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SPECIAL ISSUE

Images from the Nerve: An Atlas for Neurologists

Nerve biopsy in acquired neuropathies

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Abstract

A diagnosis of neuropathy can typically be determined through clinical assessment and focused investigation. With technological advances, including significant progress in genomics, the role of nerve biopsy has receded over recent years. However, making a specific and, in some cases, tissue-based diagnosis is essential across a wide array of potentially treatable acquired peripheral neuropathies. When laboratory investigations do not suggest a definitive diagnosis, nerve biopsy remains the final step to ascertain the etiology of the disease. The present review highlights the utility of nerve biopsy in confirming a diagnosis, while further illustrating the importance of a tissue-based diagnosis in relation to treatment strategies, particularly when linked to long-term immunosuppressive therapies,

KEYWORDS
inflammatory neuropathy, nerve biopsy, nerve tumor, neuroleukemiosis

1 | INTRODUCTION

When considering therapeutic interventions for acquired peripheral neuropathies, making a specific diagnosis is essential. A wide spectrum of therapies is now available across a range of acquired neuropathies including the demyelinating immune neuropathies such as chronic inflammatory demyelinating neuropathy (CIDP) and its variants, in addition to multifocal motor neuropathy (MMN) and vasculitic neuropathy. Across these presentations, suspected vasculitis is considered one of the most common indications for nerve biopsy, given that the diagnosis of CIDP and MMN tends to be made by clinical criteria and less invasive investigations.[1,2] However, considerable knowledge about the pathophysiology of these neuropathies has been gained through decades of nerve biopsies, mostly from an era when

other diagnostic methods were not yet available. In focal or multifocal neuropathies, malignancy may be a differential diagnosis, including nerve tumors, paraneoplastic phenomenon, and hematological malignancy. These conditions are frequently misdiagnosed, and often nerve biopsy is required to cement a definitive diagnosis and suggest a therapeutic pathway.[3]

Histopathological processing of peripheral nerve biopsies should be performed in a laboratory that is specialized in neuromuscular diseases. Neuropathological work-up should include tinctorial stains (H&E, Congo red, Turnbull or Pear's), immunohistochemistry (inflammatory cells, neurofilaments, immunoglobulin and light-chain deposition, transthyretin), and semithin resin sections to provide a comprehensive and detailed look at relevant structures. Teased-fiber preparations allow a longitudinal assessment of the nerve fibers including nodes of Ranvier. Electron microscopy of ultrathin sections allows analysis of unmyelinated fibers (however, this has been partly substituted by skin biopsy), changes in myelin structure, macrophage-mediated demyelination, small deposits, or pathological inclusions. In the cases reported in this article, we provide examples of how these different methods and stains can, in combination, lead to the correct diagnosis.

The present review will highlight the insights that nerve biopsy has provided for the auto-immune inflammatory neuropathies, and how this has shaped current views about pathogenesis. Attention is also drawn to less common entities that can easily be mistaken or overlooked, if not included in the differential diagnoses of peripheral nerve manifestations of the disease.

2 | CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: THE ROLE OF MACROPHAGES

Although CIDP is usually diagnosed based on clinical manifestations and electrophysiological findings, physicians may encounter difficulties in diagnosing CIDP due to the lack of specific biomarkers. We present the case of a 61-year-old female, with distal-predominant global weakness and sensory disturbance, who was found to have CIDP with pathological evidence of demyelination resulting from phagocytosis of myelin by macrophages. This case demonstrates the ongoing importance of nerve biopsy to confirm the diagnosis and further delineate the underlying pathogenesis of CIDP.

2.1 | Patient history

A 61-year-old woman noted numbness in the fingertips and toes at 60 years of age. The numbness gradually extended to the proximal limbs, and she became aware of unsteadiness of gait and weakness in both hands 2 months prior to admission. History included cervical cancer 7 years ago, which was resected. There was no family history.

2.2 | Neurological examination

Neurological examination demonstrated symmetrical weakness in the upper and lower limbs. Weakness was more prominent distally. Sensory examination identified a glove and stocking pattern of impairment. Light touch and pain sensation were reduced mildly in the upper limbs and moderately in the lower limbs. Vibration sense was mildly reduced in the upper limbs and severely impaired in the lower limbs. Joint position sense was mildly affected in the toes. Romberg's sign was positive. Deep tendon reflexes were reduced in all four limbs. Plantar responses were flexor bilaterally.

2.3 | Laboratory tests, electrophysiological, and imaging studies

Cerebrospinal fluid examination revealed an increased protein level (87 mg/dL; normal, 15-45 mg/dL) and a normal cell count. In the right median, ulnar, and tibial nerves, motor nerve conduction velocities (MCV) were decreased to 12.5, 11.7, and 10.4 m/s, and distal motor latencies (DML) were prolonged to 12.6, 8.1, and 22.1 ms, respectively. Compound muscle action potentials (CMAPs) in these nerves were, respectively, 3.4, 1.7, and 0.1 mV. Sensory nerve action potentials (SNAPs) in the median, ulnar, and sural nerves were absent. The neurophysiological findings were consistent with a demyelinating neuropathy. Magnetic resonance imaging revealed thickening of cauda equina. Blood tests revealed normal levels of IgG, IgA, and IgM subclasses. A monoclonal protein was not detected by serum immunoelectrophoresis.

2.4 | Nerve biopsy findings

Sural nerve biopsy revealed moderate endoneurial edema and mild reduction of myelinated fiber density on transverse sections. Teased-fiber preparations showed segmental demyelination (2.5% of myelinated fibers) without tomaculous appearance. On electron microscopic examination, phagocytosis of myelin by macrophages was observed (Figure 1). Onion bulbs were also infrequently detected. Unmyelinated fibers were well preserved. Thus, macrophage-induced demyelination seems to play a role in the pathogenesis of neuropathy in this patient, which is compatible with the classical concept of chronic inflammatory demyelinating polyneuropathy (CIDP).

2.5 | Discussion

CIDP is one of the major immune-mediated demyelinating neuropathies frequently encountered in clinical practice.[4] According to a study by Dyck et al., who established an entity of CIDP in 1975, a characteristic feature of this disease is macrophage-induced demyelination.[5] Since then, further pathological evidence of demyelination in CIDP patients has been reported.[6] The diagnostic criteria proposed by the

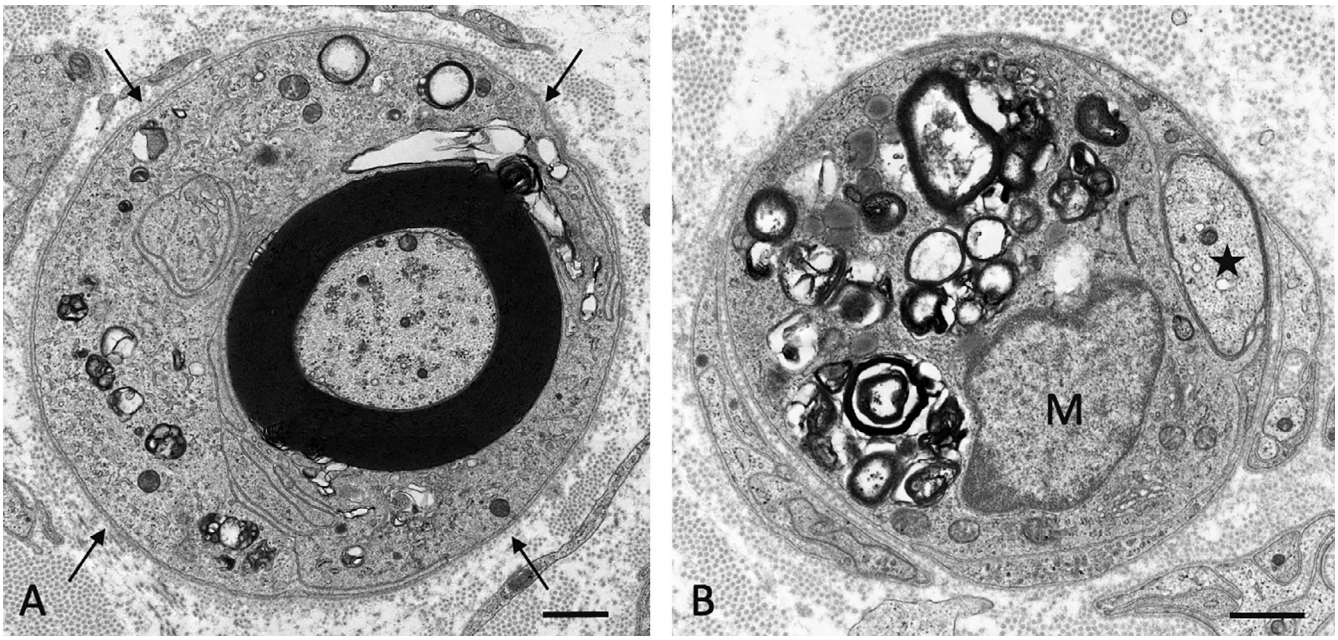

FIGURE 1 Representative electron microscopic photographs of myelin phagocytosis by macrophages in patients with CIDP. Transverse sections of sural nerve biopsy specimens. Uranyl acetate and lead citrate staining. A, A myelinated fiber is surrounded by macrophage cytoplasm that contains a small amount of myelin debris. The thickness of the myelin seems to be normal. Arrows indicate the basement membrane surrounding the myelinated fiber. B, A demyelinated axon is surrounded by macrophage cytoplasm abundant in myelin debris. An asterisk indicates an axon. A macrophage nucleus is indicated by M. Scale bars = 1 μm

Ad Hoc Subcommittee of the American Academy of Neurology AIDS Task Force in 1991 regarded the presence of demyelination using either electron microscopy or teased-fiber study mandatory for a definitive diagnosis of CIDP.[7] In contrast, in the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS) guideline, pathological evidence of demyelination is regarded as a supportive criterion.[8] At present, CIDP is usually diagnosed based on clinical manifestations and electrophysiological findings in daily practice. However, the diagnosis of CIDP is sometimes difficult. For instance, some patients diagnosed with neuropathy associated with lymphoma or amyloidosis, fulfill the electrophysiological criteria for CIDP.[9-11] Hence, demyelination resulting from myelin phagocytosis by macrophages will help to confirm the diagnosis of CIDP; however, lipid laden macrophages may also be evident in the acute inflammatory demyelinating polyneuropathy variant of Guillain-Barré syndrome.[6,12] Consequently, nerve biopsy remains useful when physicians cannot confirm a diagnosis of CIDP.

3 | CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY: A CASE WITH ANTI-NEUROFASCIN 155 ANTIBODIES

Electron microscopy, undertaken on longitudinal sections of nerve biopsy specimens, plays an important role in identifying distinct pathologies from typical-CIDP. In this case, evaluation of a sural nerve biopsy specimen with electron microscopy revealed the presence of characteristic paranodal lesions distinct from conventional macrophage-induced demyelination. Thus, demonstrating the importance of nerve biopsy with electron microscopy to elucidate the typical pathogenesis observed in patients with anti-neurofascin 155 antibodies.

3.1 | Patient history

A 15-year-old boy presented with a 7-month history of lower limb weakness. Numbness developed in the legs 1 month later. Weakness and numbness in the hands appeared soon afterwards, and he was unable to walk without assistance 2 months prior to admission to the hospital. Autonomic symptoms were absent, and there was no family history of neuropathy.

