Chapter

Peripheral Neuropathy in ANCA Vasculitis

Mouna Snoussi, Faten Frikha and Zouhir Bahloul

Abstract

Antineutrophil cytoplasmic antibodies (ANCA)-associated diseases are necrotizing systemic vasculitides that affect small blood vessels (arterioles, capillaries and venules). This entity represents three main systemic vasculitides: granulomatosis with polyangiitis (GPA; formerly Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA; formerly known as Churg-Strauss' syndrome). Their clinical manifestations are polymorphous, being the most frequent respiratory, oto-laryngo-pharyngeal and renal involvement. Peripheral neuropathy (PN) is reported in almost 50% of the patients. The aim of this chapter is to discuss the prevalence, clinical presentation, treatment and prognosis of PN in ANCA-associated vasculitis.

Keywords: ANCA vasculitis, peripheral neuropathy, granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis, eosinophilic granulomatous with polyangiitis

1. Introduction

Anti-neutrophil cytoplasmic antibodies-associated vasculitides (AAV) are rare autoimmune diseases of unknown etiology. They are characterized by cell inflammatory infiltration and necrosis of small vessels [1]. They are classified as microscopic polyangiitis (MPA) granulomatosis with polyangiitis (GPA, previously known as "Wegener's granulomatosis") and eosinophilic granulomatosis with polyangiitis (EGPA, formerly known as "Churg-Strauss syndrome") [2]. The systemic inflammation seen in these vasculitis result in organ- and life-threatening diseases with a polymorphous clinical presentation. AAV can affect the peripheral nervous system and that could be difficult to diagnose and treat. In cases of pre-existing systemic vasculitis, the diagnosis is easier to make, but when the vasculitis neuropathy is the initial or unique manifestation of the vasculitis, it requires careful clinical, neurophysiological, laboratory and sometimes histopathological investigation. The frequency of vasculitis-related neuropathy is variable and depends on the type of vasculitis [3]. In this chapter, we will discuss the pathogenesis, diagnosis, treatment and prognosis of neuropathies in AAV including the MPA, GPA and EGPA.

2. Pathogenesis of peripheral neuropathy in ANCA vasculitis

Peripheral neuropathy in AAV is caused by thrombosis and ischemic damage of the vasa nervorum. Different etiological agents may induce vascular

inflammation [4]. Vascular injury is associated with neoantigens (usually infectious) on the endothelium and neutrophils. Eosinophils contribute to vessel inflammation, as seen in GEPA [5]. Immune complexes with certain immunochemical characteristics activate a complement cascade that induces neutrophil-mediated damage to the vessel wall. The presence of granulocytes is associated with fibrinoid necrosis as they release toxic enzymes during inflammation. Antineutrophil cytoplasmic antibodies identify constituents of neutrophil cytoplasm including proteinase 3 (PR3), myeloperoxidase (MPO) and elastase. The release of these cytoplasmic components induces the release of inflammatory mediators such as TNFα [6]. Inflammation of vasa nervorum leads to ischemia with axonal degeneration that mainly presents as mononeuritis multiplex [7].

3. Epidemiology of peripheral neuropathy in ANCA-associated vasculitis

Peripheral neuropathy is common in ANCA-associated vasculitis and can be the first manifestation of the disease. The prevalence of PN is variable depending on the type of AAV. It is particularly higher in EGPA (60–80%) than in MPA (40–50%) and GPA (20–25%) [8–14]. Vasculitis-related neuropathies are also seen in other systemic diseases such as cryoglobulinemic vasculitis associated with chronic hepatitis C virus (HCV) with a prevalence of 60% and in primary Sjogren syndrome [14] and rarely in large-vessel vasculitis [14] and other connective tissue diseases such as systemic lupus [15].

4. Symptoms and clinical features of the neuropathy in ANCA-associated vasculitis

PN is usually the first clinical presentation of systemic vasculitis especially in EGPA and MPA. In other cases, the PN is associated with systemic symptoms of the disease such as asthenia, weight loss, fever, arthralgia or arthritis and vascular purpura. PN is characterized by an acute onset of pain, weakness and sensory loss that predominantly affects the distal portion of the extremity. Initially, the PN may present as a mononeuritis evolving over weeks or months later into multifocal neuropathy or mononeuritis multiplex [16]. The pain is described as throbbing and aching rather than burning. The lower limbs are usually affected and the most common involved nerve is the deep peroneal nerve [11–14, 17–22]. In the upper limb, the ulnar nerve is the most common affected nerve [17]. The mononeuritis multiplex pattern evolves into an asymmetrical or symmetrical polyneuropathy pattern, which can progress into a generalized sensorimotor neuropathy [17]. Muscle weakness and atrophy is also variable inially mild but subsequently prominent [23]. Uncommon presentations of PN in AAV are symmetrical polyneuropathy from onset and pure motorneuropathy [17, 24].

