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# Non-Systemic Vasculitic Neuropathy: An Enigmatic Clinical Entity

Authors' Contribution:
Study Design A
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Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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**Conflict of interest:** None declared

**Patient:** Female, 63
**Final Diagnosis:** Non-systemic vasculitic peripheral neuropathy
**Symptoms:** Paresthesia
**Medication:** —
**Clinical Procedure:** Sural nerve biopsy
**Specialty:** Rheumatology

**Objective:** Challenging differential diagnosis

**Background:** Non-systemic vasculitic peripheral neuropathy is a rare condition characterized by necrotizing inflammation resulting in luminal narrowing of the vasa nervorum, leading to ischemic injury to peripheral nerves. Here, we present the case of 63-year-old woman with subacute onset of severe hyperesthesia of the lower extremities accompanied by foot drop.

**Case Report:** A 63-year-old woman with prolonged history of uncontrolled diabetes mellitus presented with subacute onset of severe bilateral lower extremity hyperesthesia and motor weakness along with left-sided foot drop. She had multiple emergency room visits with no relief of her symptoms. High doses of analgesics were insufficient to control pain. Laboratory tests were positive only for high erythrocyte sedimentation rate and C-reactive protein. A skin biopsy obtained 5 cm above the left lateral malleolus revealed medium-sized dermal vasculitis with dense mononuclear infiltrate. Electromyography showed peripheral neuropathy. A nerve biopsy was needed to reveal the exact diagnosis.

**Conclusions:** Diagnosis of non-systemic vasculitic peripheral neuropathy can be delayed or missed in patients with uncontrolled diabetes mellitus, leading to significant morbidity. Elevated markers of inflammation in the absence of a possible explanation should prompt the clinician to perform a nerve biopsy; however, it is an invasive procedure and is associated with complications of post-neuropathic pain and delayed wound healing. Magnetic resonance angiography of the lower limbs, if combined with skin biopsy, can save the patient from undergoing nerve biopsy.

**MeSH Keywords:** Angiography • Electromyography • Vasa Nervorum

**Full-text PDF:** http://www.amjcaserep.com/abstract/index/idArt/894601

## Background

Non-systemic vasculitic peripheral neuropathy (NSVN) is an uncommon disorder first defined by Dyck et al. in 1987 [1]. NSVN is characterized by necrotizing inflammation resulting in luminal narrowing of the vasa nervorum, leading to ischemic injury to peripheral nerves. A definitive diagnosis requires nerve biopsy, but the diagnostic sensitivity is no more than 50–60% [2]. Though NSVN has a characteristic presentation involving only the peripheral nervous system, the pathogenesis is unknown. Here, we report the case of a 63-year-old woman with subacute onset of severe paresthesia of the lower extremities accompanied by foot drop, later diagnosed as NSVN. However, the diagnosis was delayed because the patient had a history of uncontrolled diabetes mellitus for years, confounding the diagnosis of NSVN with diabetic neuropathy. We propose a new idea based on published literature that the combination of magnetic resonance angiography (MRA) of the lower limbs below the knee level [3] and skin biopsy of the affected area [4] may be used in the diagnosis of NSVN, thus avoiding the definitive diagnostic test of nerve biopsy, which itself is associated with morbidity, especially in diabetic patients.

## Case Report

A 63-year-old Guyanese woman with type 2 diabetes mellitus, coronary artery disease status after 2 stents, and peripheral arterial disease with right femoral bypass presented with complaints of sudden onset of severe bilateral burning foot pain for 3 weeks. She also reported that joint pain in the hands and a rash on the feet coincided with the onset of pain. She developed lower-extremity weakness with inability to walk 1 week after the start of the above symptoms. There was no history of autoimmune disease or vasculitides. Her glycemic control had been suboptimal for several years, with Hba1c persistently over 9.0%. She had visited the emergency room multiple times in the prior 3 weeks for the same complaints, without relief. Physical examination revealed a non-raised, non-blanching petechial rash present over the dorsum of the feet and ankles. Nervous system examination showed decreased muscle strength, 3/5 as per the Medical Research Council (MRC) scale, of left lower extremity, with left foot drop. Motor strength of the right lower extremity was 4/5 with weak dorsiflexion and planter flexion of the right foot. Deep tendon reflexes were normal. She had hyperesthesia of the lower extremities.