3.2 | Neurological examination

Neurological examination demonstrated mild facial diplegia. Although the other cranial nerves were unremarkable on inspection, a nasal quality of voice was noted. The patient was wheelchair bound. Symmetrical limb weakness, which was predominantly distal, was evident throughout although more conspicuous in the lower upper limbs. His grip strength was 3/2 kg (right/left side). Muscle atrophy was observed distally in all four limbs. A sensory deficit was conspicuous, particularly in the lower limbs. Although light touch and pain sensations were relatively preserved, vibration and joint position sense was

severely reduced. Mild postural and action tremor in the hands was observed. The deep tendon reflexes were reduced in four limbs and the plantar responses were flexor bilaterally.

3.3 | Laboratory tests, electrophysiological, and imaging studies

Cerebrospinal fluid examination revealed an increased protein level (199 mg/dL) and a normal cell count. The findings of nerve conduction studies indicated demyelinating neuropathy. Specifically, MCV, DML, and CMAPs in the median and ulnar nerves were 21.2 and 28.3 m/s, 11.7 and 8.6 ms, and 1.3 and 2.9 mV, respectively (right side). Conduction block was not observed. CMAPs in the tibial nerve and SNAPs in the median, ulnar, and sural nerves were not elicited. Cranial magnetic resonance imaging revealed no abnormalities. Blood tests revealed normal levels of IgG, IgA, and IgM. Monoclonal protein was not detected by serum immunoelectrophoresis. An enzyme-linked immunosorbent assay revealed anti-neurofascin 155 autoantibodies.

3.4 | Nerve biopsy findings

Sural nerve biopsy revealed mild endoneurial edema and normal myelinated fiber density on transverse sections. Teased-fiber preparations showed no segmental demyelination and very little axonal degeneration (2%). On electron microscopic examination, neither macrophage-induced demyelination nor onion bulb formation was observed. Unmyelinated fibers were well preserved. On longitudinal sections, detachment of myelin terminal loops from the axolemma (ie, paranodal dissection) was observed (Figure 2). These findings suggested that the aberrant nerve conduction in this patient is caused by anti-neurofascin 155 antibody-induced axo-glial detachment, but not by macrophage-induced demyelination.

3.5 | Discussion

Recent studies have revealed that sural nerve biopsy specimens from some CIDP patients show paranodal lesions induced by IgG4 autoantibodies against paranodal junction components, such as neurofascin 155 and contactin 1.[13-15] In particular, 5% to10% of CIDP patients have anti-neurofascin 155 antibodies. Patients with these antibodies can manifest characteristic features such as sensory ataxia, tremor, and poor response to intravenous immunoglobulin treatment.[6] Studies of longitudinal sural nerve sections reveal IgG4 deposition at paranodes and paranodal myelin terminal loop detachment from the axolemma.[14] As these patients lack classical macrophage-induced demyelination, the mechanisms of neuropathy are considered to be distinct from those in conventional CIDP patients. Recognition of this different pathophysiology has altered treatment paradigms in CIDP with paranodal antibodies, with the appreciation that these patients may be more responsive to rituximab.[16,17] Clinical trials are ongoing to prospectively evaluate treatment response to rituximab in CIDP with paranodal antibodies (NCT03864185).

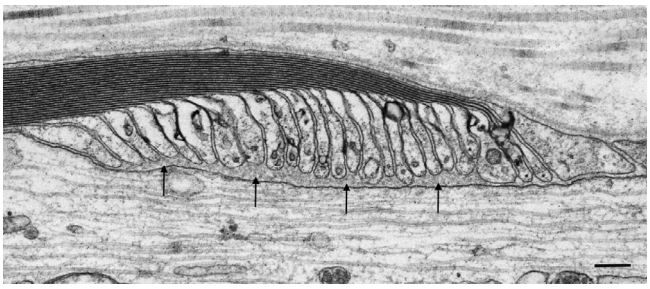

FIGURE 2 Representative electron microscopic photograph of paranodal dissection in patients with CIDP with anti-neurofascin 155 antibodies. Longitudinal section of the sural nerve biopsy specimen. Uranyl acetate and lead citrate staining. A clear space is observed between the paranodal myelin terminal loops and the axolemma (arrows). Scale bar = 0.2 μm

4 | NEUROPATHY WITH ANTIBODIES TO MYELIN ASSOCIATED GLYCOPROTEIN (ANTI-MAG-NEUROPATHY)

Anti-MAG neuropathy is a distal demyelinating neuropathy, distinct from CIDP, characterized by sensory ataxia and tremor. This case demonstrates the typical pathological finding of widely spaced myelin (WSM) on electron microscopic examination, which helps to confirm the diagnosis of this neuropathy.

4.1 | Patient history

A 68-year-old man noticed unsteadiness of gait at 65 years of age. Numbness in the toes appeared 1 year later and gradually spread to the lower legs and hands. He became aware of tremor in his hands at 67 years of age. As the unsteadiness and numbness gradually progressed, he was referred to our hospital for further investigation. Although a mild degree of glucose intolerance was previously noted, he had no other remarkable personal or family history. Autonomic symptoms were not noted.

4.2 | Neurological examination

Cranial nerves were intact. Distal predominant weakness was present bilaterally in both the upper and lower extremities. His grip strength was 9/7 kg (right/left side). A sensory deficit was noted in a distally accentuated glove and stocking pattern. Light touch and pain were mildly impaired, while vibration was severely reduced in the distal portions of the lower limbs. Joint position sensation was moderately reduced in the toes. Romberg's sign was positive. Deep tendon reflexes were absent in all four limbs. The plantar responses were flexor bilaterally.

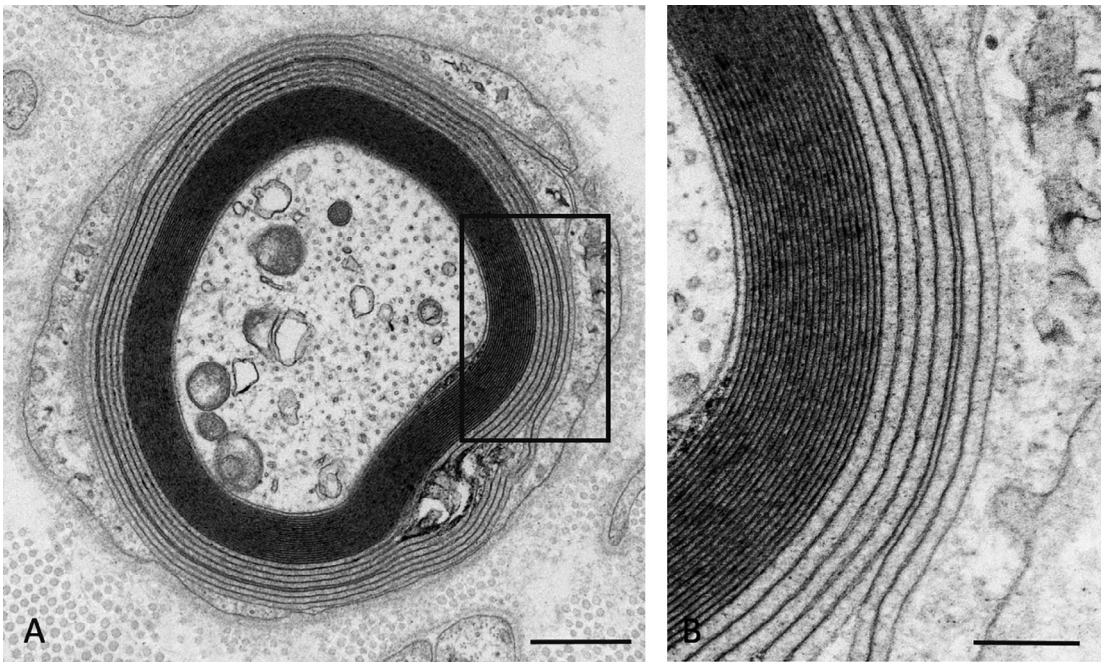

FIGURE 3 Representative electron microscopic photographs of widely spaced myelin in patients with neuropathy with IgM monoclonal gammopathy and anti-MAG antibodies. Transverse section of the sural nerve biopsy specimen. Uranyl acetate and lead citrate staining. Widely spaced myelin, defined as two or more wraps of myelin with a regularly separated intraperiod line and an intact major dense line, is observed in the outer layers of the myelin lamellae. A high-powered view of the region shown in the box in A, is shown in B. Scale bars = 0.5 μm A and 0.2 μm B

4.3 | Laboratory tests, electrophysiological, and imaging studies

Cerebrospinal fluid examination revealed an increased protein level (157 mg/dL) and a normal cell count. Nerve conduction studies demonstrated severely prolonged DML and a slowing of MCV in the median and ulnar nerves (12.8 and 8.5 ms for DML, 16 and 15 m/s for MCV, respectively). CMAPs in these nerves were also decreased (0.4 and 2.8 mV, respectively). CMAPs in the peroneal and tibial nerves were not elicited. SCV and SNAPs in the ulnar nerve were 11 m/s and 1.1 μV, respectively, whereas SNAPs in the median and sural nerves could not be elicited. Electromyography of the right anterior tibial muscle revealed fibrillation potentials and positive sharp waves, consistent with active denervation. Brain and spinal MRI were normal. Serum investigations identified an increased level of IgM (994 mg/dL, normal 35-220 mg/dL), and serum immunofixation demonstrated the presence of an IgM-kappa type monoclonal protein. Enzyme-linked immunosorbent assays and western blot analysis indicated the presence of antibodies against myelin-associated glycoprotein (MAG).

4.4 | Nerve biopsy findings

Sural nerve biopsy revealed mild endoneurial edema and a slight reduction of myelinated fiber density on transverse sections. Teased-fiber preparations showed a mixture of segmental demyelination (6%) with a tomaculous appearance and axonal degeneration (7%). On electron microscopic examination, WSM, defined as two or more wraps of myelin with a regularly separated intraperiod line and an intact major dense line was observed (Figure 3A,B). In contrast, neither demyelination caused by macrophages or onion bulbs were detected. Unmyelinated fibers were well preserved. Thus, the diagnosis of neuropathy with IgM monoclonal gammopathy and anti-MAG antibodies was confirmed.

4.5 | Discussion

Neuropathy with IgM monoclonal gammopathy and anti-MAG antibodies (ie, anti-MAG neuropathy) is another demyelinating neuropathy characterized by slow progression and predominant sensory symptoms, particularly sensory ataxia.[18] Nerve biopsy specimen studies suggest that the occurrence of widely-spaced myelin (WSM) results from the deposition of IgM and complement on myelin, where MAG is localized.[18] As WSM is a characteristic feature, and macrophage-induced demyelination is not found in anti-MAG neuropathy, this neuropathy is now considered to be distinct from CIDP.[8] Findings from neuropathy caused by IgG4 antibodies to paranodal components and anti-MAG neuropathy indicate the ongoing use of nerve biopsy to understand the pathophysiology of acquired neuropathy.

5 | VASCULITIC NEUROPATHY

Vasculitis remains a typical indication for nerve biopsy with important treatment implications. This case demonstrates an atypical phenotype of vasculitis with a diagnosis confirmed by typical nerve biopsy features. Thus, indicating the need to consider nerve biopsy in seemingly indolent neuropathies.

