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Uncompacted Myelin Lamellae in Two Cases of Peripheral Neuropathy

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Summary. Peripheral nerve biopsies from two patients with chronic sensorimotor neuropathy were studied. The first case was a non-Hodgkin malignant lymphoma and did not show any dysglobulinemia. The second case had a benign monoclonal gammopathy IgG, Lambda type. Direct immunofluorescence showed no deposits in the first case and slight deposits of anti IgG sera on a few myelinated fibers in the second case. There were numerous fibers showing uncompacted myelin lamellae, 7% in the first case and 4% in the second case. Some of these fibers had axons containing more tubules than filaments. The very few cases reported on neuropathies showing that uncompacted myelin lamellae were frequently associated with dysglobulinemic neuropathy. However, this ultrastructural abnormality of the myelin sheath can be observed without any dysglobulinemia.

Key words: Malignant lymphoma – Monoclonal gammopathy – Myelin – Peripheral neuropathy

Introduction

Peripheral neuropathies associated with monoclonal gammopathy are well known but the lesions seen upon ultrastructural examination vary considerably. Some are very peculiar. Widening of some lamellae of the myelin sheath has only been observed in human peripheral neuropathies that were associated with monoclonal gammopathies [6, 12, 15–17]. Uncompacted lamellae represent another interesting abnormality of the myelin sheath. Ohnishi and Hirano [11] reported recently three cases of dysglobulinemic neuropathy. We had the opportunity to examine two cases. One patient had a benign monoclonal gammopathy and the other a non-Hodgkin malignant lymphoma without any dysglobulinemia.

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Materials and Methods

Case Reports

Case 1. A 69-year-old woman presented in our hospital with a bilateral sensorimotor peripheral neuropathy. She also had enlarged superficial lymph nodes together with enlarged liver and spleen. A study of conduction speed showed severe peripheral axon damage in which demyelination was predominant. A peripheral nerve biopsy was performed on the right leg at that time before chemotherapy was started. A follow-up 6 months later showed a stationary state. A peripheral nerve biopsy was performed on the left leg for repeated immunopathologic examination. A non-Hodgkin lymphoma of the plasmocytoid type was diagnosed on the basis of several lymph node biopsies.

Case 2. An 84-year-old woman presented in hospital with peripheral sensorimotor neuropathy. Neurologic examination revealed a weakness in the anterior tibial musculature without amyotrophy. There was disturbance of pinprick, touch pressure, and thermal discrimination in a stocking and glove distribution. Upon immunoelectrophoresis of the serum, a monoclonal gammopathy, IgG, Lambda light chain, was detected. Bone marrow contained 10% of plasma cells. A skeletal radiography was normal. An electrophysiologic study showed motor nerve velocities to be remarkably slow in almost all the nerves studied, with markedly prolonged terminal latencies. A nerve biopsy was performed on the right superficial peroneal nerve. A follow-up 5 years later in February 1982 revealed an improvement of the motor defects, but sensory disturbances were still present in the lower extremities. In serum the monoclonal protein was present, and bone marrow contained 4% plasmocytes. An electrophysiologic examination showed a moderate improvement of the motor nerve velocities. A nerve biopsy was performed on the left superficial peroneal nerve.

Methods

Each peripheral nerve specimen was divided into three portions. Standard techniques were used on paraffin sections. Direct immunofluorescence microscopy was performed on transverse cryostat sections of second portion. The third fragments were immediately fixed in 5% glutaraldehyde and postfixed in 1% osmium tetroxide. Epon-embedded thin and ultrathin sections were prepared for light- and electron-microscopic examination. The number and diameter of

myelinated fibers were measured in micrographs of nerve fascicles enlarged to a final magnification of ×900. Fiber diameters were counted with a Kontron MOP-AMO2 planimeter.