5. Diagnosis and clinical results of peripheral neuropathy in ANCA-associated vasculitis

The diagnosis of vasculitis neuropathy in AAV is usually easier in patients already presenting with multiorgan involvement and mononeuropathy multiplex. However, the diagnosis may be more cumbersome in less typical presentations of AAV or when peripheral neuropathy is the unique manifestation of the disease.

In these situations, the diagnosis is helped by focusing on the medical history, physical examination, electrodiagnostic study and nerve biopsy. Electrodiagnostic testing reveal an axonal neuropathy with reduced sensory and motor nerve action potential amplitudes [25–28] with better preservation of the nerve conduction velocities and distal latencies. These findings are more often in the lower limbs [28]. The nerve biopsy should be guided by the nerve conduction studies and include the nerve and neighboring muscle, such as sural nerve and neighboring gastrocnemius or superficial peroneal nerve biopsy and peroneus brevis muscles [17, 22, 29–31]. Muscle biopsy may increase the diagnostic sensitivity when concomitantly performed with the nerve biopsy [32]. Nerve biopsy results supportive of vasculitic neuropathy include the presence of vessel wall inflammation with vascular damage; vascular deposits of immunoglobulin M, C3, or fibrinogen, hemosiderin deposits on direct immunofluorescence, asymmetric nerve fiber loss, prominent active axonal degeneration, and myofiber necrosis, regeneration, or infarcts in the peroneus brevis muscle biopsy [23, 32].

6. Particularity of PN in ANCA-associated vasculitis

6.1 PN in eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis formerly named Churg–Strauss syndrome is a systemic small-vessel vasculitis associated with asthma and eosinophilia. It was first described in 1951 by Churg and Strauss [33] who remarked the association between asthma, eosinophilia, systemic symptoms and the presence of necrotizing and granulomatosis vasculitis in different organs especially in the peripheral nerves [33]. EGPA is a rare disease, with an annual incidence of 0.5–4.2 cases per million inhabitants [34]. It affects people aged between 40 and 60 years with no gender predominance or ethnic predisposition [35, 36]. In 1990, the American College of Rheumatology (ACR) defined the classification criteria for EGPA to include asthma, eosinophilia >10%, neuropathy, non-fixed lung infiltrates, paranasal sinus abnormalities and extravascular eosinophils on biopsy (**Table 1**) [37].

A histologic diagnosis was required in the Chapel Hill classification in 1994 and 2012 [2, 37, 38]. EGPA is a necrotizing vasculitis with an eosinophilic-rich, granulomatous inflammation affecting small- to medium-sized blood vessels in the respiratory tract.

EGPA should be suspected in a patient with an adult-onset asthma in association with multiple systemic symptoms and a subacute asymmetric neuropathy. Asthma of variable severity is noted in 95–100% of patients and could precede the systemic manifestations by many years. Allergic rhinitis, recurrent sinusitis and nasal polyposis are also seen in the prodromic EGPA phase [39–41]. Eosinophilic cell infiltrates are

1. Asthma
2. Eosinophilia >10%
3. Neuropathy (mono- or poly-neuropathy)
4. Non-fixed pulmonary infiltrates
5. Paranasal sinus abnormalities
6. Extravascular eosinophil infiltration on biopsy
At least four of the six ACR criteria are required.

Table 1.
ACR classification of EGPA [37].

found in the lung, heart and gastrointestinal tract. The lung parenchyma is affected in up to two-thirds of EGPA patients [41]. Chest X-ray abnormalities generally consist of mainly peripheral, patchy and migratory infiltrates. On high-resolution CT, they appear as ground-glass opacities or poorly defined areas of consolidation, which often coexist with abnormalities due to lower airway involvement, such as tree-in-bud signs, bronchial wall thickening and small centrilobular nodules [41]. The second type of lung involvement is alveolar hemorrhage, which affects 3–8% of the patients [13, 41]. Heart involvement is a poor prognostic factor of the disease and correlated with the level of eosinophilia. Endomyocardial infiltration is the dominant feature, but coronary vasculitis, pericarditis and valvular defects may also occur [42]. Venous thromboembolic events, such as deep venous thrombosis and/or pulmonary embolism, are associated with eosinophilia [43]. Renal involvement can also be seen ranging from isolated urinary abnormalities (i.e., microscopic hematuria, proteinuria) to rapidly progressive glomerulonephritis. Skin lesion such as purpura, nodules, urticaria, livedo, and skin ulcers could also be reported mainly in the lower limbs [41].