5.1 | Patient history

The 54-year-old female patient was admitted for diagnostic work-up of a distal symmetric axonal sensorimotor peripheral neuropathy. She reported sensory deficits and dysesthesia that had started in the feet 8 months prior were slowly progressive and now extended to the distal half of the lower legs. She complained of unsteady gait and loss of muscle strength that started 6 months ago. Further symptoms included Raynaud's phenomenon and intermittent lower limb skin rash, both of which were not evident at the time of review. There was no family history of peripheral neuropathy. The patient suffered from Crohn's disease since 1982 (in remission from 1986 onward) and associated spondyloarthritis.

5.2 | Neurological examination

At the first admission, neurological examination revealed reduced upper limb deep tendon reflexes and absent ankle reflexes. In addition, there was bilateral weakness of shoulder abduction and toe extension. Hypoesthesia and dysesthesia were evident in both feet and distal lower limbs.

5.3 | Laboratory tests, electrophysiological studies

Routine laboratory tests were normal except for slightly elevated C reactive protein (2.19 mg/dL). Vasculitis screening revealed elevated ANA and ASMA titers (1:10240) and elevated rheumatoid factor (IgA 87 U/mL, IgM >500 U/mL). Type 2 cryoglobulins were detected. CSF was completely normal.

5.4 | Nerve, muscle, and skin biopsy findings

Skin biopsy revealed reduction of intraepidermal nerve fiber density in the sample from the lower leg (lower leg 3.6 fibers/mm, upper leg: 13.1 fibers/mm) and detected perivascular macrophages and T cells (Figure 4A,B). The latter raised the suspicion of vasculitis and nerve and muscle biopsies were performed.

Sural nerve biopsy showed extensive perivascular inflammatory infiltrates around epineural vessels invading the vessel wall (Figure 4C,D). Three thrombosed vessels could be seen (Figure 4E,F), without intramural fibrinoid necrosis. No fragmentation of the internal elastic membrane, endothelial, or media disruption was observed, and there was no edema (Figure 4G). Immunohistochemical staining with anti-Leu4 (pan T cell marker) and anti-CD68 (macrophage marker), disclosed the presence of macrophages and T cells (CD8-positive T cells) within vasculitic infiltrates (Figure 5B,C). Semithin sections revealed axonal loss, some clusters of regenerating fibers, and some fibers undergoing Wallerian degeneration, but no thinly myelinated fibers or onion bulbs, thus demonstrating axonal pathology (Figure 5D).

Muscle biopsy of the gastrocnemius muscle showed some angular atrophic fibers, nuclear clumps, and fiber type grouping, thus presenting a histopathological pattern of neurogenic atrophy. Vasculitic infiltrates, immunohistochemically characterized as macrophages and T cells, were detected around peri- and endomysial vessels (Figure 5A-C). Definite vasculitis was diagnosed due to invasion of vessel walls by inflammatory cells and acute thrombosis.[19]

5.5 | Work-up regarding systemic vasculitis

Sonography of the abdomen was normal. CT scan of the thorax showed ground-glass opacity, consistent with vasculitis, and a CT scan of the nasal sinuses revealed maxillary sinusitis. Otorhinolaryngeal evaluation resulted in a diagnosis of chronic sinusitis, and ophthalmological assessment led to a diagnosis of keratoconjunctivitis sicca. FDG-PET revealed evidence of pulmonary, pericardial, and pleural vasculitis. Biopsies of the lung could not definitely confirm pulmonary vasculitis, although this was highly suspected.

5.6 | Treatment and follow-up

Intravenous methylprednisolone (1 g/d for 3 days) was started immediately after biopsy and was continued as a tapering oral treatment (10 mg/d finally). Due to systemic involvement, according to interdisciplinary consensus with the Department of Rheumatology, treatment with rituximab was initiated. Systemic involvement as well as neurological symptoms improved: Muscle strength recovered except for toe flexors (MRC 5-). Hypoesthesia and paresthesia of the feet remained, but gait was no longer impaired. Nerve conduction studies have not improved to date, with the last measurement performed 7 months after treatment.

5.7 | Discussion

This case presents a patient with the common clinical picture of distal-symmetric axonal sensorimotor neuropathy without evident signs or symptoms of systemic vasculitis (except for Raynaud's phenomenon and skin rash, which were not present at the time of review). The patient finally turned out to suffer from systemic vasculitis and was successfully treated with corticosteroids and rituximab. Diagnosis was predominantly made by nerve, muscle, and skin biopsy.

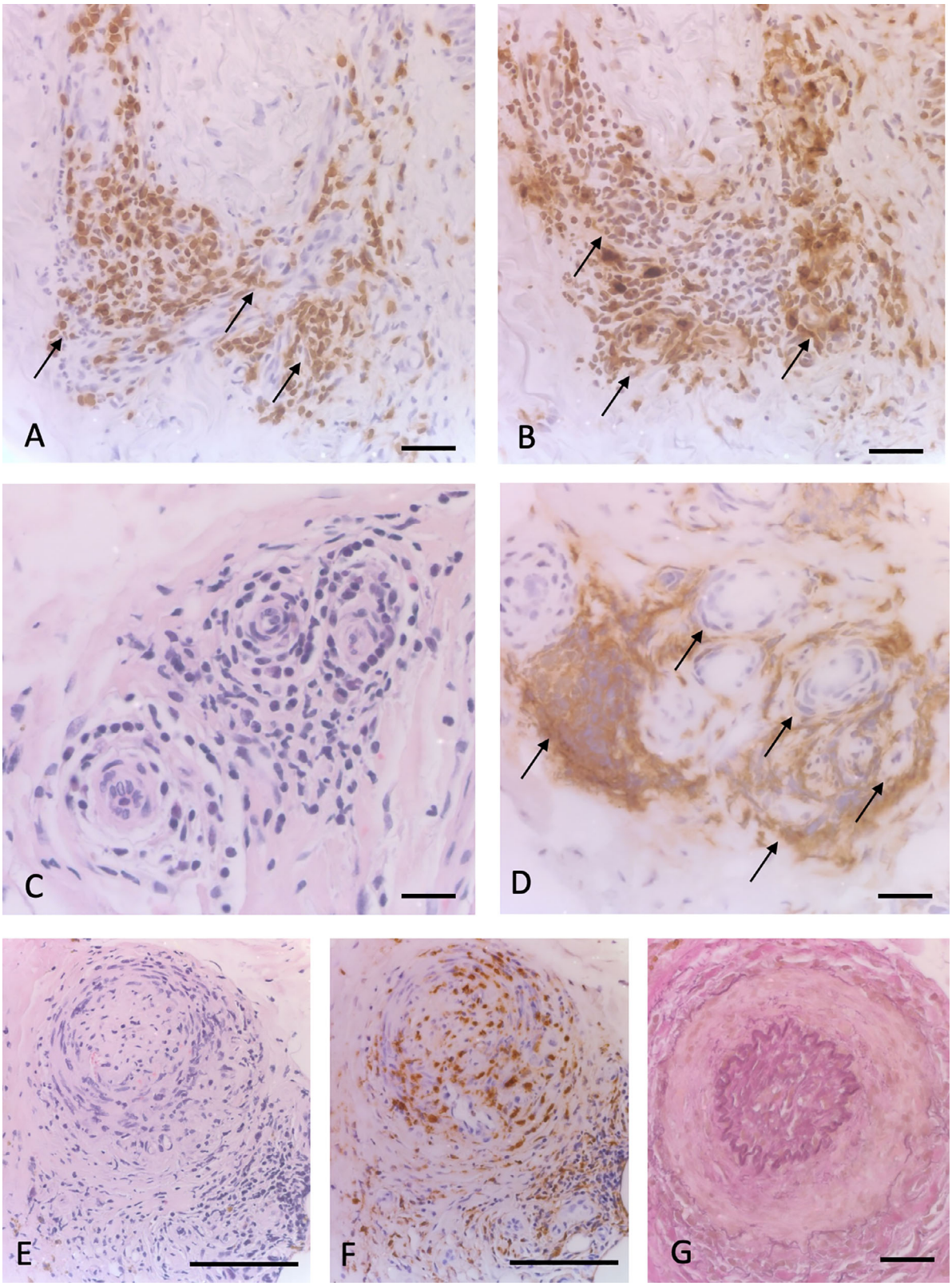

FIGURE 4 Photomicrographs of the patient's skin and nerve biopsy. A and B show an immunoreacted skin biopsy (of intact skin) with anti-CD3 (T cell marker, A) and anti-CD68 (macrophage marker, B). Numerous T cells A and macrophages B are found around dermal vessels (arrows), also invading the vessel walls. C-G are photomicrographs of the patient's nerve biopsy. Inflammatory cells in the hematoxylin-eosin stain C are further specified as T cells in immunohistochemistry with anti-Leu4 (T cell marker) D and are found around vessels (arrows) infiltrating the vessel wall of smaller vessels. Photomicrograph of hematoxylin-eosin staining E, immunohistochemistry with anti-CD68 (macrophage marker, F) and Elastica van Gieson staining G of the patient's nerve biopsy. A thrombosed epineural vessel (hematoxylin-eosin, E) with macrophages within the vessel wall (anti-CD68, F), but intact internal elastic membrane in the Elastica van Gieson staining G can be seen. Bar = 50 μm

