Peripheral Nerve Amyloidosis

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Introduction

Provided is an overview of the pathology, clinically defining features, and subcategorization of peripheral nerve amyloidosis. This condition is pathologically hallmarked by infiltrative amyloid deposition in varied peripheral neural tissue localizations with associated clinical manifestations. Peripheral nerve involvement is a frequent presenting feature of systemic amyloidosis [1]. As with other organ systems, the diagnosis of amyloid involvement of peripheral nerve is often delayed because the clinical features may mimic many varieties of peripheral neuropathy. Therefore, pathologic discovery of unsuspected amyloidosis is common. The particular amyloid protein can determine the clinical course and preferred treatment modality, as well as potentially alert patients to familial predisposition. Advances in laboratory technology, including most notably mass spectrophotometric evaluation of nerve, continue to improve the accuracy and sensitivity of amyloid subtyping [2–4]. Appropriate directed peripheral neural biopsy can therefore be instrumental in identifying the diagnosis providing the specific amyloid type, informing prognosis, and directing care in each case.

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Historical Pathologic Observations of Nerve Amyloid

In 1938 De Navasquez and Treble demonstrated amorphous material in dorsal roots around small blood vessels, displacing nerve fibers in the endoneurium, and lining epineurial fat deposits [5]. They reviewed the nerve biopsy described in the 1929 paper by De Bruyn and Stern as "hypertrophic polyneuritis", and identified the described "plasmatic bodies" as amyloid deposits [6]. They also noted amyloid in the sympathetic ganglia, where it was thought to compress ganglion cells. Krücke et al. later described similar changes, and demonstrated prominent dorsal root ganglia changes, outlining their findings in two major pathologic reviews in 1959 and 1963 [7, 8]. A large Portuguese family demonstrating inherited peripheral nerve amyloidosis was described by Andrade in 1952 [9] and Horta and Trincao in 1963 [10]. In 1969, Dyck and Lambert outlined ultrastructural findings in sural nerve biopsies taken from cases of dominantly inherited amyloid neuropathy, showing marked loss

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of small unmyelinated fibers, and association of endoneurial extracellular amyloid fibrils with collagen replacement [11]. Cohen and Calkins first noted in 1959 that the deposits in various types of amyloidosis appeared essentially similar when viewed by electron microscopy (EM), demonstrating a non-branching, fibrillar structure [12]. In time, fibrils have been shown to measure 70–120 Å in diameter with indeterminate length [13]. We utilize EM rarely in nerve for clinical practice because of the relative sensitivity of tinctorial amyloid staining with Congo red and methyl violet, taken together with the nonspecific EM appearance of the various amyloid types.

Clinical Overview Important in Nerve Amyloid Pathologic Discovery

Amyloidosis is a relatively rare cause of peripheral neuropathy. Rajani et al. reported 13 of 1098 sural nerve biopsies with amyloid deposition [14]. In our own tertiary service-based peripheral nerve laboratory we diagnosed amyloid neuropathy in 62 of 2011 nerve biopsy cases from January 1st 2007 to March 22nd of 2011. Primary amyloidosis (AL) is more common than the other major subset of peripheral nerve amyloidosis, familial amyloid polyneuropathies (FAPs). Both AL (κ-kappa, λ-lambda) and FAPs (TTR-transthyretin, GEL-Gelsolin, APOA1-apo-A1) are subcategorized based on their major amyloid component protein. The familial amyloid varieties have germline nuclear DNA mutations that alter amino acid sequence leading to amyloidogenic potential. In contrast to other forms of amyloidosis, secondary amyloidosis, which can occur in the context of chronic systemic inflammatory conditions such as rheumatoid arthritis, is not known to involve peripheral nerve tissues [2].

The AL and FAP amyloid forms clinically affect the peripheral small nerve fibers or their ganglia early in the course of the disease (aδ fibers conveying cold sensation; c fibers conveying pain and diverse autonomic functions) resulting in a clinical presentation dominated by acral extremity pain and autonomic features of hypohidrosis, gastrointestinal dysmotility, orthostasis and impotence [1, 11, 14]. There is typical sparing of Schwann cell function compared to the myelin ensheathed axons, as evidenced by axonal electrophysiologic findings (absence of conduction velocity slowing) and sural nerve pathologic review [11]. Affected persons at the time of presenting to medical attention typically also have clinical involvements of large myelinated fibers (Aβ fibers subserving vibration, gross sensation, and power), causing prominent distal lower extremity weakness and sensory ataxia [15]. Instances of amyloid neuropathy straying from this clinical archetype do occur—most commonly in AL amyloidosis, in which mononeuropathies, plexopathy, asymmetric motor or sensory polyradiculopathy, or selective small-fiber involvement with insensitivity to pain can be seen [16–24]; and in gelsolin amyloidosis, characteristically presenting with insidious facial-onset weakness with corneal lattice dystrophy [25–27]. Rare examples have been reported in TTR amyloid including length-dependent neuropathy with hearing loss or leptomeningeal spread [28, 29]. This variable selective involvement of only certain regions is not understood, but seems important in future discovery for potential strategies to treatment to limit scope of systemic amyloidosis.