Laboratory work-up showed leukocytosis of 12.0 K/mcl, hemoglobin of 10.9 mg/dl, platelets of 486 k/mcl, erythrocyte sedimentation rate (ESR) of 106 mm/Hr, C-reactive protein (CRP) 13.7 mg/dl, normal liver function test (LFT), normal blood urea nitrogen/creatinine, and urine analysis with no proteins and no blood. Hepatitis B and C panels were negative. Human immunodeficiency virus was negative. Antinuclear antibody, antineutrophil cytoplasmic antibody, cryoglobulins, and antiganglioside antibodies were also negative. A skin biopsy obtained 5 cm above the left lateral malleolus (Figure 1. Hematoxylin and Eosin (A): Low-power view; (B): High-power view) revealed medium-sized dermal vasculitis with dense mononuclear infiltrate. CD68, CD3 and Protein Gene Protein 9.5 staining was not done. Malignancy work-up, including computerized tomography (CT) scan of the chest, abdomen, and pelvis, was negative, ruling out para-neoplastic vasculitis. MRA of the lower extremities was not performed.

High doses of gabapentin along with opioids were insufficient to control the pain. The rash disappeared in a few days without immunosuppressive therapy. Nerve conduction studies

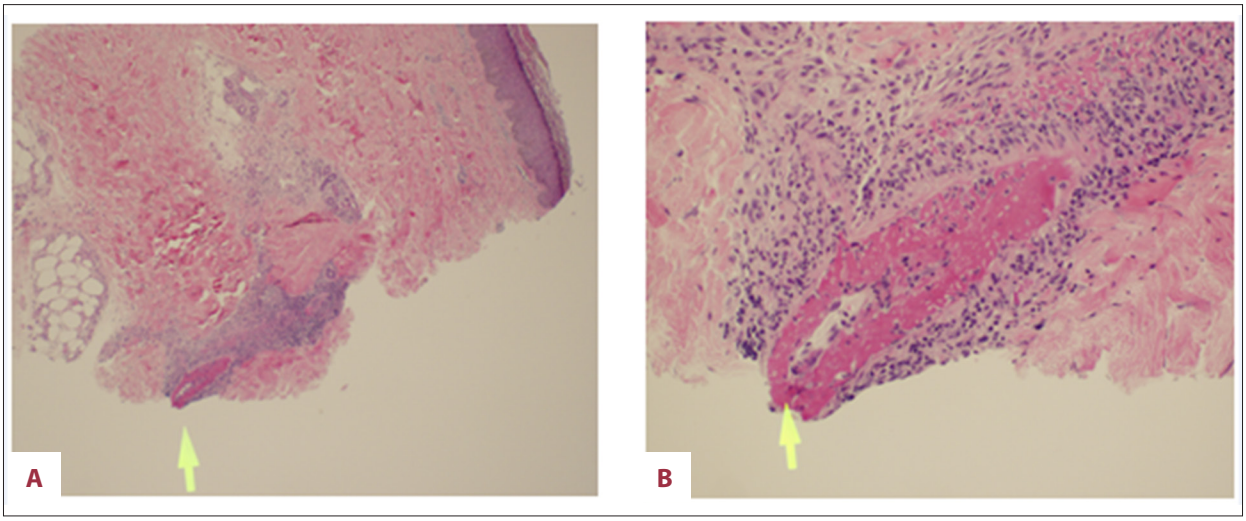


**Figure 1.** Hematoxylin and eosin (HE) staining (**A**): Low-power view and (**B**): high-power View: Arrow showing medium sized vessel in the deep dermis surrounded by dense mononuclear infiltrate; part of the vessel showing fibrinoid change in its wall.