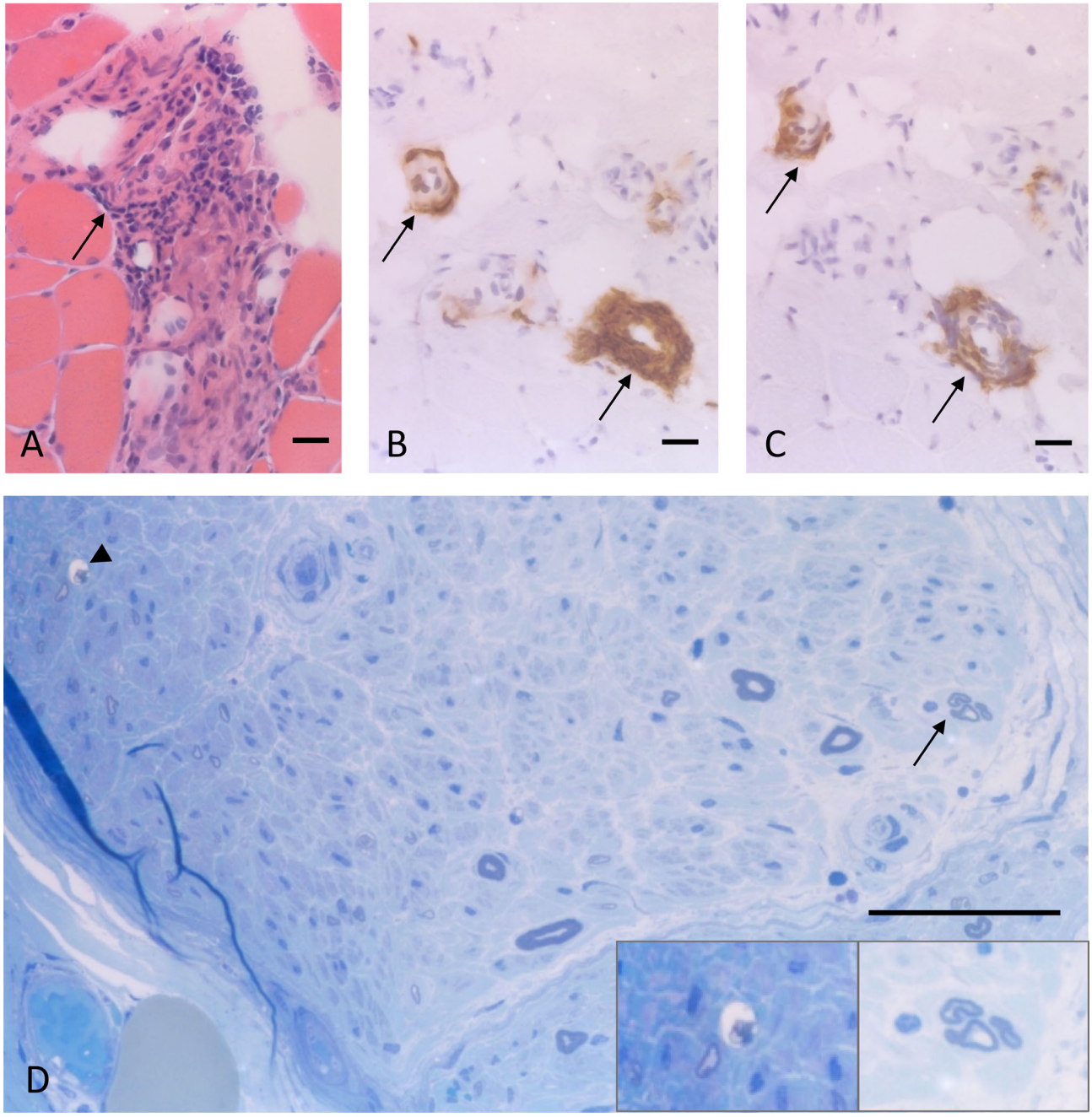

FIGURE 5 Photomicrographs of hematoxylin-eosin stain A and immunohistochemistry with anti-Leu4 (T cell marker, B) and anti-CD8 C of the patient's muscle biopsy, showing inflammatory infiltrates around perimysial vessels (A, arrows), also invading the vessel wall B, C and identified as T cells/cytotoxic T cells B, C. Photomicrographs of a semithin section of the patient's nerve biopsy are shown in D, revealing severe axonal loss, few clusters of regenerating fibers (D, arrow, right inlay) and some degenerating fibers (D, arrowhead, left inlay), but no onion bulbs or thinly myelinated fibers. Bar = 50 μm

Vasculitic neuropathy is typically characterized by an acute or subacute onset, multifocal or asymmetric involvement and fast, often step-wise, progression.[20] Distal symmetric sensorimotor axonal neuropathy is the most common phenotype of peripheral neuropathies of many etiologies and, hence, may not raise suspicion for vasculitis. However, a distal symmetric neuropathy can be found in up to 40% of patients with necrotizing vasculitis.[21] In the present case, skin biopsy provided the first evidence of a possible vasculitic neuropathy that could be confirmed by nerve and muscle biopsy, supporting the potential use of skin biopsy as a diagnostic tool in vasculitic neuropathy.[22] Inflammatory cells invading vessel walls were found in the nerve and muscle biopsies, as well as acute thrombosis of a vessel, thus fulfilling diagnostic criteria for definite vasculitis. However, we did not detect any vessel wall pathology, particularly there was no evidence of fibrinoid necrosis or fragmentation of the internal elastic lamina, media or endothelium or vascular hemorrhage. This is not

uncommon with a recent study identifying fibrinoid necrosis in only 4% and disruption of endothelium or media in 0% of 16 patients with definite vasculitic neuropathy.[23] Although systemic involvement of multiple organs could be determined, histopathological confirmation was restricted to the peripheral nervous system, supporting the importance of sural nerve biopsy, not only in non-systemic, but also in systemic vasculitic neuropathy.

6 | NEUROLYMPHOMATOSIS

Neurolymphomatosis, and less commonly neuroleukemiosis, remains a typical and necessary indication for nerve biopsy. We present the case of a 78-year-old male, with a rapidly progressive, painless polyneuropathy, who was found to have neuroleukemiosis due to chronic lymphocytic leukemia (CLL), demonstrating the ongoing requirement of nerve biopsy to make a correct diagnosis.

6.1 | Patient history

A 78-year-old male presented with a 4-week history of rapidly progressive, painless asymmetric proximal, and distal weakness with associated wasting of the intrinsic hand muscles, but no objective sensory examination findings. This was associated with a significant deterioration in gait, from independent mobility to the use of crutches, and impaired function due to the development of profound hand weakness. This occurred on a background of CLL diagnosed 1 year prior.

6.2 | Laboratory tests, electrophysiological, and imaging studies

Neurophysiology revealed absent or attenuated sensory potentials with motor conduction block and temporal dispersion at sites of non-compression, and prolongation of F-wave latencies. Needle electromyography showed severe ongoing denervation in the first dorsal interosseus and tibialis anterior muscles with reduced recruitment. The findings were consistent with a severe, subacute, asymmetrical, sensorimotor neuropathy with mixed axonal and demyelinating features. A wide differential diagnosis was considered, including vasculitis, paraneoplastic phenomenon, neoplastic infiltration, AMSAN, or POEMS syndrome.

On initial blood testing, a lymphocytosis was noted (78.1×10^9/l, normal range $4\text{-}10 \times 10^9$/l), with mild anaemia and hypogammaglobulinemia, and elevated free lambda light chains. Biochemistry, vasculitic, viral, and auto-immune blood screening was negative. Bone marrow biopsy showed 93% lymphoid infiltration with reduced hematopoietic reserve. Subsequent cytogenetic and FISH analysis demonstrated trisomy 12. MRI revealed no nerve root impingement, thickening or enhancement, cord lesion, canal stenosis, or cord compression. Incidentally, prominent lymphadenopathy, measuring up to 3.5 cm, was identified in cervical, supraclavicular, axillary, mediastinal, and para-aortic regions, consistent with CLL. CSF was bland with no atypia seen on cytology or flow cytometry, and a normal protein of 0.36 g/L (normal range 0.15-0.45 g/L).

Vasculitis with pseudo-conduction block was felt to be the most likely etiology, and the patient was treated with a 5-day course of intravenous 1 g/kg methylprednisolone, with limited improvement. As a result, a sural nerve biopsy was performed.

6.3 | Nerve biopsy findings

Sural nerve biopsy revealed a marked reduction in myelinated fiber density with frequently observed actively degenerating axons (Figure 6A). Teased-fiber preparations revealed active axonal degeneration in 5% of fibers. Extensive perivascular, monomorphic inflammatory cell infiltrates surrounding epineurial, subperineurial, and endoneurial vessels were seen, with wall invasion but no fibrinoid necrosis (Figure 6B-D). Immunohistochemistry identified a CD5+, CD23+, mildly CD20+ clonal population consistent with nerve infiltration by CLL (Figure 6E).

6.4 | Treatment and follow-up

The patient was treated with a CLL specific chemotherapeutic regimen including Obintuzumab, a CD20 monoclonal humanized antibody, chlorambucil, and dexamethasone. Treatment resulted in rapid and significant improvements in functional status with return to independent mobility within a month of treatment, with mild residual hand weakness and persistence of right-predominant, dorsiflexion weakness. Serial neurophysiology demonstrated minor improvements in previously observed conduction blocks. His white cell count improved to a nadir of 2×10^9/l (normal range $4\text{-}10 \times 10^9$/l). Over the last 4 years, he has continued to improve to near normalization of power, with residual asymmetrical sensory disturbance to the ankles and neuropathic pain.

6.5 | Discussion

Neurolymphomatosis, or more rarely neuroleukemiosis, as depicted in this case, is characterized by the direct infiltration of nerve roots, dorsal root ganglia, plexus or peripheral nerves with clonal populations of lymphomatous or leukemic cells, occurring in 5% of cases of lymphoma.[24] Neuroleukemiosis is less commonly seen[25-28]; however, was well described in the pre-chemotherapeutic era. Peripheral nerve infiltration is described in both acute and chronic leukemias.[26] CLL is typically thought of as an indolent disease characterized by lymphocytosis, lymphadenopathy, and B-symptoms, with complications resulting from immunodeficiency, deranged immune responses resulting in auto-immune phenomenon, and treatments. Neuropathy is a less recognized complication, occurring in 2.2% of CLL cases in one cohort,[29] resulting from viral infection or as a result of treatment,

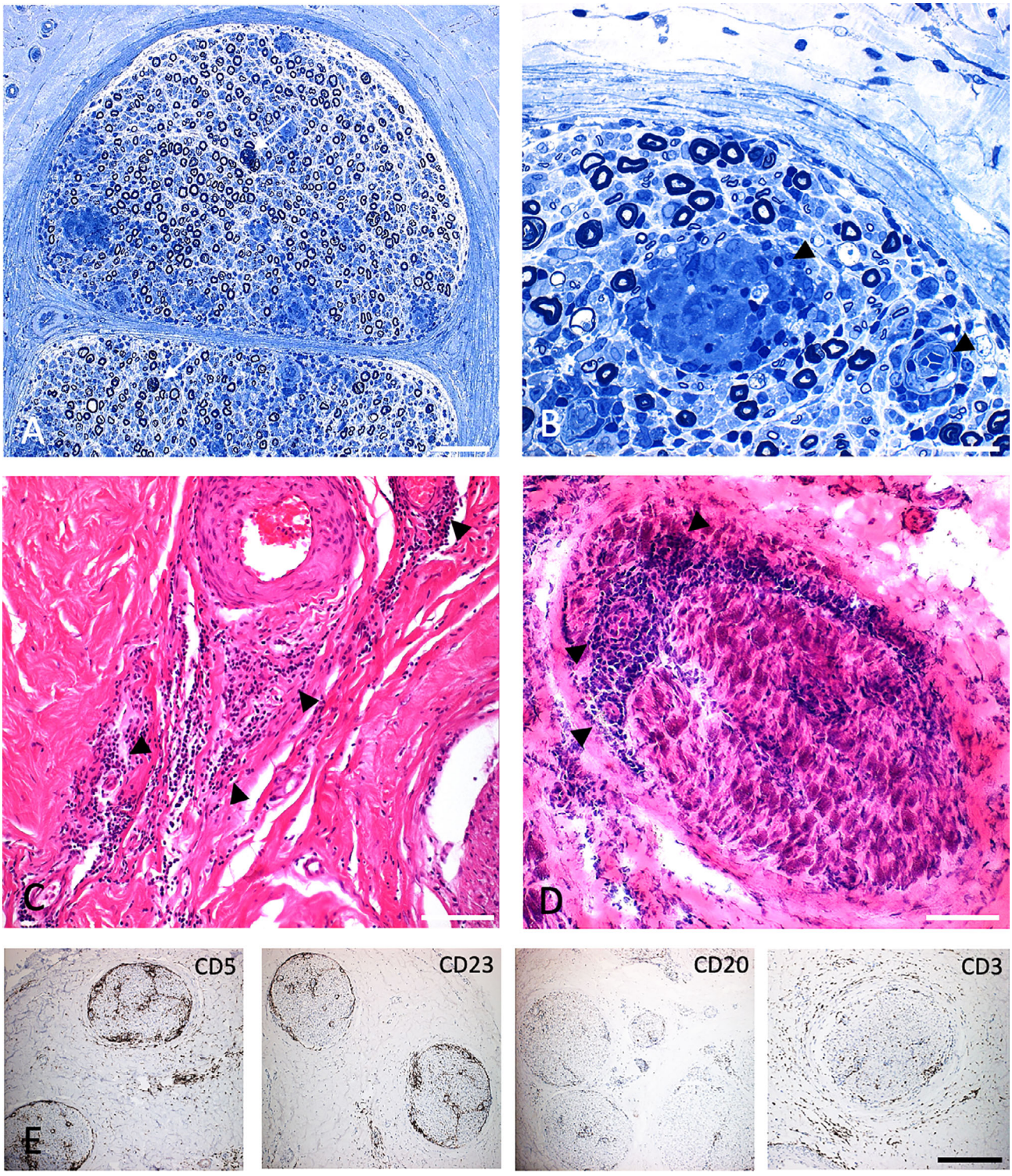

FIGURE 6 Sural nerve biopsy demonstrating features of neuroleukemiosis: A: marked reduction in myelinated fiber density with active degeneration of axons (white arrows), Toluidine Blue, Scale bar = 0.2 mm B-D: perivascular, monomorphic inflammatory cell infiltrate surrounding and invading, endoneurial B, epineurial C and subperineural D blood vessels (black arrow heads), B: Toluidine blue, Scale bar = 0.02 mm C-D: H&E Paraffin, Scale bars = 0.1 mm; E: Immunohistochemical staining for CD markers demonstrates a CD5+, CD23+, mildly CD20+ population, consistent with CLL, with occasional reactive CD3+ T cells Scale bar = 0.2 mm

more rarely due to secondary auto-immune processes (GBS, CIDP), or as a result of cryoglobulinemia or vasculitis. Neurolymphomatosis and neuroleukemiosis have similar clinical phenotype, investigational and nerve biopsy findings and are considered here as similar entities, although most data are derived from neurolymphomatosis cohorts.