Biopsy Sites in Peripheral Nervous System Amyloidosis

In such a clinically heterogeneous condition, the differential diagnosis can be especially broad and proper biopsy location is emphasized to increase yield and limit patient injury (Figs. 31.1 and 31.2). Attempts at evaluating other remote clinically asymptomatic tissues in determination of a person's remote amyloid neuropathy have been generally unsuccessful. By example fat aspiration is commonly attempted in evaluation of neuropathy in question of amyloid but with low yield, i.e., only 6 % of persons with clinical features consistent with amyloid neuropathy [30]. In our own experience, persons with neuropathy and positive fat aspiration for amyloid often have

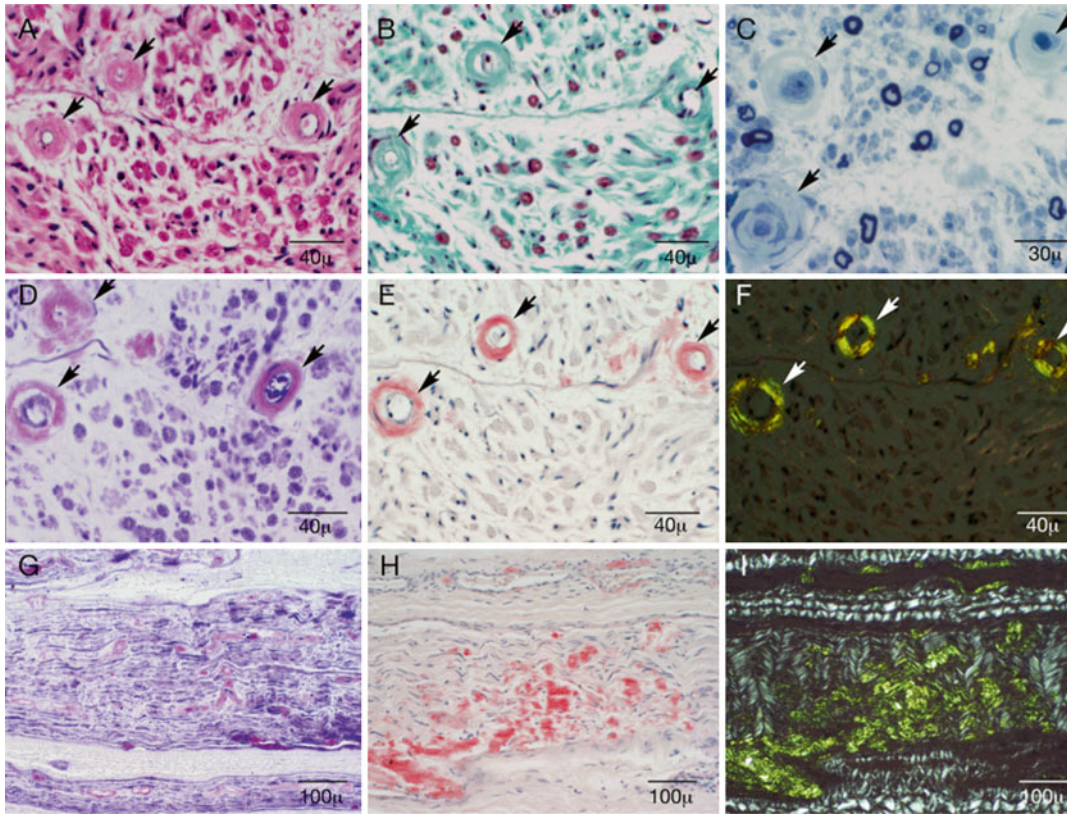

Fig. 31.1 Shown are the characteristic features of amyloid deposition in peripheral sural nerve biopsy tissue studied by light microscopy. Paraffin-stained sections show an acellular and homogenous proteinaceous material on light microscopy on different preparations (**a–f**) and diffuse endoneurial infiltration of amyloid (**g–i**) in a 35-year-old man with primary AL amyloidosis. Vessel walls (*arrows*) are seen to be thickened and acellular on hematoxylin and eosin (**a**), Masson trichrome (**b**), and epoxy-embedded methylene blue-stained sections (**c**). Semithin sections also demonstrate decreased myelinated fiber density with relatively greater loss of small myelinated fibers (**c**). Amyloidal deposits demonstrate magenta metachromasia on methyl violet preparation (**d**, **g**) and *Congo red* positivity (**e**, **h**). Demonstrated is the "Maltese cross" appearance under polarized light (**f**)

found alternative non-amyloid neuropathy as cause, i.e., false-positive results. Therefore, currently fat aspiration is insensitive and nonspecific in evaluation of amyloid neuropathy. The implications for a false-positive test are grave with potential application of chemotherapeutic, transplant, and other interventions. Most persons tolerate well different nerve biopsy localizations in amyloid as their pre-biopsy deficits are generally severe, limiting post-procedure new numbness or pain. Since amyloid neuropathy most commonly presents as a distal, sensory and motor neuropathy, whole sural nerve biopsy is most often an appropriate choice for site. Specifically, a 3 cm portion of whole sural nerve is harvested 8 cm above the lateral malleolus. On average 5–13 fascicles are seen. Because the saphenous vein runs juxtaposed to the sural nerve, care in avoiding harvesting this mimic of nerve is emphasized. Helpful in distinction is that the venous branches slope downward (30–60°) in contrast to the sural nerve where its branches arise at right angles (90°) from the main nerve segment. When harvested at the described site the sural nerve typically has 5–13 fascicles allowing for adequate tissue to see amyloid deposits. This sensory nerve provides sensation for the lateral foot, and therefore is consented to be lost post-procedure.

