CHAPTER 6

Peripheral Nerve Pathology

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Spectacular progress has been made in the application of immunohistochemical and immunocytochemical techniques, molecular genetics, ultrastructural and morphometric studies, and teased nerve analysis to nerve biopsies in the evaluation of patients with peripheral neuropathy and related disorders. The has resulted in greater accuracy in the assignment of specimens, for diagnostic purposes, to more certain proposed mechanisms of injury, and the more rational selection of immunomodulating and immunosuppressive therapies. This chapter reviews aspects of peripheral nerve microscopic anatomy, morphologic and immunopathologic alterations in peripheral nervous system disorders, and the contribution of nerve biopsy to neuropathic motor disorders.

GENERAL CONSIDERATIONS

Exclusive of the pathologic alterations of individual nerve axons, disease processes that affect the peripheral nerve often lead to specific alterations of the epineurial, perineurial, and endoneurial compartments described in more detail below.

Epineurium

The fibrous adipose tissue of the epineurium invests the whole nerve trunk and space between the individual fascicles and is the site of entry of the vasa nervorum (Fig. 1). The vascular anatomy of the nerves of the limbs has been recognized for over 50 years since the detailed studies of Sunderland (1,2). The nutrient vessels ramify within the nerve trunk, anastomosing longitudinally and penetrating the perineurium, ending in an unbroken network of endoneurial microvessels (Fig. 2A and B). The proximal circulation of named nerves of the arm and leg may be sustained by long stretches of a single arterial vessel, such as in the axilla-to-elbow and knee-to-elbow segments (Fig. 3) (1–4), most often located peripherally in the nerve trunk, but this does not generally translate into watershed zones unless there is associated vasculitis or abrupt thrombosis of large named vessels (5).

The epineurium provides mechanical support, cushioning nerve trunks as they pass by bony prominences. Focal nerve compression is enhanced when there is a reduction in the epineurial fat cushion due to chronic disease or malnutrition with accompanying weight loss in association with syndromes of severe generalized weakness and chronic bedridden or immobile states and prolonged stays in the intensive care unit. The sites most prone to compression are the ulnar nerve at the elbow, the sciatic nerve in the buttock and thigh, and the peroneal nerve at the fibular head.

FIG. 1. The distribution of blood vessels in the peripheral nerve trunk. A cross-section of sural nerve is shown in low magnification stained with hematoxylin and eosin and counterstained with anti-actin smooth muscle antibody. ep, epineurium; en, endoneurium; p, perineurium.

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Perineurium

Individual nerve fascicles are surrounded by alternating layers of specialized densely packed cells, the pericytes, and longitudinally oriented collagen fibers. The perineurium is subject to nonspecific morphologic alterations such as thickening of the basal lamina as a consequence of a variety of disorders and normal aging. There is a primary inflammatory syndrome of the perineurium, termed perineuritis (6), which classically presents with sensory loss; however, one reported patient had prominent motor involvement (7).

Endoneurium

The endoneurium is the supporting matrix for myelinated and unmyelinated nerve fibers contained within a single fascicle. This compartment reacts to a vast number of nonspecific processes with a limited number of alterations. Collectively, the observed pathologic findings generally point toward either segmental demyelination or axonopathy as the primary pathologic process. Segmental demyelination is generally attributable to a primary disturbance of Schwann cell function or immune-mediated injury of internodal myelin segments; however, in both instances, the axon is left essentially intact. Standard cryostat- and paraffin-stained sections do not adequately demonstrate the histologic features of demyelination and remyelination in a given nerve specimen. However, plastic embedded, 1-μm, semithin sections can show demyelinated axons and thinly myelinated fibers because of the production of a new myelin sheath. Teased nerve fiber studies are ideally suited to show the segmental character of the lesions. Repeated episodes of demyelination and remyelination lead to onion bulb formations, visible by electron microscopy as concentrically laminated Schwann cell processes.

Active axonal degeneration due to nerve ischemia, compression, trauma, infection, and primary or secondary degeneration of motor axons is suggested by the presence of myelin ovoids, myelin debris, and macrophage recruitment along the course of degenerated fibers, best seen in longitudinally stained sections. The signs of chronic axonopathy are a marked depletion of
myelinated and unmyelinated nerve fibers and endoneurial fibrosis.

IMMUNOPATHOLOGY

Significant advances have been made in the basic understanding of immune reactions of the peripheral nerves (8), and these in turn have had wide-ranging impacts on the immunopathologic evaluation of nerve tissue. Under normal circumstances, the peripheral nervous system is protected from immune reactions by the blood–nerve barrier that consists of perineurial and endoneurial vascular tight junctions. In the early phases of inflammation, there is enhancement of vascular permeability by vasoactive substances, complement activation, and cytokine secretion. These alterations lead to leakage of inflammatory mediators and the immigration of lymphocytes and macrophages in the endoneurial compartment. Much has been learned about each of these constituents in the past decade.