In both conditions, a multifocal mononeuritis pattern is most commonly identified, however, a symmetric polyneuropathy with proximal and distal weakness can be found.[11,25,30] Often invasion of monoclonal cells is more pronounced in the proximal nerve trunks resulting in demyelination and secondary axonal degeneration in distal nerve portions.[11] Similarly, neurophysiology can demonstrate partial conduction block, as seen in this case, suggesting segmental demyelination.[11,25,31] It is important to note that, neurophysiological findings can often fulfill the EFNS/PNS criteria for CIDP, in one series 34% of patients with pathologically or radiologically confirmed neurolymphomatosis.[11] As such, a lack of response to IVIg in presumed CIDP should prompt repeat evaluation for alternative etiologies including neurolymphomatosis. Conversely, a response to steroids, in this situation, does not rule out neurolymphomatosis. Axonal degeneration does typically ensue and is, either alone or with demyelinating features, the predominant finding on nerve conduction testing in the chronic setting.[11,31]

In some, but not all, cases, there is evidence of meningoradicular disease on CSF cytology or magnetic resonance imaging, and FDG-PET/CT can, non-invasively, identify FDG-avid disease in peripheral nerves.[11] It is estimated that the diagnostic yield of MRI and PET in neurolymphomatosis is 80% and 88% respectively.[32] Despite this, nerve biopsy remains the gold standard for the diagnosis of neurolymphomatosis and is extremely important for diagnosis in primary disease. As the peripheral nervous system is a sequestered site, with intact blood-nerve barrier, neurolymphomatosis is also a common site of secondary disease recurrence.[11,33] In secondary lymphomatosis a biopsy is not definitively required, however, can be useful if there is any diagnostic uncertainty, or if the neuropathy occurs remotely to the primary lymphoma, thought in remission.[25]

Sural or focal nerve biopsy specimens typically demonstrate a reduction in myelinated and unmyelinated fiber density, with axonal degeneration observed on teased-fiber preparation.[11] Lymphomatous cell infiltration can be seen, often most conspicuously in and around the perineurium, thought due to greater lymphatic flow, with secondary extension to the endoneurium.[11] Invading cells can display obvious cellular atypia, and a clonal population can be identified further by immunohistochemical studies and PCR of the infiltrate.[11,34] PCR-based clonality testing is reported to have a sensitivity of 87% and specificity of 95% for identifying a clonal rearrangement in nerve biopsy specimens.[34] At sites of infiltration, demyelination is frequently observed, however, interestingly lymphomatous or other immune cells are not commonly seen to directly interact with the nerve or Schwann cell at these sites, suggesting an unknown soluble factor may incite demyelination.[11,35] Distal to sites of demyelination active axonal degeneration is identified with florid macrophage infiltration.[11] Infiltrating cells are often seen in a patchy distribution, and as such imaging guided localization of nerve biopsies can increase the sensitivity of nerve biopsy to 88%.[32,36] More aggressive blood-nerve and CSF penetrating chemotherapeutic regimens are required for treatment of both neuroleukemiosis and neurolymphomatosis, and due to the rarity of cases are targeted to the individual.[11,30] As such, identification of the monoclonal population, frequently by nerve biopsy, is essential to guide optimal patient management.

7 | ACQUIRED AMYLOIDOSIS

Acquired, light-chain (AL) amyloidosis, remains a frequent and important indication for nerve biopsy. We present the case of a 62-year-old male who presents with a rapidly progressive sensorimotor neuropathy on the background of a presumed toxic neuropathy. This case demonstrates the importance of nerve biopsy, in the context of negative alternate investigations, to make this important diagnosis.

7.1 | Patient history

A 62-year-old male gardener presented with a rapid onset of progressive distal and proximal lower limb weakness, distal sensory loss with peri-oral numbness, and painless ulceration of the toes. In addition, he reported postural hypotension, alternating diarrhoea and constipation, erectile dysfunction, and weight loss of 6 kg over 3 months. There was a background history of a sensory axonal neuropathy with neuropathic pain, which developed 1 year prior. At the time, all investigations were normal, including protein electrophoresis and immunofixation, and the sensory neuropathy was presumed toxic in etiology due to remote, but cleared, hepatitis C and prior alcohol excess.

7.2 | Neurological examination

At presentation, the examination revealed global weakness, areflexia, and glove and stocking sensory disturbance to the elbows and knees, with a sensory ataxia.

7.3 | Laboratory tests, electrophysiological, and imaging studies

Neurophysiology confirmed a marked deterioration with absent sensory and lower limb motor potentials, along with superimposed median neuropathies at the wrist. Given the rapidity of progression, the patient's care was transferred to a tertiary neuromuscular center for further investigation and management.

Blood testing revealed normal biochemistry, cell counts, viral, auto-immune, and paraneoplastic screens. No paraprotein was observed, however, lambda light-chain excess was identified 130 mg/L; normal range 5.71-26.3 mg/L), with a kappa to lambda ratio of 0.13 (normal range 0.26-1.65). Cerebrospinal fluid (CSF) analysis was acellular with normal protein and glucose, and negative cytology and flow cytometry. Fat pad biopsy was negative for amyloid. A right hilar mass, with an appearance suggestive of a primary lung malignancy and prominent 1 cm

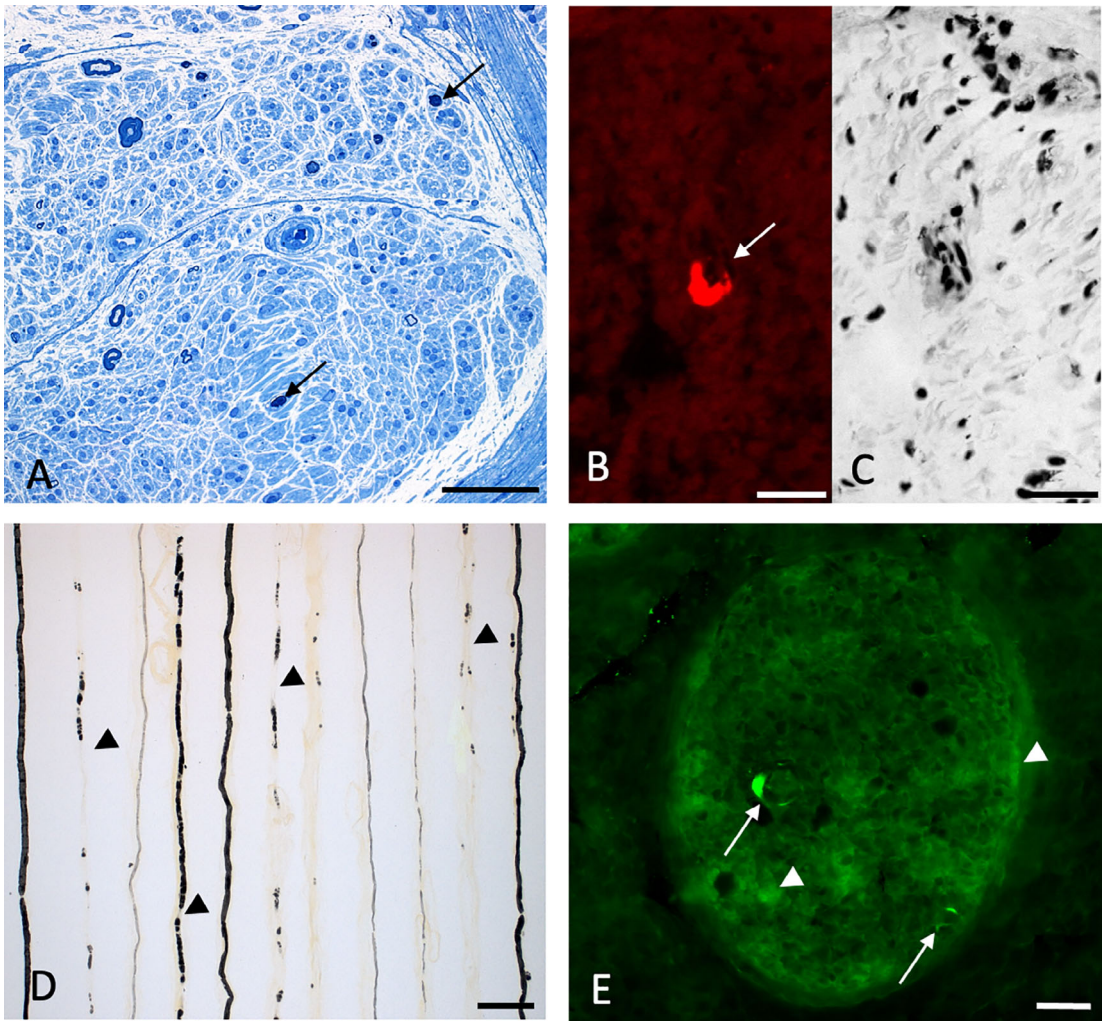

FIGURE 7 Sural nerve biopsy demonstrating typical features of AL-amyloidosis: A: Severe reduction in myelinated nerve fiber density with active axonal degeneration (black arrows), Toluidine Blue, Scale bar = 0.05 mm; B-C: Amyloid deposits in the endoneurial blood vessel wall (white arrow), Congo red stained frozen sections; B: Immunofluorescence with Texas Red filter, C: Congo red stained with transmitted light, Scale bars = 0.05 mm; D: Teased fibers demonstrate active axonal degeneration in 50% of fibers (arrow heads); Formalin-fixed nerve is incubated in 1.3% aqueous osmic acid for 48 hours, washed and suspended in a 2:1 glycerol/water solution and individual fibers are randomly teased from the specimen under a dissecting microscope, Scale Bar = 0.1 mm; E: Immunohistochemical lambda light chain staining of endoneurium (white arrow heads) and endoneurial vessel walls (white arrows), Scale bars = 0.05 mm

pre-tracheal node was demonstrated on CT scanning of the chest, abdomen, and pelvis. FDG-PET CT, however, identified no regions of abnormal metabolism to suggest an underlying high-grade tumor. An endobronchial ultrasound-guided fine-needle aspiration disclosed a moderate number of reactive lymphoid, histiocytic, and multinucleated giant cells, without malignancy, in the hilar lymph node.