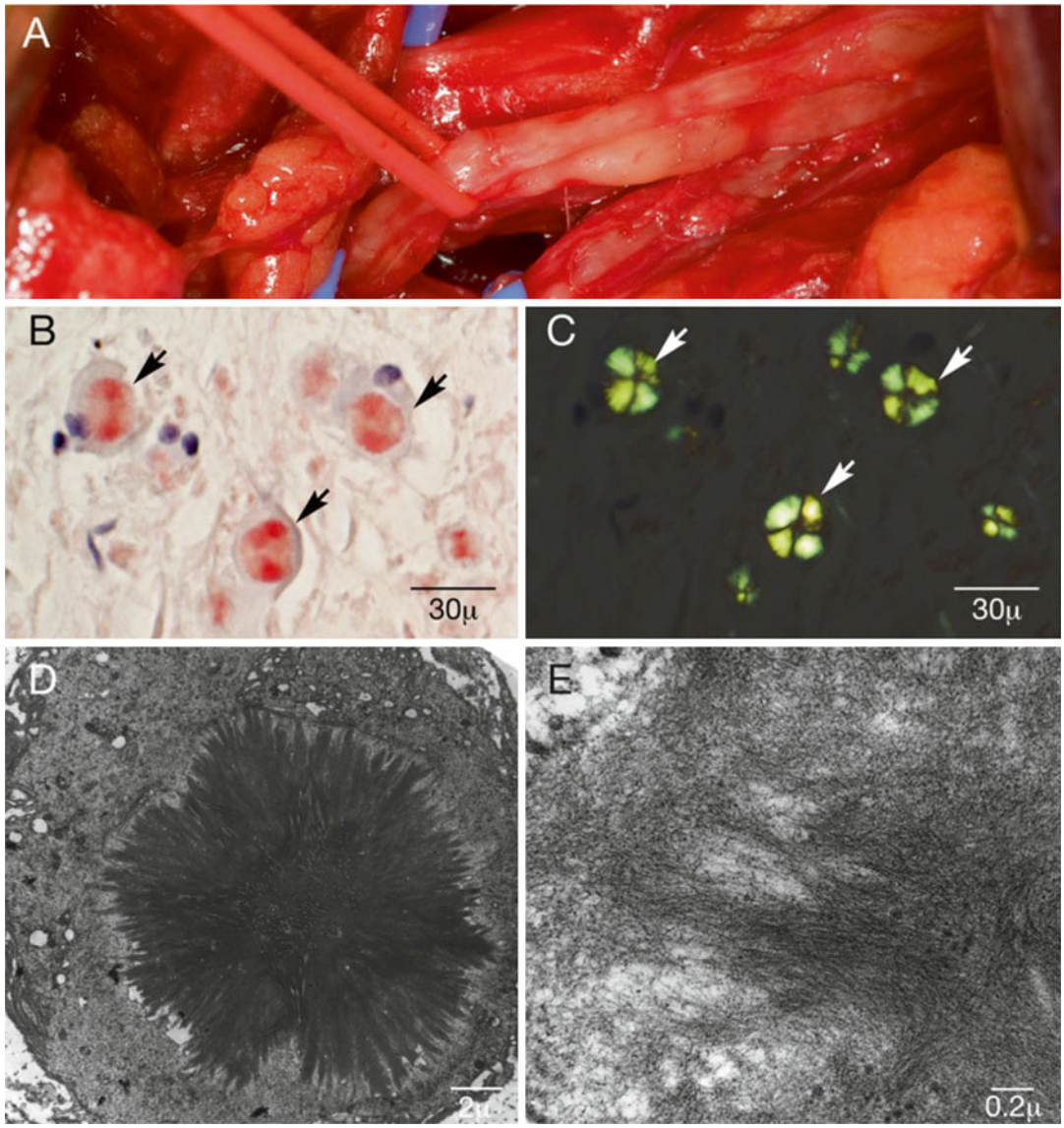

Fig. 31.2 Targeted fascicular biopsy in a 45-year-old man with infiltrative amyloidosis of the lumbosacral roots and sciatic nerve without serum monoclonal protein. Enlarged segments of the peroneal and tibial divisions of the sciatic nerve are seen just distal to the sciatic notch during a fascicular biopsy of the tibial division, with two selected fiber groups held in place with a *red* band (**a**). The biopsied material showed frequent round intracellular inclusions (*arrows*) scattered throughout the endoneurium with congophilia (**b**) and displayed Maltese crosses with polarized light (**c**) (*arrows*). Electron microscopy revealed starburst-shaped inclusions (**d**) with crisscrossing fibril formations typical of amyloid (**e**). Preoperatively he was felt to have a hypertrophic inflammatory neuropathy

Among rare cases, focal or regional amyloid (amyloidoma), reviewed below, has required targeted fascicular biopsy of proximal nerves, roots, plexus, and cranial nerves or their ganglia. In these cases, pre-biopsy suspicion for amyloid is uncommon, despite typical knowledge of circulating monoclonal proteins, with nerve sheath primary tumors or infiltrative neoplasm most commonly suspected by imaging and insidious progressive typically painful course.

Pathogenesis and Histopathologic Findings

The mechanism of tissue destruction in amyloidosis of nerve, as in other organs, is not known. Each amyloidogenic protein (immunoglobulin light chains, or mutated-TTR, GEL, APOA1) is not expressed in the perikaryon or soma of small and large myelinated and unmyelienated fibers nor in Schwann cells. We do not see within the neural tube at or beneath basement membranes or within Schwann cell cytoplasms deposition of amyloid. Rather each fibril forming protein has humoral circulation with deposition in the interstitium of affected nerve fascicules. Endoneurial microvessels most commonly have amyloid deposition with associated apparent spread of amorphous acellular amyloid (Fig. 31.1). There is typically axonal degeneration at the level of the amyloid deposition but also often remotely to the discovered protein. It has been postulated that, due to its tendency to involve blood vessel walls, amyloids' effects might be ischemic, as was initially put forth by Kernohan and Woltman in 1942 [31]. A compressive or structural effect has been suggested by pathologic studies demonstrating physical distortion of nerve fibers by endoneurial amyloid deposits, such as was described by Dyck and Lambert in 1969 [11]. Although rare patients are seen with massive amyloid deposition [19] and poor neurologic course, there seems to be little correlation with extent of deposition and neuropathy severity. This lends credence to the potential for a distal neural apoptotic effect of amyloid fibrils or their precursor proteins and/or its associated pathologic protein microenvironment [32, 33].