Results

Case 1

Upon light microscopy there were neither cellular infiltrates nor amyloid deposits. The percentage histogram for myelinated fibers showed that they were reduced in number. Estimation of the number of the myelinated fibers showed a density of 3,575/mm^2 (286 fibers were counted within 0.08 mm^2 of endoneurial space). Direct immunofluorescence microscopy was only possible on the second biopsy and no antiglobulin deposits were seen. Ultrastructural examination of the first biopsy showed alterations of some myelinated fibers. There were a few bands of Büngner. The main alterations were seen in myelin structures. There were naked axons, and other axons had excessively thin myelin sheaths. Some of these fibers were surrounded by the flattened debris of Schwann cells. The most remarkable finding was the presence of uncompacted myelin lamellae structures in 7% of the myelinated fibers. These lamellae were located both in the inner layers of the myelin sheath and in the outer part or between two compact zones of the myelin sheath (Fig. 1). Some axons were only surrounded by uncompacted myelin lamellae (Fig. 2). Between these uncompacted myelin lamellae there were stacks of Schwann cell cytoplasm or a few empty spaces and occasionally rounded structures (Fig. 3). Inside these structures small dots (Fig. 4) or lamellar patterns were seen (insets, Fig. 4). Some axons were wrapped in uncompacted myelin lamellae and contained more tubules than filaments (Fig. 4). Some unmyelinated fibers were altered with flattened axons. The endoneurial space contained a few scattered lymphocytes. We could not be sure that they were of tumoral origin even though they sometimes contained polylobed nuclei. Ultrastructural examination of the second peripheral nerve biopsy showed the same alterations. The percentage of fibers presenting uncompacted myelin lamellae was not measured.

Case 2

Upon light microscopy there were neither cellular infiltrates nor amyloid deposits. Direct immunofluorescence microscopy showed slight deposits of anti IgG sera on a few myelinated fibers. The percentage histogram for myelinated fibers showed that they were reduced in number. Estimation of the number of the myelinated fibers showed a density of 1,985/mm^2 (119 fibers were counted within 0.06 mm^2 of endoneurial space). On ultrastructural examination there were a few fibers showing myelino-axonal degeneration and numerous changes in myelin structure. Many axons were wrapped in an excessively thin myelin sheath. These remyelinating fibers were frequently surrounded by Schwann cell processes (Fig. 5). Moreover, 4% of the myelinated fibers exhibited uncompacted myelin lamellae. Some axons were naked and others were surrounded by only a few uncompacted lamellae. The uncompacted lamellae were sometimes linked by desmosome structures. The axons of demyelinated fibers contained numerous filaments. Within some axons surrounded by uncompacted myelin lamellae tubules were more numerous than filaments (Fig. 6). Some unmyelinated axons were flattened, and regenerating fibers were scarce. A few scattered plasmocytes were seen in the endoneurium. Similar findings were seen in

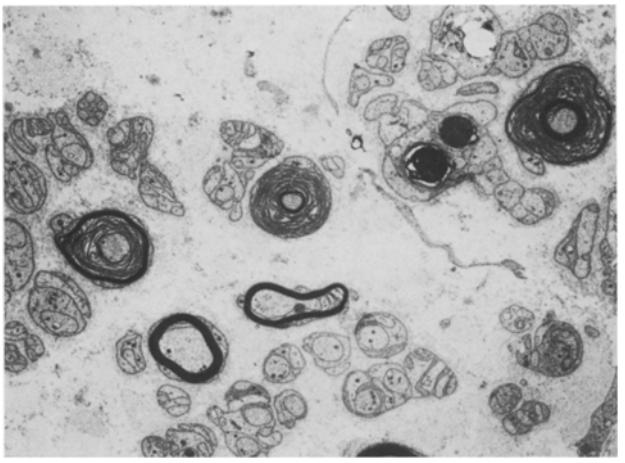

Fig. 1. Three fibers show uncompacted myelin lamellae occupying various locations inside the myelin sheath. Two bands of Büngner are also visible. ×2,665

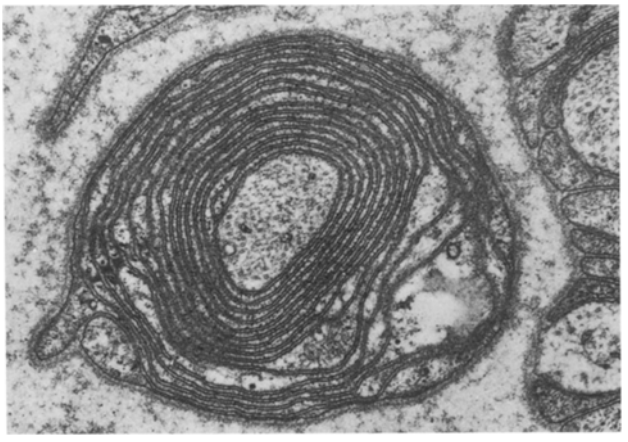

Fig. 2. This axon is only wrapped in uncompacted myelin lamellae. Three desmosomes-like structures are seen at the beginning of the spiral. ×21,600

