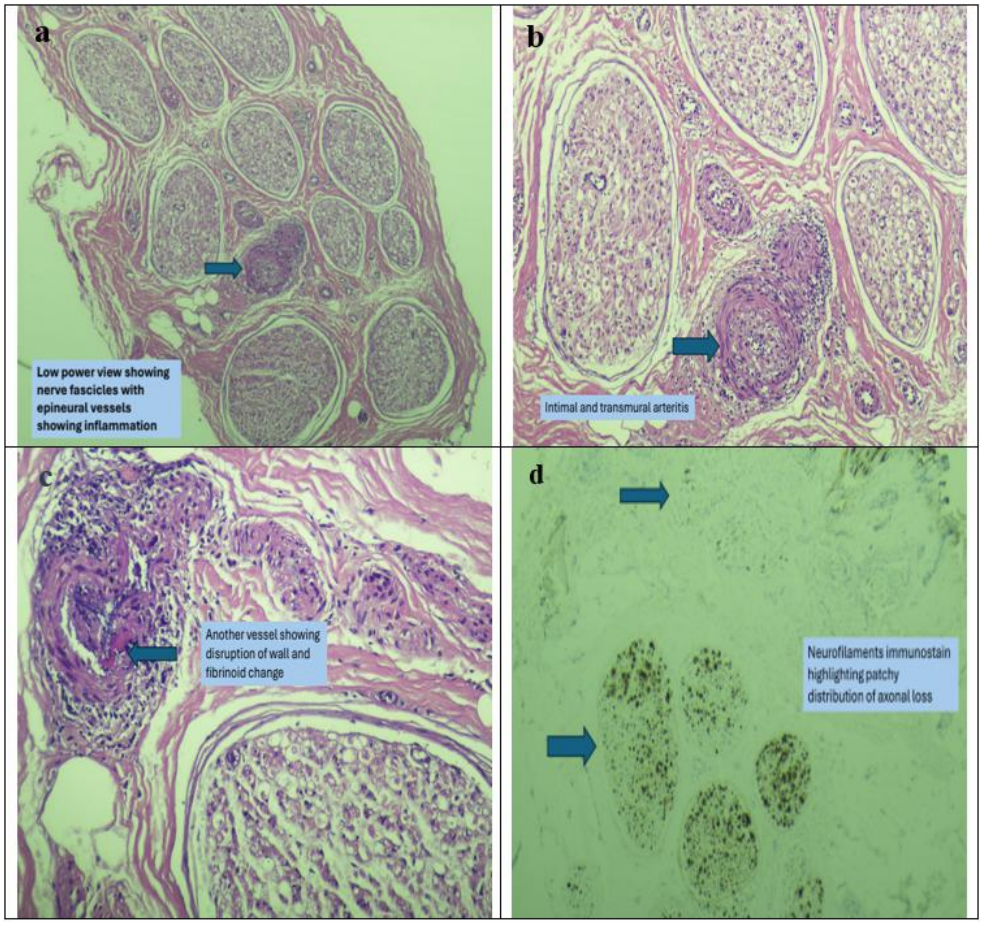


Figure 2: Common peroneal arteries and dorsalis pedis arteries appeared irregular, narrowed, thickened and attenuated bilaterally.

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The patient was initiated on pulse therapy with intravenous methylprednisolone 1 g once daily for five days, followed by oral prednisolone for maintenance. As there was no significant clinical response to corticosteroids, five sessions of plasma exchange were administered on alternate days. For symptomatic management, the patient was prescribed tablet Cilostazol 100 mg orally twice daily and subcutaneous Low Molecular Weight Heparin (LMWH) 40 mg once daily.

The patient demonstrated significant improvement in pain symptoms. A rheumatology consultation was obtained and it was decided to initiate treatment with Rituximab. Unfortunately, despite medical therapy, the patient ultimately required limb amputation.

Discussion

This case highlights the rarity of peripheral nerve involvement and gangrene as initial presentations of vasculitis, particularly ANCA-associated types. Granulomatosis with polyangiitis, formerly called Wegner's granulomatosis is a systemic small to medium vessel vasculitis. A focal necrotizing vasculitis involving the small arteries and veins of the ear, nose and throat, the lungs, the kidneys and the heart is the pathological hallmark of GPA. Although it characteristically involves with upper or lower respiratory tract or kidneys with a prevalence of 90% and 78%, respectively, other organ system involvement also occurs later on in the disease course [2].

GPA also involves the PNS by affecting the vasa nervorum of the peripheral nerve and its involvement has been reported to occur in as much as 10.6%-43.8% of GPA patients [4,5]. However, peripheral neuropathy occurring as a sole manifestation of GPA is as rare as 2.4%-8% [4]. Mononeuropathy multiplex is the most common pattern of vasculitic neuropathy whereas distal sensory-motor polyneuropathy is fairly uncommon [5]. About 10%-40% of biopsy-proven vasculitic neuropathies can occur as distal-symmetric neuropathy [6]. The guidelines from the Peripheral Nerve Society provides diagnostic criteria for probable and definite vasculitic neuropathy. The diagnosis of definite vasculitic neuropathy includes (1) the presence of inflammatory cells in the vessel wall accompanied by pathologic evidence of acute or chronic vascular wall damage and (2) no evidence of another primary disease that mimics vasculitis pathology (lymphoma, lymphomatoid granulomatosis or amyloidosis). Probable vasculitic neuropathy can be suspected, if (1) the criteria for definite vasculitic neuropathy are not completely fulfilled, (2) the neuropathy is predominantly axonal and (3) perivascular inflammation plus signs of vascular damage or pathological predictors of vasculitic neuropathy [7].