Amyloid infiltration of nerve is associated with primary axonal degeneration. Rare examples of demyelination are known to have occurred, though in at least one case demyelination may have been the result of a paraneoplastic effect of an IgM monoclonal gammopathy in association with antibodies to myelin-associated glycoproteins [34] (Fig. 31.3). An increased rate of axonal degeneration and an increased number of empty fibers are the most common abnormalities seen on teased fiber preparation (Fig. 31.4). Additionally, frequently seen in teased fibers is a flocculent deposition at various portions of the nerve fibers (Fig. 31.3).

Depending on chronicity of disease, either active axonal degeneration or resultant fiber loss may be relatively prominent. Semithin sections

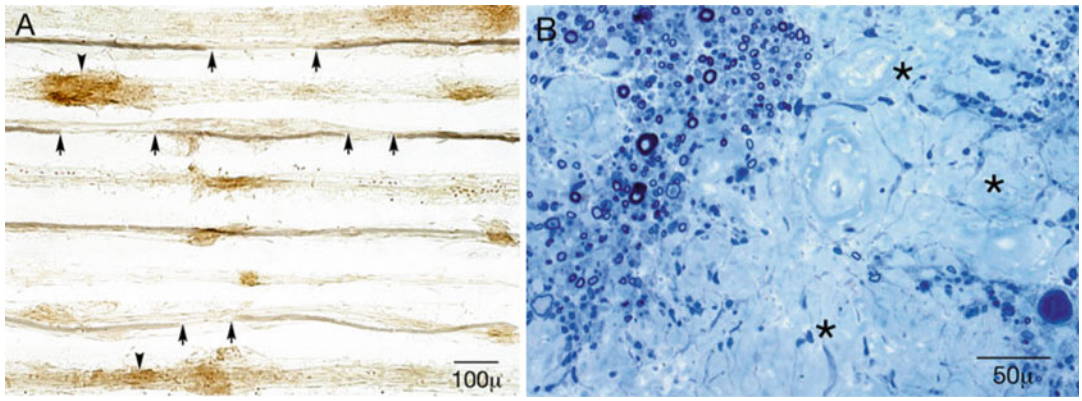

Fig. 31.3 L3 nerve root mass (pre-operatively "indeterminate mass") from a 72-year-old man who presented with cauda equina syndrome without features of systemic primary amyloidosis (cardiac, kidney, sural nerve), with monoclonal IgM kappa. Closely approximated osmium tetroxide-stained teased fiber preparation (**a**) shows segmental demyelination (*arrows*), as well as flocculent material (*arrowheads*) adhering to empty strands, normal fibers, and fibers demonstrating segmental demyelination. An epoxy-embedded methylene *blue*-stained semithin section preparation (**b**) reveals large acellular endoneurial deposits (*asterisks*) with multifocal fiber loss, and fibers with abnormally thin myelin

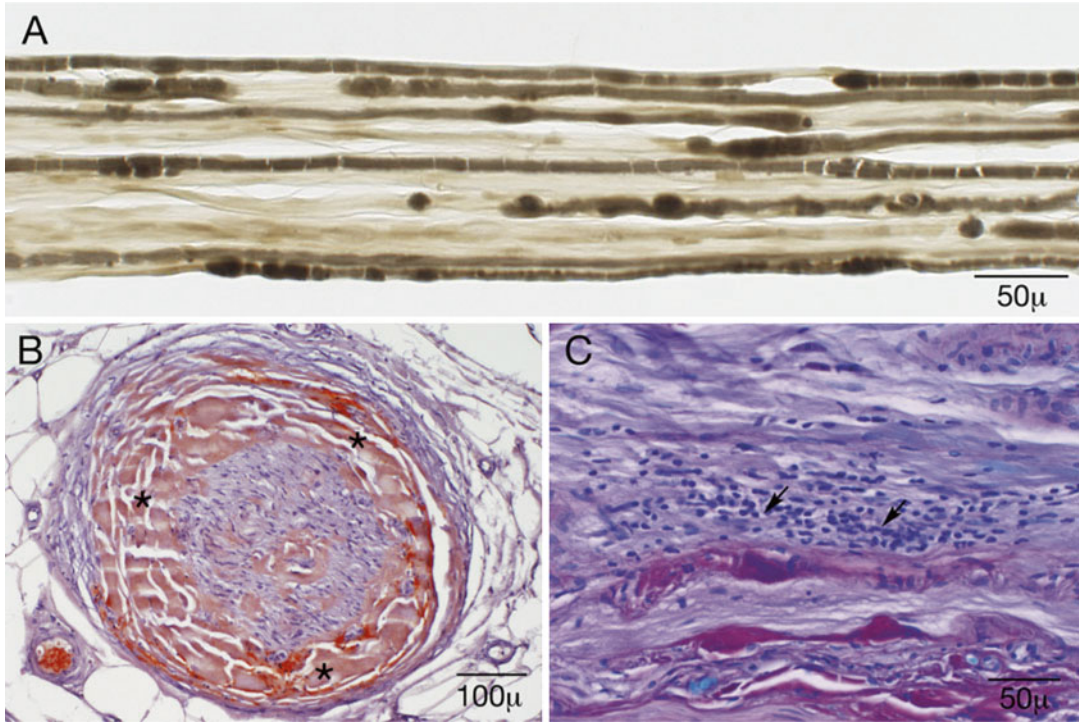

Fig. 31.4 Nerve biopsy from a 76-year-old woman with systemic amyloidosis. Teased fiber preparation (**a**) shows fibers demonstrating axonal degeneration with myelin wrinkling and empty nerve strands. *Congo red* preparation (**b**) shows extensive endoneurial deposition of amyloid, most prominent subperineurially (*asterisks*). Luxol fast blue–periodic acid Schiff preparation (**c**) demonstrates a moderate size collection of mononuclear cells (*arrows*) adjacent to a small epineurial blood vessel