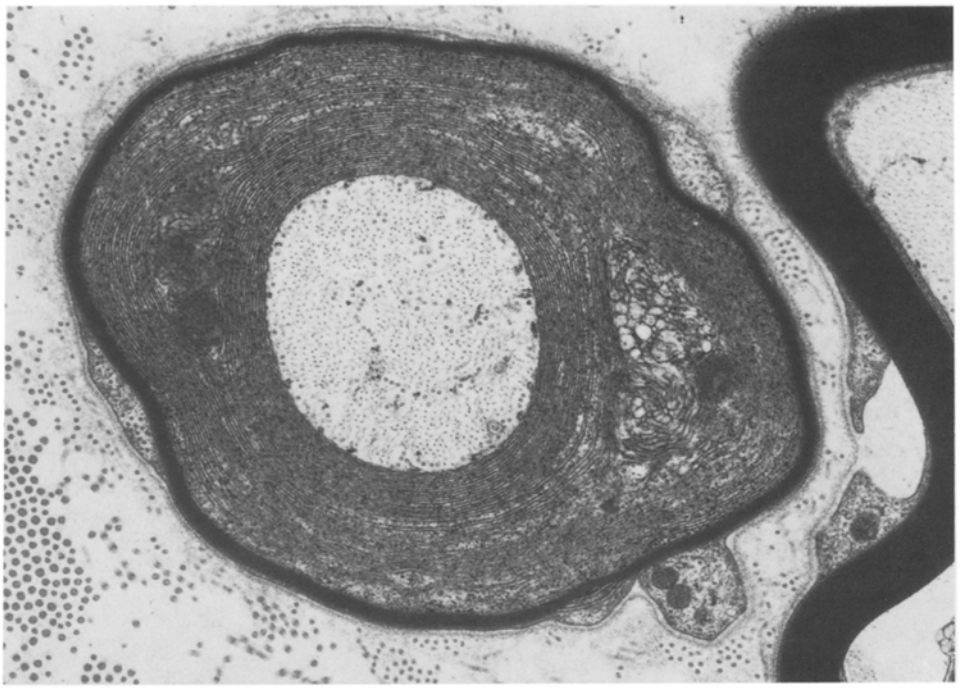

Fig. 3. This uncompacted portion of the lamellar structure contains three rounded structures. ×20,000

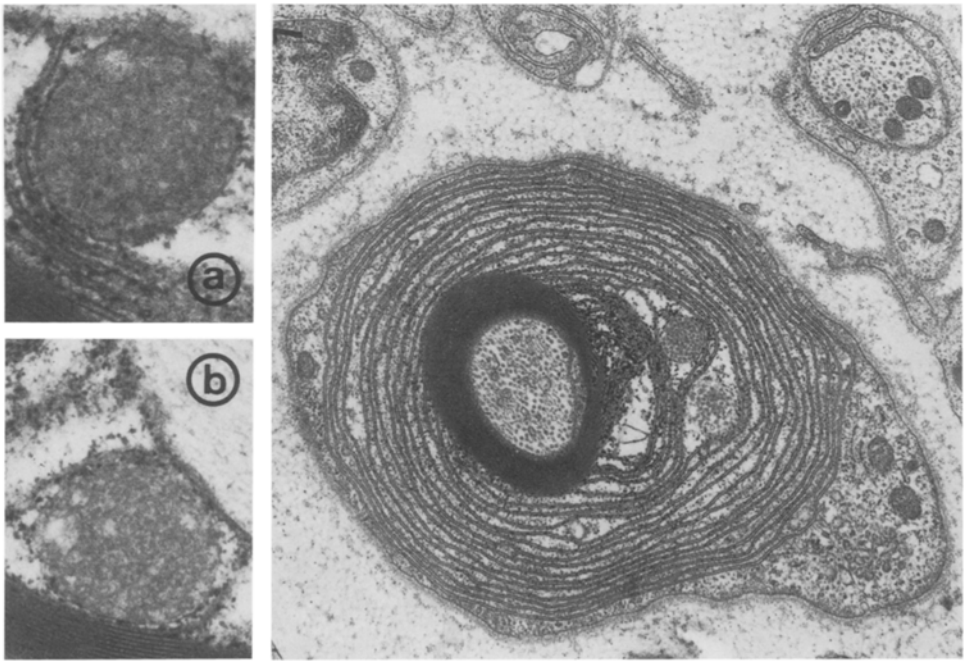

Fig. 4a, b. The outer portion of the myelin sheath is uncompacted. Among these lamellae there are two rounded structures containing small dots. ×17,000. Two rounded structures contain some filamentous patterns. **a** ×63,000; **b** ×42,700

the second biopsy, and uncompacted myelin lamellae were observed in 4% of the myelinated fibers. A few mature plasmocytes were seen in the endoneurium.