7.4 | Nerve biopsy findings

Sural nerve biopsy revealed severe reduction in myelinated and unmyelinated nerve fiber density (Figure 7A) with active axonal degeneration (Figure 7A,D). Congo red staining with apple green birefringence was positive for amyloid deposits in the endoneurial and epineurial vessel walls (Figure 7B,C) with positive immunofluorescence for lambda light chains (Figure 7E), consistent with AL-amyloidosis.

7.5 | Staging, treatment, and follow-up

Follow-up investigations revealed a 10% plasma cell clone on bone marrow biopsy, without bony lesions on skeletal survey. Cardiovascular involvement was identified by increased intraventricular septal diameter (19 mm, normal ≤12 mm) and reduced global longitudinal strain (−13%, normal >−15%) on echocardiogram, along with extensive infiltration of ventricular walls with late gadolinium enhancement on cardiac MRI. Furthermore, proteinuria (5.4 g/24 hours, normal <150 mg/24 hours) was identified without renal dysfunction. Transthyretin gene testing was negative. Consequently, systemic

AL-amyloidosis with nerve, cardiac, and renal involvement was diagnosed in the context of a low-volume plasma cell myeloma.

The patient was treated with bortezomib, cyclophosphamide, and dexamethasone chemotherapy with a very good partial hematologic response, but limited organ response. Three years later, he relapsed with worsening mobility, autonomic dysfunction, proteinuria, and hematemesis and increasing lambda light-chain levels. He was commenced on lenalidomide after amyloid deposits were confirmed on gastric biopsy samples. To date, there have been no significant improvements with lenalidomide treatment, and as a result, the patient is under consideration for proteasome inhibition with ixazomib.

7.6 | Discussion

Light-chain (AL) amyloidosis, caused by the tissue deposition of monoclonal kappa or lambda light chains, is the most common cause of amyloid-associated neuropathy. Hereditary transthyretin and gelsolin amyloidosis may also cause neuropathy, with the latter disclosing the characteristic phenotype of corneal lattice dystrophy and multiple cranial neuropathies. Clinically, nerve involvement in hereditary transthyretin (ATTRv) amyloidosis is difficult to distinguish from AL-amyloidosis, although renal involvement is more frequently observed in AL-amyloidosis, as illustrated in the current case. AL and ATTRv can be distinguished by blood and urine parameters, although definitive testing of tissue specimens may often be required. This case demonstrates the importance of complete testing for a monoclonal protein by the combined use of serum and urine electrophoresis and immunofixation, and serum-free light chain analysis. If these tests are used in combination, a monoclonal protein can be identified in 99% of cases.[37] Given that monoclonal gammopathies and hereditary amyloidosis can coexist in ~20% of cases,[37] tissue analysis remains indispensable to identifying the causal amyloidosis subtype, in particular, if a monoclonal protein is identified.

Amyloid can be identified in numerous tissues, and to prevent potential morbidity due to biopsy of a target organ, biopsies can be taken from the subcutaneous fat, salivary gland, or rectum with yields of up to 75%, 86%, and 81%, respectively.[38-40] Due to the patchy nature of amyloid deposition, target organ biopsies may be required. Sural nerve biopsies exhibit a sensitivity of up to 83%,[38] disclosing an amorphous eosinophilic substance, with a fibrillar ultrastructure on electron microscopy. Amyloid is typically deposited extracellularly within the endoneurium, perineurium, and epineurium,[41] exhibiting Congo red staining and apple green birefringence under polarized light. Moderate to severe axonal loss with active degeneration and occasionally chronic inflammation cell infiltrates are evident pathologically.[41] Concomitant muscle biopsies typically demonstrate amyloid deposition, thereby increasing the diagnostic yield.[41,42]

The prognosis and management of amyloid-associated neuropathies are specifically linked to the underlying causative amyloid protein. As such, methods to ensure accurate diagnosis of amyloid subtype are essential in order to appropriately manage patients with these conditions. Distinguishing between amyloid protein subtypes is typically performed on tissue specimens by immunohistochemical staining and immunofluorescence. However, immunohistochemical staining can be challenging, failing to definitively type the amyloid in 30% of cases.[43] Immunohistochemical staining can be limited by the use of different staining methods and antisera, operator experience, cross-linking of antigenic epitopes by formalin fixation, contamination of nerve biopsy tissues by serum proteins, such as transthyretin or monoclonal proteins, and inaccuracy of comparative staining intensities of different antibodies.[43,44] Furthermore, intrinsic variability in the hypervariable region of the immunoglobulin light chains comprised in amyloid fibrils also impacts upon the sensitivity and reliability of IHC staining.[43]

Recent advancements in techniques have allowed for improved identification of amyloid protein subtype in nerve biopsy specimens. Specifically, mass spectrometry (MS) of amyloid plaques derived by laser microdissection (LD) from formalin-fixed paraffin-embedded tissues can accurately identify the amyloid subtype, and even specific TTR mutations, independent from the presence of serum proteins or clinical information.[44] In tissue samples negative on immunohistochemical staining, LDMS is able to identify the constituent amyloid fibril protein in 80% of cases.[43]

8 | IGM DEPOSITION DISEASE

IgM deposition disease is a rare cause of polyneuropathy characterized by the direct deposition of pentameric IgM into the nerve. We present a case of a 69-year-old male with a slowly progressive sensorimotor neuropathy developing over 8 years. Diagnosis of IgM deposition disease can only be made on nerve biopsy and carries significant treatment implications.

8.1 | Patient history

A 69-year-old male presented with a 12-month history of painful, glove, and stocking sensory disturbance and recent inability to run or raise his eyebrows. He described no autonomic or systemic symptoms. This occurred on the background of recurrent lower limb cellulitis 4 years earlier, in the context of which he was identified to have a mild axonal sensorimotor neuropathy. Four years after presentation he developed an acute decline over 3 weeks characterized by the development of significant bilateral foot drops, more profound lower motor neuron facial diplegia, dysarthria, and weight loss.

8.2 | Neurological examination

On examination, there was bilateral lower motor neuron facial weakness without facial sensory impairment, along with wasting of intrinsic foot muscles and weakness of toe extension and flexion. Ankle reflexes were absent with associated reduction of light touch, pain,

and temperature sensation to the mid-calf, vibration to the medial malleoli, and proprioception at the toe.

8.3 | Laboratory tests, electrophysiological and imaging studies

Initial neurophysiology revealed absent lower limb sensory and motor responses. Ipsilateral and contralateral blink reflex latencies were prolonged, suggestive of a possible demyelinating process affecting the trigeminal or facial nerves, or both. EMG revealed mild active denervation changes in frontalis and orbicularis oculi, without reinnervation, and chronic neurogenic changes in the lower limb musculature.

A 13 g/L IgM-kappa paraprotein was identified, with a small urinary monoclonal kappa band of 0.02 g/L. Anti-MAG and ganglioside antibodies were negative. Bone marrow revealed a small kappa light chain restricted B-cell population, consistent with Waldenstrom's macroglobulinemia. There was no leptomeningeal enhancement or thickening of the cranial nerves or parenchymal lesions seen on MRI of the brain. While the facial involvement was felt to be unusual, these features were thought most consistent with an indolent, axonal, paraproteinemic sensorimotor neuropathy, and a watch and wait approach was adopted.

Repeat neurophysiology, performed after the deterioration 4 years later, revealed absent lower limb sensory and motor potentials. However, in the upper limbs, the left ulnar sensory amplitude was reduced with slowing of distal motor conduction velocity (41 m/s) and prolongation of F-wave latency, but otherwise normal bilateral median and right ulnar, sensory, and motor responses. EMG revealed widespread acute and chronic denervation changes.

The findings were felt suggestive of a severe generalized sensorimotor neuropathy with predominantly axonal, and milder demyelinating, features. A bone marrow biopsy demonstrated a small B-cell NHL population with plasmocytic differentiation now making up 25% to 30% of marrow cellularity. Congo red staining of the bone marrow was negative. CSF protein was elevated (1.91 g/L, normal range 0.15-0.45 g/L) but was otherwise bland. An FDG-PET/CT revealed an enlarged spleen, but no FDG-avid disease.

8.4 | Nerve biopsy findings

Sural nerve biopsy revealed near total loss of large and small myelinated fibers with evidence of active axonal degeneration (Figure 8A). Endoneurial and subperineurial vessels had thickened hyalinized walls (Figure 8A,E), which stained positive for Congo red and demonstrated apple green birefringence (Figure 8B,D,E). In addition, large deposits of homogenous, amorphous, eosinophilic material were seen in the subperineurial space between perineurial cells, surrounding Schwann cells throughout the fascicles, and surrounding endoneurial vessels, with a peripheral more so than central distribution (Figure 8A-C). These deposits resembled amyloid, however Congo red staining was negative (Figure 8B). Immunohistochemical staining for IgM (Figure 8F) and kappa light chains (Figure 8G) were positive with complement 3 staining seen on some endoneurial vessels (not shown). Electron microscopy revealed that the eosinophilic deposits consisted of dense granular and granulofilamentous material, with occasional clumps of wavy 8 to 12 mm fibrils seen adjacent to the granular material (not shown). These ultrastructural features, with the immunohistochemical staining, were consistent with an amyloid-like IgM deposition-associated neuropathy.

8.5 | Treatment and follow-up

The patient was initially treated with Intravenous Immunoglobulin, however after the diagnosis was confirmed on nerve biopsy, he was given an additional course of rituximab. Unfortunately, the patient died from an unrelated cause while undergoing rituximab treatment.

8.6 | Discussion

IgM deposition neuropathy is a less appreciated form of paraproteinemic neuropathy where amyloid-like deposits are identified in nerve biopsy specimens. However, these deposits do not stain with Congo red and have a fibrillar ultrastructure distinct to AL-amyloidosis. This pathological finding has been consistently described since at least the 1960s,[45] with affected individuals having similar phenotypic characteristics. Onset is often in the seventh and eighth decade and patients, typically, have a painful, asymmetric, distal, lower limb predominant, sensory axonal neuropathy.[45-52] Motor involvement and distal amyotrophy occur late in the course of disease.[46,47] Cranial nerve involvement has been described.[45,48,49] There is typically no autonomic or additional organ involvement during long-term follow-up.[46] Patients most commonly have an underlying IgM lambda or kappa paraprotein, in the context of an underlying Waldenstrom's macroglobulinemia, or IgM MGUS. Patients may have a concurrent anti-MAG antibody[46,48]; however, the neurophysiology is not concordant, displaying typical axonal features rather than the prominent distal motor latency prolongation and conduction velocity slowing seen in an anti-MAG neuropathy.[53] Importantly, compared to AL-amyloidosis, and despite progression often to a severe neuropathy, patients have favourable long-term outcomes with survival reported up to 13 years.[46] As such, making a positive diagnosis is important to guide prognosis and prevent morbidity from inappropriate AL-amyloidosis treating chemotherapeutic regimens.