stained with methylene blue typically show decreased myelinated fiber density (Fig. 31.1). Amyloid infiltrates connective tissues and aggregates in blood vessel walls, more frequently in the endoneurium (Fig. 31.1), though rarely deposits can be seen in nerve arterioles in the epineurium. The amorphous, acellular deposits of amyloid are relatively eosinophillic and PAS positive. Congo red preparations demonstrate congophilia and apple-green birefringence of deposits, and metachromasia can be seen with methyl violet preparations (Fig. 31.1). The absence of congophilia or metachromasia in amorphous, acellular deposits argues strongly against the presence of amyloid, and can be suggestive of amyloid mimicking conditions such as non-amyloidal monoclonal immunoglobulin deposition disease [35], see below section, (Fig. 31.5), or thickening of the basement membrane of endoneurial blood vessels, as can be seen in chronic diabetes [1]. Due to directionality of beta-pleated sheets, cross sections of spherical or tubular deposits of amyloid can demonstrate alternating areas of apple-green birefringence, in some cases manifesting as a Maltese cross appearance of deposits under polarized light (Figs. 31.1 and 31.2) [36]. The examination of Congo red stained slides by fluorescence microscopy using a TRITC (tetramethylrhodamine isothiocyanate) filter shows marked hyperluminescence in areas of amyloid deposits (see Fig. 17.3c, Chap. 17). Collections of perivascular inflammatory cells may be seen in the epineurium and endoneurium, though the frequency and etiologic significance of this finding have not been described (Fig. 31.4).

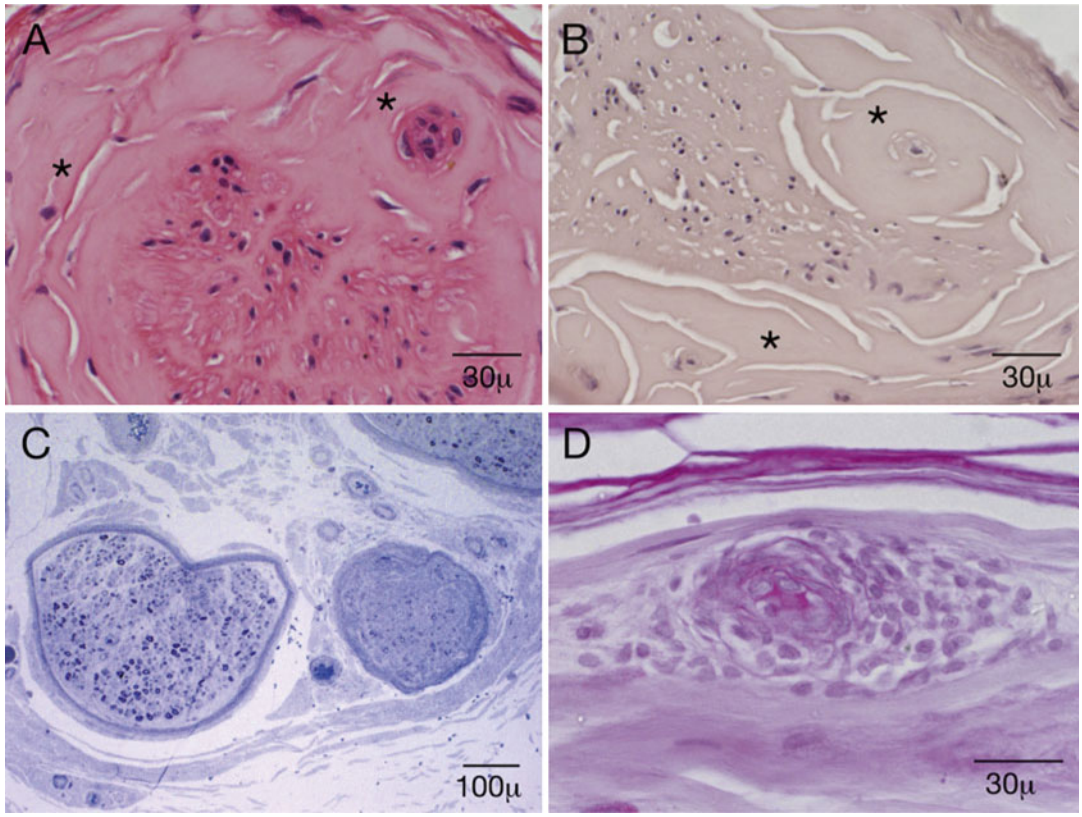

Fig. 31.5 IgM deposition disease (amyloid mimic) in sural nerve biopsy of a 69-year-old man with IgM monoclonal gammopathy. H&E (**a**) and *Congo red* (**b**) preparations show extensive endoneurial infiltration by acellular material involving endoneurial blood vessels (*asterisks*), which was not congophilic. Epoxy-embedded methylene blue-stained semithin sections (**c**) show multifocal myelinated fiber loss with relatively greater loss of small myelinated fibers. (**d**) Luxol fast blue–periodic acid Schiff preparation demonstrates a moderate sized perivascular collection of mononuclear cells in the epineurium, which disrupts the vessel's walls. Mass spectrometry of microdissected deposits detected IgM lambda pentameric macroglobulin with immunoglobulin mu heavy chain constant region, immunoglobulin lambda-light chain constant region, and immunoglobulin J chain, with no evidence of amyloid-associated proteins, serum amyloid protein (SAP), and ApoE, confirming a diagnosis of amyloid-like IgM neuropathy