Discussion

Only three cases of peripheral neuropathy showing frequent uncompacted myelin lamellae have been reported in detail [11]. These three patients suffered from dysglobulinemic neuropathy. Uncompacted myelin lamellae have been occasionally encountered in a case of dysglobulinemic neuropathy [2], in chronic infantile demyelinating neuropathy [1], and in cases of relapsing polyneuropathy [18, 19]. Ohnishi and Hirano [11] found uncompacted lamellae located predominantly in the inner layers of the myelin sheath. However, they are

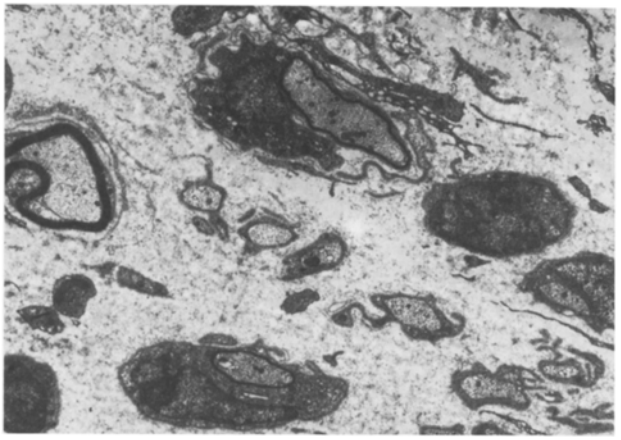

Fig. 5. There are three remyelinating fibers. Two of them are surrounded by flattened Schwann cell debris. ×4,100

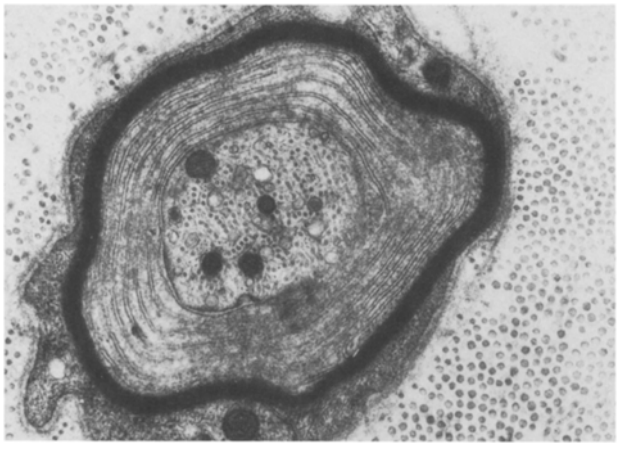

Fig. 6. This axon is in part wrapped in uncompacted myelin lamellae and contains 138 tubules to 62 filaments. ×22,235

also seen in the outer parts and can be the only formation of the myelin sheath. They also develop far from the axon [19]. Ohnishi and Hirano [11] pointed out that abnormally wide Schmidt-Lanterman incisures and abnormal paranode-like structures give rise to uncompacted lamellae. We think that this alteration may develop during remyelination since our two cases exhibited several examples of extremely thin myelin sheaths totally or in part composed of uncompacted myelin lamellae. Loosened myelin can also be observed during serum-induced demyelination from experimental allergic neuritis [13, 14]. They are not observed during normal remyelination in the peripheral nervous system [3].

The mechanism of dysglobulinemia on the Schwann cell has not yet been elicited. Deposits of M components on myelin sheath have been observed by direct immunofluorescence in several cases [5–7, 9, 12]. Moreover Nardelli et al. [10] showed binding of IgM kappa with the myelin sheath using the immunoperoxidase technique. Then, by electron microscopy, widenings of some lamellae of the myelin sheath could be seen [10]. In human pathology this myelin change seems specific of monoclonal gammopathy and has only been reported during multiple myeloma [15, 16] and Waldenström's macroglobulinemia [6, 10, 12, 17]. It was observed in only three of ten cases of Waldenström's macroglobulinemia [20]. This phenomenon was seen by Lampert et al. [8] in chickens developing allergic neuritis and by Raine and Bornstein [13] in peripheral nervous system cultures during serum-induced demyelination. Even though they can be observed in the same experimental material [13] the uncompacted myelin lamellae and the wide-spaced configuration of the myelin (widening of some lamellae) must be differentiated. First of all, their ultrastructural patterns are quite different. Furthermore, immunopathologic studies of frozen sections were negative or only slightly positive in the present cases. Finally, obvious and frequent images of uncompacted myelin lamellae may be observed in a patient without any dysglobulinemia. Endoneurial mature plasmocytes could play a role, but they are few and only encountered in the case presenting a monoclonal gammopathy. The mechanism of uncompacted myelin lamellae formation remains unclear. However, this phenomenon has been encountered frequently only in the field of plasma cell dyscrasia.

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