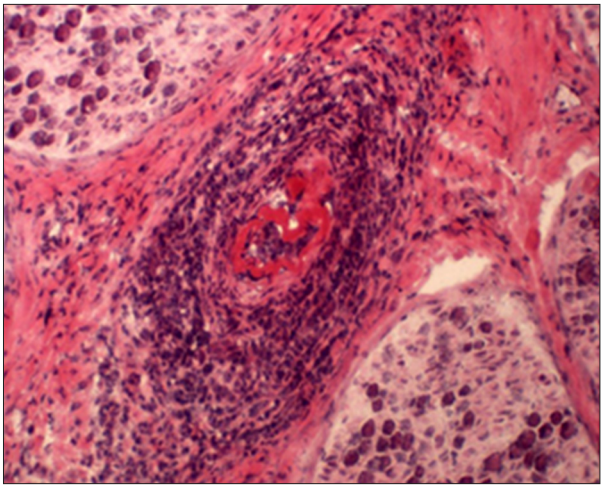

**Figure 2.** Showing dense collection of chronic mononuclear inflammatory cells surrounding and infiltrating epineural blood vessel and intraluminal microthrombi. Large foamy and lipid-laden macrophages are also seen.

revealed absent or reduced amplitude of bilateral peroneal (motor) nerves and bilateral tibial (motor) nerves. The left and right sural (sensory) nerves showed no responses bilaterally. F wave studies of the right peroneal and right tibial nerves were unelicitable. H-reflex studies of the left and right tibial nerves showed no responses. This was consistent with axonal neuropathy involving motor and sensory nerves of the lower extremities bilaterally.

Due to elevated markers of inflammation with negative systemic vasculitis work-up and electromyography (EMG) confirming peripheral neuropathy, the suspicion of non-systemic vasculitis was high, and was further supported by local skin biopsy. Intravenous immunoglobulins (IVIG) were empirically started and sural nerve biopsy was performed. Steroids were not initially started due to uncontrolled diabetes and history of cardiac disease. However, due to suboptimal response to IVIG, persistent pain, and weakness of the lower legs, Prednisone 60 mg daily (based on the body weight 1 mg/kg/day) was started. She was not started on any anticoagulant or antiaggregant treatment. Sural nerve biopsy (Figure 2) confirmed severe vasculitic neuropathy with active necrotizing vasculitis and axonal degeneration. Pain improved significantly and weakness started to improve. Motor strength on MRC scale improved to 4/5 on left lower extremity and 5/5 on the right lower extremity 2 weeks following the initiation of treatment. ESR and CRP normalized with treatment.

## Discussion

Non-systemic vasculitic neuropathy (NSVN) is an autoimmune localized vasculitic neuropathy restricted to the nerves of the peripheral nervous system and possibly muscles. The autoimmune response is directed towards small or medium-sized vessels. The onset of NSVN is subacute. Patients typically present with stepwise progressive painful asymmetric multifocal distal predominant neuropathy. Except for mild-to-moderate ESR