Regional or Focal Peripheral Nervous System Amyloidosis (Amyloidomas)

Amyloidomas are focal, macroscopic aggregate of amyloid, and an uncommon manifestation of amyloidosis in general. Cases affecting peripheral nerve are exceedingly rare. In several reported cases, nerve roots are affected by amyloidomas arising from vertebral bodies [18, 22, 37]. Only very few cases of amyloidoma arising primarily from peripheral nerve have been reported, involving the lumbosacral plexus (Fig. 31.2), lumbar nerve root (Fig. 31.3), Gasserian ganglion, sciatic nerve, cervical root, brachial plexus, and infraorbital nerve [16, 17, 19–21, 38, 39].

Mass Spectrophotometric Evaluation of Amyloid in Peripheral Nerve Tissues

None of the above described approaches distinguish type of amyloid. One of the most difficult issues arising after the discovery of histologic amyloid in nerves is the correct typing of the

specific amyloid proteins. Historically, immunohistochemical staining (anti-TTR, -lambda-light chain, and kappa-light chain) is performed but is challenging. The difficulties in immunocharacterization have been highlighted also in other tissues where misdiagnosis of amyloid type was common and for complex reasons [40, 41]. Contributing to the difficulty in immunocharacterization is the following: (1) antigenic epitopes may be lost by formalin cross-linking in amyloid; (2) circulating contaminant TTR and AL-light chain proteins may produce false-positive results; (3) comparing staining intensities between the different amyloid antibody stains may be unreliable; (4) Pathologic consideration based on clinical, family history and monoclonal serum positivity may be misleading in pathologic interpretation.

We have recently validated application in nerve the use of liquid chromatography tandem mass spectrometry (LC-MS/MS) with laser microdissection (LMD) of amyloid deposits from formalin-fixed, paraffin-embedded sections [4]. This approach eliminates the described problems with immunophenotyping and can be done independent of often misleading clinical information. Our initial validated studies showed that 21 persons with either sural nerve biopsies or proximal root biopsy with amyloid were able to have defined AL, TTR, or GEL cause, whereas earlier attempts at immunophenotyping had failed. Included in the important result was that not only can the predominant amyloid protein be defined, but the specific TTR mutation is determined. This is important as TTR is a normal circulating protein and frequently older persons have circulating incidental circulating monoclonal proteins. The approach has had immediate clinical application in routine practice with large potential for future research with the proteomic microenvironment defined by the approach. Based on our experience we have streamlined interpretation away from immunophenotyping.

AL Primary Amyloidosis

Among systemic acquired amyloidoses, only immunoglobulin light chain amyloidosis (AL) has been thought to cause neuropathy. This dogma will require further review with the proliferation of proteomic analysis of amyloid by mass spectrophotometry [4, 42]. Lambda-light chains are more commonly involved than kappa-light chains, roughly by twofold [1, 43]. Monoclonal gammopathy, in amyloidosis as in other conditions, develops in the setting of plasma cell dyscrasia, multiple myeloma, or MGUS-associated lymphoma including Waldenströms [44, 45]. When monoclonal proteins are identified by serum or urine analysis in patients with amyloidosis, AL variety is often given major consideration. However, studies have emphasized that the presence of monoclonal protein, particularly in older patients, may be incidental [41, 46]. Therefore, caution should be used in assuming the causality of circulating monoclonal proteins when amyloid is found in peripheral nerves. Conversely, circulating monoclonal proteins may be small, and their detection dependent on the sensitivity of the laboratory methods utilized. The inclusion of serum light chain ratio and 24-h urine analysis provides increased sensitivity beyond that of serum protein electrophoresis and immunofixation [44, 47].

The variability of peripheral nervous system involvements in AL amyloid is most dramatic compared to familial forms of systemic amyloidosis affecting nerve. Asymmetric and variable combinations of motor, sensory, and autonomic nerves, roots, and plexus can be involved. However, most commonly, AL causes polyneuropathy involving in length-dependent severity (distal worse than proximal) small nerve fibers, often earlier or more apparently than large nerve fibers, and lower limbs earlier than upper limbs, manifesting in neurologic deficits distally more than proximally (i.e., length dependent). However, isolated mononeuropathy, plexopathy, and radiculopathy are possible, i.e., amyloidoma [16, 17, 19–21, 38, 39] (Figs. 31.2 and 31.3). Involvement of autonomic ganglia and peripheral c fibers are common, and dysautonomic features may include gastrointestinal dysmotility with intractable diarrhea, orthostatic hypotension, urinary incontinence, and erectile dysfunction. Simultaneously, multiple organ systems may be involved, including cardiovascular, renal, hepatic, gastrointestinal, and skin [1, 2, 24, 38, 48–50].

Occasionally, isolated peripheral nervous system amyloidosis may precede spread to other organ systems by years. Presentation with somatic (sensory loss and weakness) non-autonomic peripheral neuropathy in amyloidosis portends on the whole better prognosis. Heart failure and gastrointestinal bleeding being the most common causes of death in systemic AL amyloidosis, though early involvement of autonomic nerves (orthostasis, cardioadrenergic) may also contribute specifically to poorer prognosis [45, 51, 52].