Local immune activation requires the interaction of a specific autoantigen, a main histocompatibility (MHC) Class II antigen-presenting cell and antigen-specific T cells in the trimolecular complex. This interaction leads to the proliferation of specific helper (CD4+) and cytotoxic (CD8+) T cells, with expression of human leukocyte antigen-DR, interleukin-2 receptor, and the secretion of tumor necrosis factor-α and other interleukins. Macrophages are the primary antigen-presenting cell of the peripheral nervous system (9). They appear as immunoreactive CD68+ cells with elongated or cylindrical cell bodies, scattered in the endoneurium, often in proximity to blood vessels. Intensely stained MHC Class II-positive macrophages appear in excessive numbers at foci of acute axonal degeneration and in other primary immune-mediated neuropathies. They also have a role in the initiation of myelinated nerve fiber regeneration (10). The complement system also contributes to vascular and neural injury. Activation of the classic or alternative pathways leads to cleavage of C3 to C3d that then results in activation of the terminal lytic sequence C5b-9 or membrane attack complex (MAC).

Commercially available monoclonal and polyclonal antibodies directed against T-cell subsets, B cells, macrophages, immunoglobulins, complement proteins, cytokines and other inflammatory mediators, and MHC class antigens can be easily applied to clinical and research protocols for the evaluation of patients with various immune-mediated neuropathies (11).

NERVE BIOPSY: GENERAL CONSIDERATIONS

Over the past decade, the demand for nerve biopsy has increased along with advances in the assessable process and treatment of diverse neuropathic disorders, and the availability of outpatient biopsy surgery has allowed far easier and less expensive access of the procedure to patients. The nerve chosen for biopsy should be clinically and electrophysiologically involved. A segment of the sural, superficial peroneal, and femoral intermedius nerves can be surgically removed, depending on the clinical circumstances, without incurring a serious deficit; each has the advantage of allowing biopsy of underlying muscle, respectively, from the soleus, peroneus brevis, and rectus femoris (Fig. 4A–D). The estimated risk of residual pain, paresthesia, analgesia, or anesthesia from a sural nerve biopsy is about 5% (12). There is a technique for the biopsy of the gracilis motor nerve in the medial thigh that does not lead to a noticeable deficit (13); however, it entails a deeper dissection. Examination of a specimen of muscle tissue is useful to exclude unsuspected myopathy. It also increases the yield of vasculitic lesions and provides useful information about the severity of an underlying neuropathy. Full-thickness nerve biopsy is preferable to a fascicular biopsy; however, some still prefer the latter technique to minimize dermatomal sensory loss and afford regeneration across the gap.
SPECIFIC NEUROPATHIC MOTOR DISORDERS

Nerve biopsy is useful in the diagnosis of several neuropathic motor disorders, discussed in more detail below.

Peripheral Nerve Vasculitis

In 1938, Harry Lee Parker recommended biopsy of a peripheral nerve to diagnose cases of polyarteritis nodosa (14). Coers and Woolf (15) later described the suitability of the superficial peroneal musculocutaneous nerve and peroneus brevis muscle that was later implemented in the diagnosis of other similar patients with mononeuritis multiplex (16,17). A quarter century later, Dyck et al. (18), Kissel et al. (19), and Said et al. (20) established an important role for sural nerve biopsy in the definition of peripheral nerve vasculitis.

Necrotizing arteritis affects small- and medium-sized epineurial vessels of the range found in the vasa nervorum leading to narrowing, occlusion, and recanalization of vessel lumina in individual nerves (Fig. 5). The resulting lesions interrupt nutritional and oxygen support, leading to ischemia and infarction of a portion of the nerve fascicle, usually in a centrafascicular or wedge-shaped area and best seen in cross-section of the nerve trunk. Nerve biopsy is essential in the proper management of peripheral nerve vasculitis because unrecognized and therefore untreated, the outcome is often fatal (21). Conversely, the risk of potentially fatal medication side effects in histologically unproved cases outweighs the potential benefits of empiric immunosuppressive therapy (22).

Cholesterol Emboli Syndrome

Nerve biopsy is essential in the antemortem diagnosis of cholesterol emboli syndrome (23). The neurologic disorder includes myalgia, livedo reticularis, mononeuritis multiplex or distal symmetrical polyneuropathy, increased erythrocyte sedimentation rate, and weight loss. Vascular