PN is considered a cardinal feature of the vasculitic phase with a prevalence of 70% [41, 44, 45]. PN is often associated with generalized signs and symptoms of fever, weight loss, and weakness. It usually presents as a mononeuritis multiplex, often complicated by asymmetric foot or wrist drop, but it may also evolve into a symmetric or asymmetric polyneuropathy [41]; sensory deficits and neuropathic pain are frequent [19, 26]. PN is more frequent in ANCA-positive patients than in patients without ANCA antibodies [41, 44].

Laboratory findings in EGPA include a marked peripheral eosinophilia (usually >1500 cells/μL), which correlates with disease activity [46]. C-reactive protein and erythrocyte sedimentation rate are also high in the active phase [41]. ANCA with perinuclear immunofluorescence is noted in 74–90% [41]. Histologic confirmation is the key diagnosis with leukocytoclastic vasculitis with eosinophilic granulomas in biopsy sites such as the lung or kidney. Granulomas are rarely found in peripheral nerves [41].

6.2 PN in granulomatosis with polyangiitis

GPA is a systemic ANCA-associated granulomatous vasculitis whose lesions primarily affect the respiratory tract and kidneys [47]. Its annual incidence is 5–10/million with a prevalence of 24–157 cases per million. It occurs in both sexes at 65–74 years of age [48, 49]. GPA can affect the central and peripheral nervous system. Centrally, it can be responsible for strokes, brain masses, seizures, and meningitis. Peripherally, in the systemic form of the disease, it can present with a sensorimotor neuropathy or as a mononeuritis multiplex. Nasosinus involvement is observed in 70–100% of patients and present with epistaxis, nasal ulcers, nasal septum perforation and deformation (**Figure 1**) [50, 51]. The lungs are the second most common affected organ in 50–90% of patients and present with lung nodules, cavitations, infiltrates, pleuritis, pleural effusions, or alveolar capillary hemorrhages. Renal involvement affects 40–100% of patients with hematuria, proteinuria and renal failure due to segmental necrotizing and pauci-immune glomerulonephritis. Skin manifestations include vascular purpura, ulcers and nodules. The systemic symptoms include myalgia, arthralgia, anorexia, weight loss, ocular scleritis, episcleritis, uveitis, retinal alterations, retinal, thrombosis, orbital masses granulomatosis, myopericarditis, intestinal perforation and mesenteric vasculitis [50]. To make the diagnosis of PN related to GPA, it is necessary to consider all the clinical manifestations suggestive of systemic vasculitis like C-ANCA (anti-PR3) determination and histological evidence of necrotizing vasculitis, necrotizing glomerulonephritis or granulomatous inflammation from a relevant organ biopsy. In 1990, the American College of Rheumatology established criteria to help the diagnosis of GPA (**Table 2**) [52].