Diagnosis of amyloid-like IgM deposition disease can only be made by nerve biopsy. Typically, severe, but multifocal, loss of myelinated nerve fibers with axonal degeneration is seen. Extensive, acellular deposits of homogenous, formless eosinophilic, carbohydrate-rich, Periodic acid-Schiff (PAS) positive material, resembling amyloid, is observed in the endoneurium, in particular surrounding endoneurial vessels and in subperineurial spaces.[45-52] In some cases, this material is seen to replace most of the endoneurium and disrupt normal nerve architecture, in others only small deposits have been observed.[46,48,52]

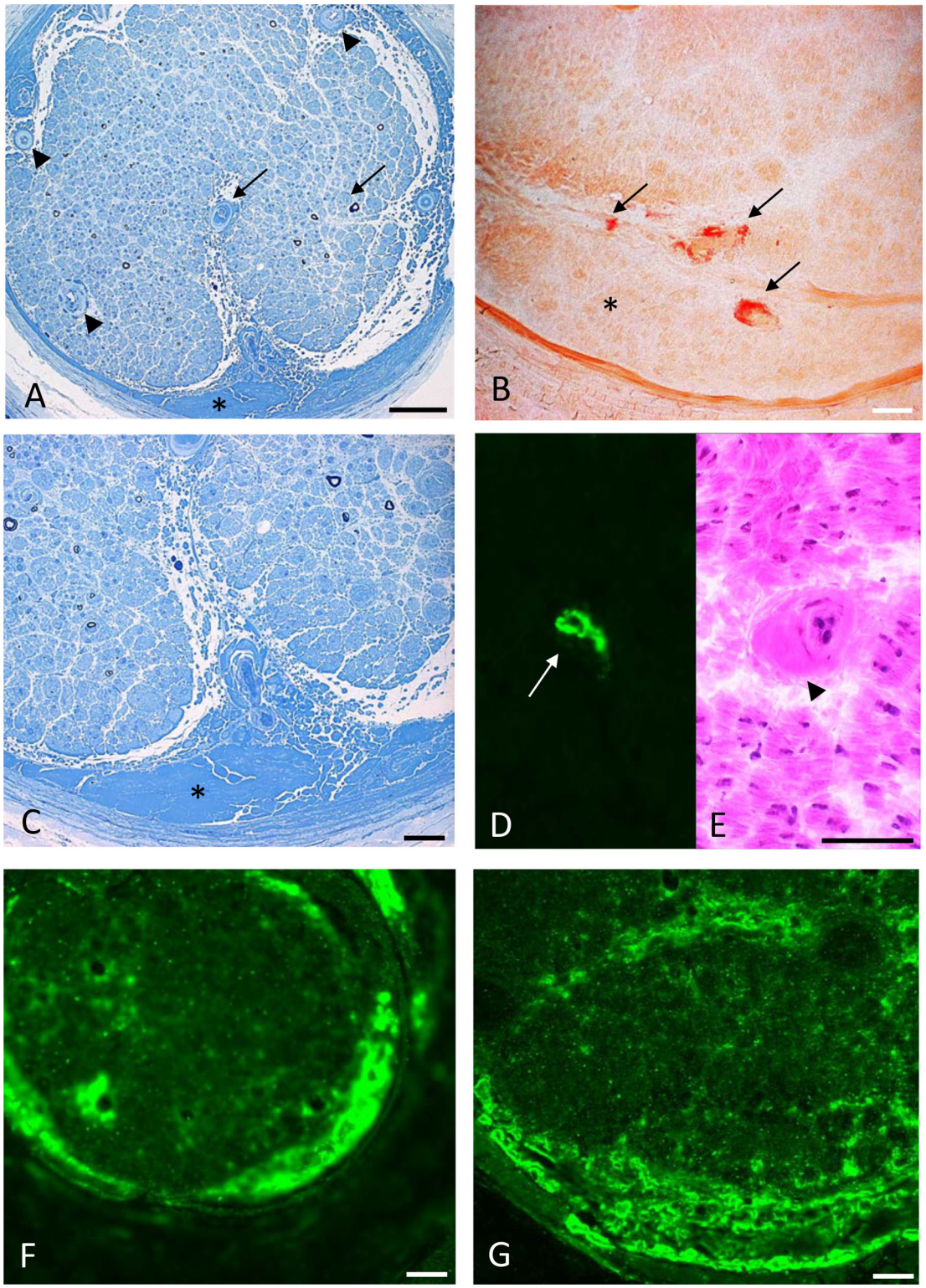

FIGURE 8 Sural nerve biopsy demonstrating IgM deposition disease. A: near total loss of large and small myelinated fibers with evidence of active axonal degeneration, black arrows), blood vessels with thickened hyalanized walls (black arrowheads) and large deposits of homogenous, amorphous deposits (asterisk), Toluidine Blue, Scale bar = 0.05 mm; B-C: Large deposits of Congo red negative amorphous eosinophilic material in the subperineurial space (asterisk) with Congo red staining of vessel walls (black arrows), B: Congo red stained, Scale bar = 0.05 mm, C: Toluidine Blue, Scale bar = 0.05 mm; D-E: Endoneurial and subperineurial vessels had thickened hyalinized walls which stained positive for Congo red and demonstrated apple green birefringence, (white arrow). D: Congo red with polarized light, Scale bar = 0.05 mm; E: H&E, Scale Bar = 0.05 mm. F-G: Immunohistochemical staining of the amorphous subperineurial deposits were positive for IgM F and kappa light chains G, Scale bars = 0.05 mm

Immunohistochemical testing identifies IgM and/or light chain, but constituent amyloid proteins are negative.[46-48] Electron microscopy reveals a granulofibrillar ultrastructure consisting of straight 9 to 10 mm diameter fibrils and granular material, in an endoneurial, perivascular distribution.[46,47,52] Varying degrees of polyclonal epineurial inflammation is seen, without lymphomatous infiltration, and there is occasional disruption of vessel walls with hemosiderin deposition,[46,47,49] suggesting secondary ischemic insult, either by a vasculitic or mechanical compressive process.[46,51] MS of deposits identifies heavy, light and J-joining chains, suggesting the material is comprised of pentameric IgM macroglobulin.[46] In addition, constituent amyloid proteins SAP and ApoE are absent.[46]

Despite the good long-term survival rates, patients with amyloid-like IgM deposition develop marked morbidity due to neuropathic pain, gait and hand dysfunction due to both sensory ataxia and distal amyotrophy. As such, amyloid-like IgM deposition disease should be an early consideration in the context of an IgM paraprotein and a severe, progressive, axonal neuropathy. While there is limited clinical data regarding treatment outcomes, early institution of therapy to treat the underlying lymphoproliferative disorder and reduce circulating IgM paraprotein levels, prior to the development of profound axonal degeneration, may have the potential to dramatically improve morbidity and quality of life. The incidence of amyloid-like IgM deposition is likely underestimated and nerve biopsy remains the only way to recognize this condition,[46,52] and as such, nerve biopsy remains an essential part of the armamentarium for this condition and neuromuscular diagnostics.

9 | INTRANEURAL PERINEURIOMA

Intraneural perineurioma is a rare cause of mononeuropathy. A case is presented with a 5-year history of slowly progressive weakness and mild sensory loss of the right lower extremity that demonstrates the importance of imaging and biopsy to make a correct diagnosis.

9.1 | Patient history

A 26-year-old woman presented with a 5-year-history of slowly progressive weakness of her right foot, atrophy of her right thigh muscles, mild sensory loss of the right foot and thigh and intermittent pain of the right thigh. Except for relapsing pyelonephritis, the patient's medical history was uneventful. There was no history of trauma. No regular medication was taken. The family history revealed an uncle with multiple sclerosis and a mother and grandfather who both had "problems" with the ulnar nerve.

9.2 | Neurological examination

At the first visit to our department in August 2015, tests for motor function revealed the following paresis according to the Medical Research Council Scale (MRC; results given as right/left side): foot extension 2/5, foot pronation 3/5, toe extension 2/5. Furthermore, muscle atrophy of the right thigh and lower leg (circumference of the lower leg on the right 32 cm and left 35 cm), a unilateral steppage gait and mild sensory loss of the right distal and lateral thigh and the right foot between the first and the second toes was observed. Deep tendon reflexes in the right lower extremity were reduced. The remaining neurological examination was normal. From 2015 to March 2018, neurological examination findings remained largely unchanged.

9.3 | Laboratory tests, electrophysiological, and imaging studies

Extensive laboratory tests including cerebrospinal fluid analysis were normal. Nerve conduction studies showed axonal loss with reduction of compound muscle action potential amplitudes of the right peroneal nerve (distal stimulation: 0.07 mV, below fibular head: 0.03 mV, above fibular head: 0.06 mV) and tibial nerve (distal stimulation: 6.4 mV, proximal stimulation 4.7 mV). The right peroneal and tibial distal motor latency and nerve conduction velocity, and nerve conduction studies of the peroneal and tibial nerves on the left and sural nerve on the right were normal. Electromyography of the anterior tibial muscle of the right side indicated chronic denervation, but there was no spontaneous activity in the anterior tibial, gastrocnemius, and quadriceps muscles. Motor evoked potentials showed reduced amplitudes on the right side, but normal latencies. MRI demonstrated enlargement and abnormal hyperintense signal of the peroneal nerve at the fibular head on T2-weighted images. MRI of the lumbosacral plexus was normal. High-resolution ultrasonography (18 MHz probe, transverse plane) showed an enlargement of the peroneal nerve adjacent to the fibular head with hypoechogenic signal. A fascicular biopsy from this area was planned.

9.4 | Nerve biopsy findings

A small peroneal fascicular nerve biopsy showed one fascicle. Cryosections with H&E staining (Figure 9A) and semithin sections stained with methylene blue (Figure 9B) showed layers of spindle-shaped cells around a central axon, forming structures described as pseudo-onion bulbs. Immunohistochemistry showed that the perineurial cells (arrowheads) were negative for S-100 (arrows show Schwann cells close to axons, Figure 9C) and positive for epithelial membrane antigen (EMA) (Figure 9D, arrows). Thus, the diagnosis of an intraneural perineurioma was made.