Immunoglobulin Nerve Deposition a Pathologic Mimicker of Amyloid

It is important to be aware of a very rare pathologic mimicker of amyloidosis having intraneural deposition of most commonly IgM macroglobulin in patients with IgM paraproteinemic neuropathy, occurring in monoclonal gammopathy of undetermined significance and Waldenstrom's macroglobulinemia. Few cases are reported in the literature [53–55]. Described patients have presented with asymmetric onset sensory, distal large- and small-fiber deficits with painful dysesthesias which evolve to length-dependent involvements. Notably, there may be relative absence of dysautonomia and systemic organ involvement until very late in the disease course, distinguishing the condition clinically from most cases of peripheral nerve amyloidosis. The mechanism of nerve damage as in amyloidosis remains unexplained—compressive, microvascular, inflammatory, and immune-mediated mechanisms have been considered.

Histopathologically, deposits are seen like amyloid to involve endoneurial blood vessels, with infiltration throughout the endoneurium, often tracking subperineurially (Fig. 31.5). Deposits are eosinophillic, PAS positive, and very similar morphologically to amyloid, though lacking the tinctorial qualities of amyloid on methyl violet and Congo red preparations (Fig. 31.5). Epineurial perivascular mononuclear cell collections may be prominent, suggesting an inflammatory or immune-mediated process. Teased fiber preparation often shows increased numbers of empty nerve strands, floccular aggregates adhering to fibers, and segmental demyelination. Mass spectroscopy of laser microdissected deposits demonstrates that amyloid-like material is composed of μ-heavy chain, λ-light chain, and J-joining chain without serum amyloid protein (SAP) and ApoE, suggesting deposition of IgM pentameric molecules in the absence of amyloid-associated proteins [56]. Deposits show a granulofibrillar structure on electron microscopy, which is slightly distinct from the crisscrossing fibrillar structure of amyloid (Fig. 31.5).

Familial Amyloid Polyneuropathy

FAPs have been subcategorized by the three variant proteins associated with amyloid neuropathy: transthyretin, gelsolin, and apolipoprotein A1 (apo A1). Beta2-microglobulin amyloid deposition, most commonly in the context of chronic hemodialysis, is frequently associated with carpal tunnel syndrome with compressive median neuropathy at the wrist. However, this is known to be due to extraneural deposition within the carpal tunnel and is not as such considered an amyloid neuropathy. More recently, a single family with an apparent, hereditary, systemic amyloidosis, derived from a variant of Beta2-microglobulin, was reported with autonomic and subsequent symmetric sensorimotor axonal polyneuropathy [57].

Transthyretin

Missense point mutation resulting in a valine for methionine substitution at position 30 of TTR among first described by the work of Andrade et al. [9] in Portugal remains the most common alteration associated with inherited amyloid neuropathy. The mutation is inherited in autosomal dominant fashion and has generally high penetrance.

The normal transthyretin protein is a 55 kDa homotetramer of 127-residue monomers, with dimer–dimer formation. The protein has large subregions forming beta-pleated sheets. It is synthesized largely in the liver, choroid plexus, and

retina, and its physiologic function is as a transporter of thyroxine and retinol in the serum and cerebrospinal fluid [3, 56, 57]. The protein is encoded by the roughly 7 kbp TTR gene located at 18q12.1. Over 100 mutations of the gene have been reported and found to be amyloidogenic. Generally, mutations lead to destabilization of the homotetrameric formation of the protein, with a greater tendency toward dimerization and subsequently amyloid fibrils. Wild-type transthyretin is known to make up amyloid deposits in Senile Systemic Amyloidosis (SSA), where predominant cardiac involvement occurs, but with primary peripheral nerve involvement not demonstrated [50, 58–60]. However, a case of multifocal spinal column involvement in SSA with resulting compression of adjacent nerve roots and spinal cord has been described [61]. Progression of cardiac amyloidosis after liver transplantation for treatment of TTR amyloidosis has been shown to be attributable to continued deposition of wild-type TTR with a gradually increasing proportion of the wild-type molecules [3, 62–64]. The published ratios of variant to wild-type TTR in tissues were similar to those described by Liepnieks et al. for posttransplant patients with TTR amyloid neuropathy [65].

Though overall epidemiologic studies suggest better survival from the time of symptom onset than in AL amyloidosis [1] TTR amyloid neuropathy cannot be distinguished from primary amyloidosis based on clinical features alone, without the aid of laboratory or histopathologic studies. Like in AL amyloidosis, patients present most commonly with progressive, length-dependent, axonal-predominant polyneuropathy. There is prominent autonomic and small-fiber involvement, manifesting in painful acral paresthesias, thermanesthesia, erectile dysfunction, and gastrointestinal dysmotility. Malabsorption with watery diarrhea may be intractable. Variations exist in presentation, including (1) motor predominant, (2) isolated pain and insensitivity, and (3) isolated dysautonomia. Initially, genotype–phenotype correlations of specific neurologic presentations such as carpal tunnel syndrome were thought possible [66, 67]; however, with subsequent larger case series, these associations are less clear, and substantial phenotypic overlap is recognized between genotypes [68–70]. While the presence of family history of neuropathy or amyloidosis can be helpful in identifying TTR amyloidosis, its absence cannot exclude the diagnosis [69, 71].