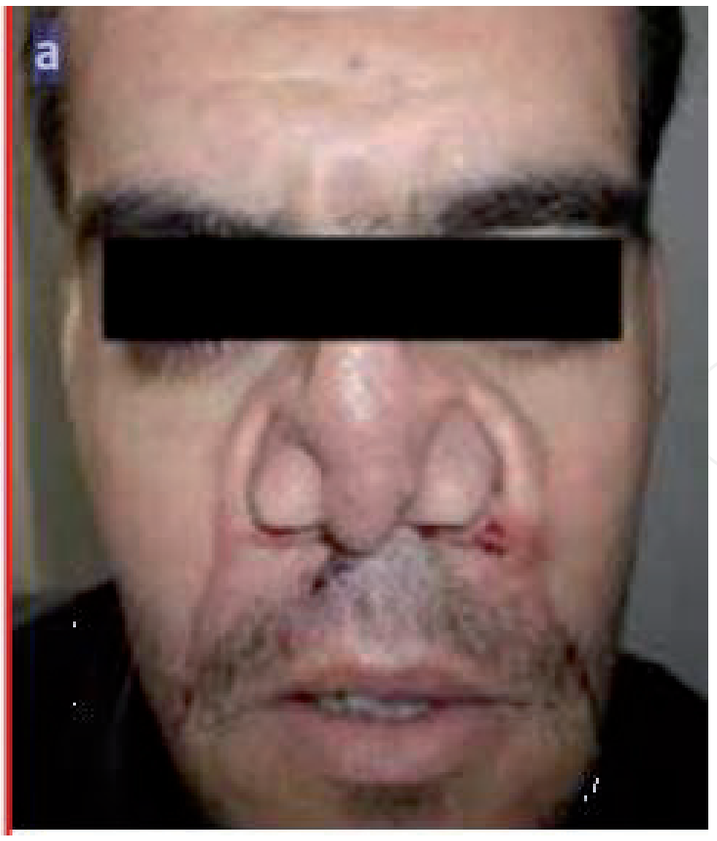

Figure 1.
Saddle nose deformity caused by bony destruction of the nasal cavity in a patient with Wegener's granulomatosis [50].

1. Sinus involvement
2. Alterations in pulmonary radiology
3. Alteration of urinary sediment (hematuria, hematic cylinders)
4. Histology revealing perivascular granulomas
At least two of the four ACR criteria are required to classify vasculitis as GPA with a sensitivity and specificity of 88% and 92%, respectively.

Table 2.
ACR classification of GPA [52].

6.3 Peripheral neuropathy in microscopic polyangiitis

Microscopic polyangiitis is an uncommon systemic vasculitis associated with perinuclear antineutrophil cytoplasmic (p-ANCA) or anti-myeloperoxidase (MPO). It was formerly considered as polyarteritis nodosa and in 1950, Wainwright and Davson used the phrase "microscopic polyarteritis" to describe this phenotype [53]. Microscopic polyangiitis predominates in men with an average age at onset between 50 and 60 years. Clinical manifestations include general symptoms of fever and weight loss in 70% of patients. Renal involvement is the main feature of MPA. It is characterized by a rapidly progressive glomerulonephritis in 80–100% of patients. It is shown by proteinuria in the nephrotic range in up to 50% of patients, microscopic hematuria, and urinary granular or red blood cell casts. Renal biopsy reveals focal segmental necrotizing glomerulonephritis in up to 100% of patients [54]. The second major organ being affected is the lung in 55% of patients. Clinical manifestations include hemoptysis and alveolar hemorrhage, infiltrates, pleural effusion, pulmonary edema, pleuritis and interstitial fibrosis. These symptoms are related to diffuse alveolar hemorrhage [55].

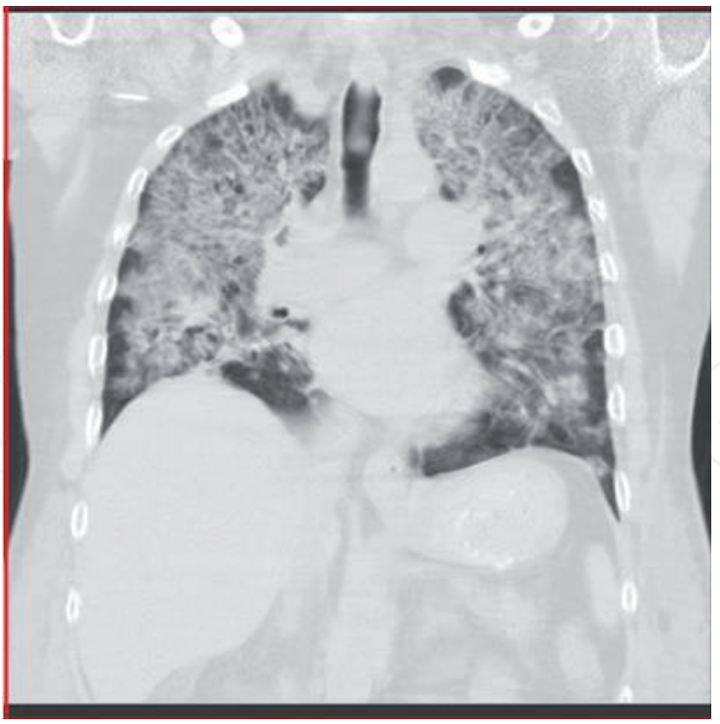

Figure 2.
Coronal chest CT scan image with diffuse bilateral ground glass infiltrates and focal areas of consolidation [55].