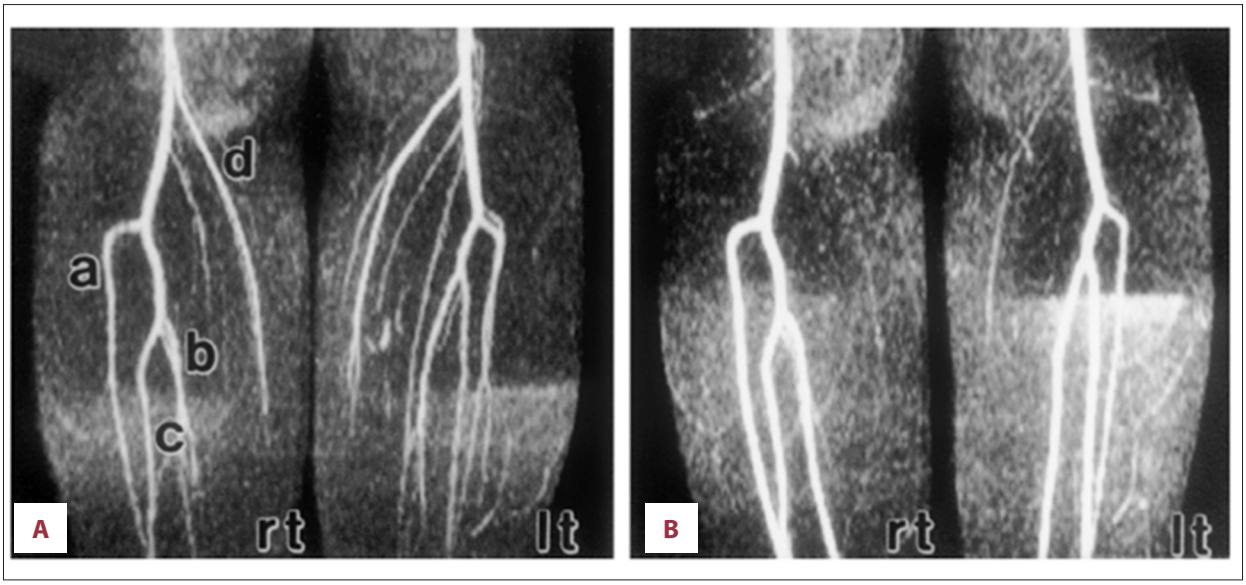


**Figure 3.** MRA of the lower limbs below the knee level. (**A**) Images obtained before corticosteroid therapy showed arterial occlusion at the distal level of limb arteries (anterior (a) and posterior (b) tibial artery, peroneal artery (c)). Collateral circulation (d) due to distal occlusion was noted at the proximal level of the femoral artery. (**B**) Images obtained 6 weeks after the initiation of corticosteroid therapy showed marked amelioration of the arterial occlusion with disappearance of collateral circulation. *Permission obtained from Dr. Yasuda. Published in Acta Radiol, 2003; 44(3): 316–18.*

elevation, the other markers of systemic inflammation are generally absent. Electromyography predominantly reveals axonal asymmetric polyneuropathy but pseudo-conduction blocks can occur [5]. NSVN may be a limited form of systemic vasculitis in which cytotoxic T lymphocytes (CTLs) are preferentially directed against the peripheral nervous system. CTLs are activated after binding to antigen-presenting cells. Markers of antigen-presenting cells (mannose receptors, CD1a, and CD1b) are up-regulated more in the epineurium compared to that of endoneurium. The matured CTLs then damage the target cells in the epineurium of the peripheral nervous system. However, the etiopathogenesis of NSVN is unknown [4, 6]. As there are no specific clinical or laboratory tests for NSVN, the diagnosis, especially in a patient with diabetes, depends on nerve biopsy, which is the criterion standard modality for NSVN diagnosis. However, sural nerve biopsy is an invasive technique leaving the patient with postsurgical neuropathic pain and sometimes delayed wound healing, especially in patients with uncontrolled diabetes mellitus.

In NSVN the preferentially affected vessels are epineural arterioles with diameter ranging from 20 to 300 microns. However, Sanada et al. [3] reported that larger arteries may be involved in NSVN, which was demonstrated by the use of magnetic resonance angiography (MRA). It was reported that MRA can be a useful test to aid in diagnosis of NSVN. Images (Figure 3; permission obtained) taken before the immunosuppressive therapy showed arterial occlusion with collateral circulation of the affected limbs. Images taken after 6 weeks of therapy showed significant improvement in arterial occlusion, with disappearance of collaterals [3]. Use of MRA is also mentioned by Collins in his literature review on recent advancements in NSVN [7].

Skin punch biopsy from an affected area can be a useful tool for diagnosis of NSVN. Uçeyler et al. [4] compared the results of skin biopsies from patients with NSVN (diagnosed by sural nerve biopsy) with those of axonal neuropathy without inflammation (also sural nerve biopsy-proven), and of healthy subjects. They found that perivascular T cells and macrophage infiltration is frequently found in skin biopsy samples of NSVN patients, but it was very rare in skin biopsy samples of patients with axonal neuropathy without inflammation. Skin biopsy also showed significant reduction of intraepidermal nerve fibers in patients with NSVN. Furthermore, they found that skin biopsies performed on patients with NSVN, who were previously treated with immunosuppressive therapy, demonstrated no T cells or macrophages. Skin biopsies from untreated NSVN patients showed variable numbers T cells and macrophages [4].