Similarly, the prevalence of digital ischemia and gangrene in the GPA population is suspected to be <1% [8]. The Pathophysiology of digital gangrene is most probably due to destruction of medium-sized vessels due to active inflammation leading to ischemia and subsequent infarct of the overlying sub-cutaneous tissues and skin [9]. The diagnosis of cutaneous involvement in Granulomatous with polyangiitis is done *via* skin biopsy with subsequent histopathological examination of affected tissues.

The diagnosis of vasculitic neuropathy is relatively straightforward when it arises in the context of an already established systemic vasculitic syndrome. However, when neuropathy represents the initial clinical manifestation, establishing the diagnosis can be challenging, particularly because only a subset of vasculitic neuropathies exhibits the classic clinical picture of mononeuritis multiplex and in such cases extensive workup pertaining to vasculitis should be done if there is a high clinical suspicion. In our case, the patient presented with neuropathy as the first indication of underlying vasculitis and notably, with an atypical pattern characterized by symmetrical polyneuropathy, further complicating the diagnostic process. The only clinical clue suggestive of a vasculitic etiology in this case was the presence of concomitant peripheral gangrene, which raised suspicion for an underlying vascular inflammatory process and ultimately guided us to further investigate for vasculitis.

Following an extensive diagnostic workup, our patient was found to have markedly elevated titers of Cytoplasmic Anti-Neutrophil Cytoplasmic Antibodies (C-ANCA). After which we subsequently performed CT angiogram of the aorta, its major branches and the upper and lower limb vasculature, which revealed mural thickening and luminal attenuation across multiple vascular territories, consistent with a diagnosis of medium to small-vessel vasculitis **(Figure 2)** High-Resolution Computed Tomography (HRCT) of the chest revealed no evidence of alveolar hemorrhage or nodular opacities. However, urinalysis report, including dipstick and Protein-to-Creatinine Ratio (PCR) demonstrated significant proteinuria, raising concern for renal involvement. Despite this finding, the patient declined renal biopsy and the nephrology team concurred with this decision, citing the potential procedural risks and deeming it clinically inadvisable under the circumstances. Based on the 2017 provisional classification criteria established by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) for Granulomatosis with Polyangiitis (GPA), a cumulative score of 5 or higher is required to support the diagnosis. This threshold yields a diagnostic sensitivity of 91% and a specificity of 94%, ensuring a high degree of accuracy in distinguishing GPA from other ANCA associated vasulutis *i.e.,* Microscopic polyangiitis and Churg Strauss Syndrome. Our patient scores 5 points based only on serological criteria.

Histopathological examination of nerve biopsy is the gold standard investigation for diagnosis of vasculitic neuropathy 7 and our patient fulfilled the criteria of definitive vasculitic neuropathy based on sural nerve biopsy findings 7 of epineural vessel inflammation with

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inflammatory cell infiltrate, luminal narrowing, fibrinoid necrosis of one of the vessel walls and sartorial loss of axons from the fascicles suggestive of axonopathy **(Figure 3)**.

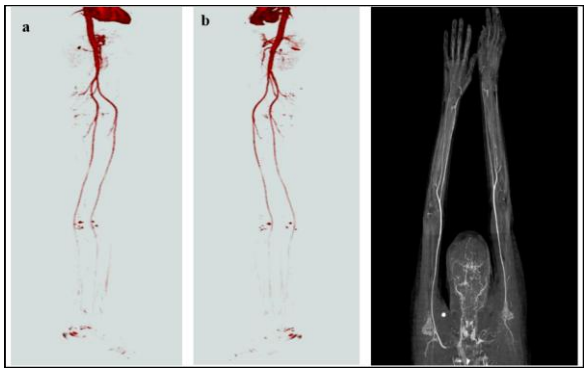


Figure 3: Vessel walls and sartorial loss of axons from the fascicles suggestive of axonopathy.

Without treatment, ischemia and gangrene can progress and lead to significant disability. Prompt initiation of therapy not only addresses current manifestations but also reduces the risk of further vascular damage and systemic involvement. Vasculiyic neuropathy should be treated according to the guidelines of the underlying vasculitis causing the disease. However, standard treatment of systemic vasculitic neuropathy are corticosteroids, usually with a dose of 1 mg/kg daily. However, it is extremely important to treat underlying vasculitis. The treatment of AAV consists of remission induction and maintenance of remission. Glucocorticoids and either cyclophosphamide or rituximab combination is the recommended treatment for remission induction in the setting of new onset organ or life-threatening AAV. Because of high cost, rituximab is restricted for specific where rituximab is preferred over cyclophosphamide. For remission maintenance, low-dose glucocorticoids in combination with either azathioprine, methotrexate, mycophenolate mofetil or rituximab are recommended with azathioprine being the most preferred. Our patient was given pulse IV methylprednisolone 1 gm /day for 5 days and cyclophosphamide, due to non-affordability of rituximab. Despite treatment the patient had non salvageable tissue and had to undergone below ankle amputation of both legs.

Conclusion

Recognizing peripheral nerve involvement and gangrene as potential initial signs of vasculitis, especially ANCA-associated vasculitis, is vital. Timely identification of underlying vasculitis *via* extensive workup is paramount, as untreated vasculitis can rapidly progress to irreversible complications. A close follow up of these patients is also essential to identify further systemic involvement. This case underscores the need for thorough investigative work-up and aggressive intervention to prevent long-term disability and improve patient outcomes.

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