Computed tomography is necessary to confirm alveolar hemorrhage demonstrating the ground-glass attenuation (seen in >90% of patients) interstitial chronic inflammation of the alveolar septa and capillaritis (**Figure 2**) [55]. Skin lesions occur in 30–60% of patients being vascular purpura the main presentation. Other skin manifestations include livedo reticularis, nodules, urticaria and skin ulcers with necrosis. Skin manifestations are usually accompanied with arthralgia [54]. Neurologic involvement is common and affects between 37 and 72% of the patients. PN is a predominant feature that presents with a mononeuritis multiplex and distal symmetrical polyneuropathy [53]. Other clinical symptoms are gastrointestinal bleeding, intestinal ischemia, and liver dysfunction [54]. ANCA is the laboratory test that facilitate the diagnosis and is positive in 50–75% of patients with MPA, but its absence does not exclude its diagnosis. Biologic markers of inflammation are elevated such as erythrocyte sedimentation rate and C-reactive protein [56]. The diagnosis of the disease is based on clinical symptoms and biopsy of the affected organs.

7. Treatment of peripheral neuropathy in ANCA-associated vasculitis

The treatment is based on induction therapy and maintenance therapy. Unfortunately, there is not an universal protocol (dose or duration) for each form of therapy. Induction therapy is based in the combination of corticosteroids and cyclophosphamideor rituximab. Standard initial therapy consist of high-dose corticosteroids (prednisone 1 mg/kg/day) or IV methylprednisolone (1 g every day for three days and then once a week for three months) followed by a taper. Pulses of methylprednisolone are used in severe cases (i.e., mononeuritis multiplex and organ-threatening disease). Pulse IV cyclophosphamide (1 g/m^2 per month for six months; or 15 mg/kg every two weeks for three doses and then every three weeks for three to six months) is simultaneously started with corticosteroids, especially in more severe cases. Cyclophosphamide is adjusted by age (>60 years) and to renal function and leukocyte counts. IV Rituximab at 375 mg/m^2 per week for four weeks

Proteinuria >1 g/24 h
Creatinemia>140 μmol/L
Specific gastrointestinal involvement
Specific cardiomyopathy
Specific CNS involvement
One point for each of these five items when present.

Table 3.
Five-factor score in AAV.

every six months in combination with corticosteroids could be also used as induction therapy [57, 58]. Rituximab is often used in less severe cases with insufficient data in more severe neurological manifestations, however, some case studies are promising [7]. The five factor score (FFS) (**Table 3**) could be used to assess the prognosis and mortality of vasculitis in the next few years and then to guide when a more aggressive therapy is required, usually when FFS > 1 [59].

After the induction therapy, a maintenance therapy follows with oral immunosuppressants drugs such as azathioprine (1 mg/kg/day to 2 mg/kg/day), methotrexate (7.5 mg to 25 mg weekly), mycophenolate mofetil (1 g to 1.5 g, 2 times per day) or IV Rituximab pulsations every six months [7, 60]. Oral cyclophosphamide is not recommended because of the risk of serious complications [60, 61] such as hemorrhagic cystitis, alopecia, leukopenia, myelodysplasia, neoplasm, etc.

The symptomatic management of neuropathic pain consist of tricyclic antidepressants (i.e., amitriptyline, imipramine, nortriptyline, etc.), serotonin-norepinephrine reuptake inhibitors (i.e., duloxetine, venlafaxine) or antiepileptic drugs such as gabapentin and pregabalin, which are preferred because their better bioavailability [58]. Kinesitherapy should be included in the management of motor disability. PN in AAV requires regular medical visits due to the relapse risk.

8. Conclusion

PN is one of the possible neurologic manifestations encountered by physicians in AAV. Therefore, it is important to take a detailed medical history and examination and adequate investigations to assess for an underlying systemic vasculitis that may be associated with the neuropathy. Mononeuritis multiplex is the most common features of PN in the AAV. The electrodiagnostic studies and nerve biopsy may help in the diagnosis of the disease and PN. When the PN precedes the diagnosis of vasculitis, the medical history and biologic test, especially ANCA test, are vital for diagnosis, but its absence does not exclude the disease. PN in AAV carries a prognostic factor because of the potential risk for motor complications. Therefore, rapid treatment with corticosteroids and immunosuppressant agents is almost warranted in all patients, especially in severe cases. Continuous follow-up of PN in AAV is essential because of frequent relapses.

Conflict of interest

Authors disclose no conflict of interest.

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