Gelsolin

Much less common among FAPs is gelsolin amyloidosis, which causes early and prominent corneal lattice dystrophy, predominant seventh cranial neuropathy, and cutis laxa, and later in the course of the disease a distal polyneuropathy [25, 72]. Gelsolin amyloidosis follows a benign course with relatively late onset, slow progression, and limited morbidity. Inheritance is autosomal dominant. An asparagine for aspartate substitution at position 187 (D187N) of the gelsolin protein has been found, resulting from a missense point mutation in the gelsolin gene. A tyrosine for asparagine substitution at the same position (D187Y) is also known to cause a similar phenotype. The gelsolin protein acts as an actin-modulator and D187N and D187Y mutations make the protein subject to cleavage by the protease molecule furin, by reduced Ca2+ binding at this mutated domain [73]. This occurs in the Golgi complex producing the amyloidogenic protein precursor which then targets the unique distribution of tissues.

Most known patients have been reported in Finland [72], but cases have been reported in the United States, Denmark, the Netherlands, and Japan [74, 75].

Apolipoprotein A1

Apo A-I, secreted by the liver and intestine, is the main protein in high-density lipoprotein (HDL). It is a cofactor for lecithin cholesterol acyltransferase (LCAT), and plays a prominent role in cholesterol transport. The 267-amino acid prepropeptide undergoes two cleavage steps resulting in a functional 243-amino acid protein. Kidney and liver serve as the major

sites of Apo A-I breakdown. Decreased plasma HDL (hypoalphalipoproteinemia), hypertriglyceridemia, and/or defective LCAT activation are associated with defects in the protein. Over eight different missense mutations are reported in Apo A-1, but only an arginine for glycine substitution at position 26 (Gly26Arg) and a histine for leucine substitution at position 174 (Leu174His) have been reported to be associated with neuropathy [76–79]. Kidney and heart involvement have been the major causes of clinical presentations.

Apo A-I IOWA was the first Apo A-I variant found to be associated with amyloidosis and peripheral neuropathy, found in an Iowan kindred of British descent 45. The Gly26Arg substitution was seen in Apo A-1 protein making up amyloid fibrils in affected family members. Genetic analysis later discovered heterozygosity for a correlating point mutation of the Apo A-1 gene 43. Variant ApoA1 Gly26Arg was subsequently found in amyloid deposits in two families without neuropathy, including a Massachusetts family of Scandinavian descent and a Canadian family of British descent. Eight additional ApoA1 variants have since been found to be associated with amyloidosis. Chronologically the next two variants to be described were Leu60Arg in a British family and Trp50Arg in an Ashkenazi family, both found to have renal and visceral involvement with variant Apo A-1 amyloid deposits, without neuropathy [80, 81]. Apo A-1 amyloidosis with a 12-residue deletion and Val–Thr insertion was found in a Spanish family [82] in which affected members had both cardiac and renal involvement without neuropathy. An Arg173Pro substitution was found to be associated with cardiac, larynx, and cutaneous involvement [83]. Variant Apo A-1 Leu178His amyloid deposits involving heart, skin, and larynx were found in a small French kindred [76]. One affected member was found to have clinical and neurophysiologic evidence of distal polyneuropathy, though this was not biopsy confirmed. Interestingly, amyloid deposits were found to be composed of both variant ApoA1 and wild-type transthyretin protein.

Treatment of Pathologic Peripheral Nerve Amyloidosis

Symptomatic management of neuropathic pain, orthostasis, weakness, and gastrointestinal complications are important in neurologic management and have been reviewed in detail elsewhere [1]. For pathogenic interventions, the treatment modality is primarily determined by the specific amyloidogenic protein found. The primary goal is to reduce the circulating fibril forming proteins. Therapy for AL-type amyloidosis can be directed at an underlying plasma cell dyscrasia using chemotherapy and stem cell transplantation. Their survival is shown to be improved [84, 85]. Treatment for TTR amyloidosis with liver transplantation has been thought to be helpful in reducing precursor mutant *TTR*. The 5-year survival rate after liver transplantation has varied results reported between 77 and 92 % [86, 87]. However, objective quantitative study of neuropathy is lacking posttransplant, and clinical neurologic progression does occur in a significant portion of treated patients from possibly extrahepatic production of transthyretin. Molecular investigations show deposition of TTR amyloid (wild-type and mutant form) does occur despite liver transplantation [65].

Most recently, pharmacologic attempts at stabilizing fibril forming TTR dimers into their more stable homotetramer state have been demonstrated to be useful in clinical application [88, 89]. The analgesic and anti-inflammatory drug diflunisal, used previously in inflammatory arthropathy, was shown to promote the homotetrameric form of transthyretin in prevention of amyloid fibrils [90, 91]. In a randomized, controlled clinical trial, over 2 years compared to placebo, diflunisal reduced the rate of progression of neurologic impairment and preserved quality of life [92]. Tafamidis was designed specifically to achieve a structure which stabilizes the tetrameric form of transthyretin [93]. In a randomized, controlled clinical trial, tafamadis was well tolerated and delayed impairment associated with peripheral neuropathy in an efficacy evaluable population, but failed to meet primary endpoints in an intention to treat analysis [94]. ISIS-TTR Rx is an anti-

sense oligonucleotide which leads to degradation of transthyretin mRNA thereby silencing expression, and has shown to reduce TTR levels by 80 % in a transgenic mouse model [95]. A phase 2/3 randomized, double-blind, controlled clinical trial began in 2013 [89].

In the case of Gelsolin, molecular therapies have been less clear, and the risk of experimental approaches has generally not been acceptable given the relatively benign course compared to AL and TTR forms. Lubrication of the eyes in prevention of further corneal injury and facial reconstructive surgery are employed in symptomatic management of Gelsolin amyloidosis. Utilization of furin inhibitors or "chemical chaperoning" to stabilize the mutant molecule has been discussed [96].

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