Based on the findings of Sanada et al. and Uçeyler et al., it can be proposed that MRA of the lower limbs combined with skin biopsy of affected area, supported by neurologic and electrophysiological examination, may prevent patients from undergoing sural nerve biopsy for the diagnosis of NSVN. NSVN can further be suggested by seeing the response on repeat skin biopsy and MRA following the initiation of immunosuppressive therapy. Along with clinical response, these factors may prove the diagnosis of NSVN.

Since systemic vasculitides (polyarteritis nodosa (PAN), microscopic polyangiitis, Churg–Strauss syndrome, Wegener's granulomatosis, rheumatoid arthritis, hepatitis B associated PAN, hepatitis C associated cryoglobulinemia, HIV vasculitis) can also present with asymmetric/multifocal neuropathy, these must be ruled out by clinical signs and symptoms, lab testing, imaging studies, and biopsy, if needed [8].

Cutaneous polyarteritis nodosa (CPN) and NSVN have similar presentation. Both have slight elevation of inflammatory markers and are treated with immunosuppressive therapy but they are distinguished by skin manifestations and the type of inflammatory cells involved. CPN presents with livedoreticularis and palpable purpura in contrast to NSVN, which has non-raised non-blanching petechial rash. Sural nerve biopsy reveals infiltration by polymorphonuclear cells and mononuclear cells in CPN and mainly mononuclear cells in NSVN [9].

The presence of uncontrolled diabetes can mislead the diagnosis of NSVN, leading to delays in treatment. However, it should be kept in mind that diabetic neuropathy seldom presents acutely. Elevated markers of inflammation contradict the diagnosis of diabetic neuropathy. The response to steroid therapy in NSVN suggests that immune system dysfunction is the likely etiology rather than uncontrolled diabetes.

Acute diabetic painful neuropathy associated with weight loss (diabetic neuropathic cachexia) is a disease entity which can mimic NSVN, but the former does not usually have motor weakness, and nerve conduction studies are usually normal or mildly abnormal [10].

Treatment of NSVN is mainly immunosuppressive therapy. Since the antigens involved in NSVN are unknown, the approach of removing antigens that trigger the pathogenic immune response cannot be applied in NSVN as in systemic vasculitis, necessitating the use of immunosuppressive therapy. The standard immunosuppressive therapy used for systemic necrotizing vasculitides is a combination of prednisone with cyclophosphamide. Similar combination therapy can be used for the treatment of NSVN. Treatment with combination therapy is advised for 7 to 12 months. If corticosteroid monotherapy is used, a follow-up is necessary. If there are any signs of neuropathy progression, cyclophosphamide should be added. The prognosis of NSVN is better than with other systemic vasculitis since it is limited to the peripheral nerve system only [7].

## Conclusions

NSVN is an enigmatic diagnosis, especially in patients with uncontrolled diabetes mellitus. Elevated markers of inflammation, such as ESR and CRP in the absence of infection or malignancy, should prompt the clinician to consider NSVN and seek nerve biopsy. Immunosuppressive therapy should be started as soon as possible to prevent morbidity.

It is important to note that skin biopsy of the affected area, combined with MRA of the lower limbs (tibial artery, peroneal artery), and supported by neurologic and electrophysiological examination, may prevent the patient from undergoing sural nerve biopsy for the diagnosis of NSVN. Skin biopsy and MRA of the lower limbs can be repeated more easily and may therefore be used for follow-up of disease activity and response to therapy. However, larger prospective studies are needed to demonstrate the diagnostic yield of combining skin biopsy with MRA for diagnosing and monitoring treatment response of NSVN.

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### Conflict of interest

There is no conflict of interest.

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