9.5 | Treatment and follow-up

An attempt at curative surgical excision was expected to cause unacceptable morbidity, as a result conservative management was implemented. At a follow-up visit in 2018, the patient reported an

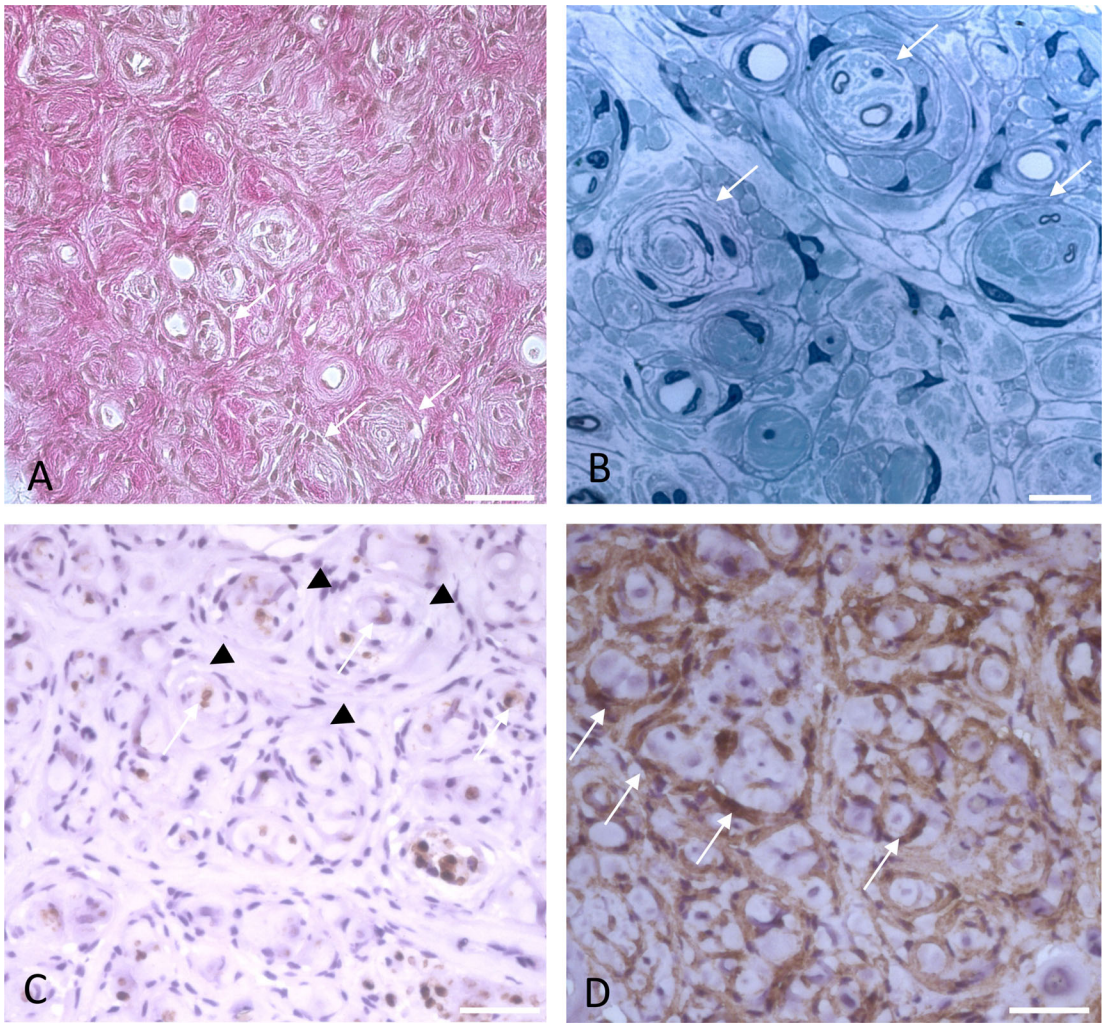

FIGURE 9 Photomicrograph of A, Hematoxylin and Eosin (H&E) sections showed layers of spindle-shaped cells around a central axon (arrows). These structures are described as pseudo onion bulbs. B, This structure becomes even clearer in semithin sections stained with toluidine blue (arrows). C, Immunohistochemistry for the Schwann-cell marker S-100 shows that the cells producing the pseudo onion bulbs (arrowheads) are S-100 negative and thus not Schwann cells, while the stain for epithelial membrane antigen (EMA) D, shows that they are perineurial cells (arrows). Scale bars = 20 μm in A, B, C, 10 μm in C

increase in pain and a progressive weakness of the right leg, but clinical, electrophysiological and MRI findings were relatively unchanged.

9.6 | Discussion

This case presented with a 5-year history of progressive weakness and mild sensory loss of the right leg. The neurological examination revealed a unilateral steppage gait, foot drop, muscle atrophy, and mild sensory loss. The electrophysiological studies identified axonal loss of the right peroneal and tibial nerves. A mononeuropathy of the sciatic nerve was diagnosed. Multiple etiologies of mononeuropathy were considered in the differential diagnosis, including inflammatory, auto-immune, toxic, metabolic, neoplastic, and entrapment, for example, hereditary neuropathy with liability to pressure palsies. Extensive laboratory tests were normal. High-resolution ultrasonography showed an enlargement of the peroneal nerve and MRI demonstrated a fusiform nerve enlargement, hyperintense on T2-weighted imaging. Due to these findings, a peripheral nerve tumor seemed to be most likely. Thus, this case demonstrates the usefulness of MRI and ultrasonography as tools in the diagnostic work-up of mononeuropathies, also assisting to identify the ideal site for biopsy.[54]

Fusiform nerve enlargement with preserved fascicular architecture can be seen in lipomatosis, schwannoma, neurofibroma, and intraneural perineurioma.[55] Some suggest that a classical clinical presentation with typical MRI findings and nerve conduction studies can make the diagnosis of perineurioma alone.[56,57] However, other MRI series of intraneural perineurioma have instead identified non-specific nerve enlargement.[55] Since the management of inflammatory mononeuritis, hereditary neuropathies, malignant peripheral nerve tumors, and intraneural perineurioma are completely different, it is important to confirm a definite diagnosis before commencing therapy. The

pathological findings in our case showed EMA-positive and S-100 negative cells. Immunohistochemistry is very specific for the diagnosis of intraneural perineurioma. Perineural EMA-positive and S-100-negative cells surround a centrally placed axon with a small number of Schwann cells that are S-100-positive.[58]

Both intraneural and extraneural perineuriomas can occur. Intraneural perineurioma was first identified 1964[59] as a benign neoplasm characterized by focal perineural cell proliferation. It commonly affects young adults, with equal involvement of males and females.[60,61] The typical presentation is a motor-predominant neuropathy of gradual onset. It may be accompanied by mild sensory loss.[55,61] Intraneural perineurioma appears equally in upper and lower limb nerves, but most often in the sciatic nerve and its branches.[55,60-62] There are a few cases of intraneural perineurioma affecting multiple nerves.[58] MRI shows a fusiform nerve enlargement over a length of several centimetres, isointense on T1-weighted imaging, and hyperintense on T2-weighted imaging with homogenous contrast enhancement after intravenous gadolinium injection.[54,57,62] The pathological examination shows concentric layers of perineurial cells around one or more centrally situated Schwann cells and axons. These layers of cells are similar to onion bulb appearance in distinct nerve disorders or after nerve lesion, leading to morphological and molecular changes of Schwann cells, but Schwann cell neoplasms arise from the endoneurial layer, whereas perineuriomas arise from the perineurial layer, which is why they are described as pseudo-onion bulbs.[63] Immunohistochemistry shows that the perineurial cells are positive for EMA, variably positive for Glut-1, Claudin-1, and CD34, and negative for S-100, whereas Schwann cells are negative for EMA and positive for S-100.[63,64] EMA expression in perineurioma is important to differentiate it from morphologic mimics.[63] Intraneural perineurioma may grow in width, but rarely grows in length and does not grow to involve new nerves or branches. Furthermore, growth does not correlate with clinical progression.[60]

The treatment of intraneural perineurioma is controversial. Some say that the natural progression of intraneural perineurioma leads to complete functional loss,[65] whereas others describe an initial phase of progressive impairment followed by a stable deficit.[56] Excision of the lesion with autologous nerve graft repair is reasonable if the affected nerve segment is non-functional. This surgery provides a possibility of some degree of recovery, but a full recovery of the functions is not probable.[66] These unsatisfactory results may be due to a long period of denervation before surgery. An early reconstruction, before muscle fibers have degenerated, might provide better results. However, the problem of early excision and grafting of an incomplete nerve lesion is that any residual function would be lost and the prospect of useful recovery is uncertain.[67] Thus, there is no standard management of intraneural perineurioma. The decision for or against an excision and grafting depends mainly on the residual function of the nerve. In our case, foot extension was possible, albeit weak, and during follow-up there was no progression, and MRI findings were unchanged. Hence, we decided against a resection of the lesion.

10 | CONCLUSIONS

Nerve biopsy is an invasive procedure and should therefore only be performed if other means have not provided a diagnosis and if making the diagnosis provides a potential benefit for the patient. The examples illustrated above have shown that this can be the case in inflammatory neuropathies, in neuropathies related to malignancy, and in intrinsic nerve tumors.

While CIDP can be diagnosed using clinical criteria, there are patients in whom, for various reasons, these criteria are negative, but nerve biopsy can confirm demyelination, inflammation, or both.[68] Given that the recently described paranodopathies and the longer known IgM-associated demyelinating neuropathies respond differently to immunotherapies than classical CIDP,[69-72] it is important not only to diagnose them clinically, but also to better understand their pathophysiology. The electron-microscopic images of the cases described in this article give a good example of how our theoretical concepts on the pathophysiology of these diseases can be supported by human pathology.

Suspected non-systemic vasculitis of the peripheral nerves (NSVN) is the classical example of an indication for nerve biopsy.[73] In contrast, in systemic vasculitis with peripheral nerve involvement, the diagnosis is often made using blood tests and other organ biopsy. As inflammatory infiltrates in NSVN can also be found in skin and muscle,[22,74] it has been discussed that there may be a transition between NSVN and systemic vasculitis. Our case 5 illustrates that in a patient with neuropathy as the main complaint, elements of systemic vasculitis may prevail, and that in such cases biopsy of the affected nerve may still be the best method of ascertaining vasculitis. This needs to be done, because resulting treatment options are effective but also carry the risk of adverse effects. In addition, the case illustrates that vasculitis does not always lead to an asymmetric neuropathy,[73] and that skin biopsy can provide supportive information to make the diagnosis.[22]

As in vasculitis, an asymmetric or multifocal pattern is the most common pattern of nerve involvement in neurolymphomatosis and neuroleukemiosis, as shown in case 6, but even here, a symmetric polyneuropathy can be found. Importantly, these cases, in particular with symmetric weakness, can be mistaken for treatment-resistant CIDP. Together with the often cited example of amyloidosis,[75] this is another potential CIDP mimic, which tells us that one should not be satisfied with a diagnosis of "treatment resistant CIDP" but consider nerve biopsy in such cases. Otherwise, optimal patient treatment may be delayed, morbidity can accrue, and medical resources may be wasted.

In view of the novel treatments for hereditary ATTR amyloidosis (ATTRv), systemic AL-amyloidosis is less often mentioned in the current literature. However, AL-amyloidosis is the most common cause of amyloid-associated neuropathy. Purely by neuropathy phenotype, it is difficult to differentiate from ATTRv. Blood tests are helpful, however, monoclonal gammopathy is frequent in the elderly, and can co-occur in ATTRv, such that a false diagnosis may be made. Thus, demonstration and subtyping of amyloid in tissue definitely help

clarify the differential diagnosis. This is of special importance in AL-amyloidosis, where with the advent of novel therapies, the previously fatal prognosis has dramatically improved.[76] The case of IgM deposition neuropathy reminds us that, on the other hand, not all intraneural deposits are amyloid. Although the neuropathy in IgM deposition disease may be severe, the overall prognosis is better than in amyloidosis, and correct diagnosis has important treatment implications.

The advent of a mononeuropathy, if not explained by an entrapment syndrome, should alert the clinician to the potential presence of a nerve tumor. As these cases are rare, expertise is not widespread, and as such patients should be referred to a center specialized in diagnosis and management of nerve tumors. Whether biopsy is warranted, and potential treatment options, depends on the specific characteristics of an individual case. Excellent reviews on peripheral nerve tumors have recently been published.[64,77]

In conclusion, with these cases, we show that the judicious use of nerve biopsy can be helpful to guide patient management in acquired neuropathies. The cases also illustrate the wide variety of treatable diagnoses that can underly the sometimes seemingly uniform clinical picture of polyneuropathy.

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