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To cite this article: Chiara Terracciano, Christa Pachatz, Emanuele Rastelli, Francesco Saverio Pastore, Mariarosa Anna Beatrice Melone & Roberto Massa (2018): Neurofibromatous neuropathy: An ultrastructural study, Ultrastructural Pathology, DOI: 10.1080/01913123.2018.1454562

To link to this article: https://doi.org/10.1080/01913123.2018.1454562

Published online: 27 Mar 2018.

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Neurofibromatous neuropathy: An ultrastructural study

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ABSTRACT
Plexiform neurofibroma is pathognomonic of neurofibromatosis 1 (NF1). An NF1-associated peripheral neuropathy has been described in a small minority of NF1 patients but its histopathological features are poorly characterized. We report the case of a 46-year-old woman presenting with bilateral supraclavicular painful masses without other stigmata of NF1. MRI showed bilateral plexiform lesions extending from cervical roots to the elbows. Nerve conduction studies documented a sensory motor polyneuropathy. Morphometric analysis of sural nerve biopsy showed a preferential loss of large-caliber myelinated fibers with a g ratio of 0.515, and the presence of regeneration clusters. By electron microscopy, marked and diffuse endoneurial fibrosis with an altered relationship between Schwann cells (SC) and collagen fibrils was observed. Moreover both myelinating and non-myelinating SC were characterized by the presence of various cell degradation products. These changes suggest that, in neurofibromatous neuropathy, a widespread axonal atrophy and degeneration take place independently on the presence of tumoral infiltration, possibly due to an impairment in SC-axon cross talk. In this case, the coexistence of plexiform neurofibromas with a peripheral neuropathy strongly suggests a diagnosis of NF1 even without fulfillment of clinical criteria. We propose that in the presence of plexiform neurofibromas, electrophysiological studies should be performed also in asymptomatic patients, in order to detect the existence of a subclinical neuropathy.

ARTICLE HISTORY
Received 31 January 2018
Accepted 15 March 2018
Published online 30 March 2018

KEYWORDS
Electron microscopy; morphometric analysis; neurofibromatosis type I; neurofibromatous neuropathy; plexiform neurofibromas

Introduction
Neurofibroma is a benign nerve sheath tumor, consisting of a mixture of cell types including Schwann cells (SC), perineural-like cells and fibroblasts. There are three major types of neurofibromas: cutaneous, subcutaneous, and plexiform. The latter is pathognomonic of neurofibromatosis 1 (NF1) although it may occur in patients without other stigmata of NF1.1,2 NF1 is an autosomal dominant disease affecting about 1 in 3500 individuals, and caused by a mutation in the Nf1 gene on chromosome 17q11. Nf1 encodes neurofibromin, a protein that functions as tumor suppressor. An NF1-associated peripheral neuropathy affecting nerves without neurofibromas has been described in a small minority of NF1 patients,3 especially those with large root diffuse neurofibromas.4,5 However, in those studies, only patients complaining of peripheral neurological symptoms were tested by electrophysiology, implying that the real prevalence of such neuropathy might be largely underestimated. Moreover, histopathological and ultrastructural studies have been performed only in few patients.

In this study we describe the histopathological and ultrastructural features of peripheral neuropathy detected in a patient with multiple spinal roots neurofibromas.

Case report
We report the sporadic case of a 46 years old woman presenting with bilateral painful masses in supraclavicular region. Her neurological
examination showed diffuse hypo-reflexia, pain and thermal sensory reduction in the hands, and a reduced vibration and deep touch sensation in the distal portions of the lower limbs. None of the typical cutaneous lesions of NF1, such as "café au lait" macules, dermal fibromas, and axillary or inguinal freckling, were present. Ophthalmological evaluation ruled out the presence of Lisch nodules. Routine blood tests were unremarkable.

Electrophysiological examination, performed using standard technique, evidenced a severe bilateral brachial plexopathy characterized by absent SAPs and reduced cMAPs of ulnar, median, and radial nerves. Moreover, in the lower limbs, a sensory axonal neuropathy with reduced SAPs in the peroneus and sural nerve bilaterally was detected.

An MRI study of the entire spinal cord evidenced multiple large neurofibromas arising from cervical spinal roots C4 to C7, extending into brachial plexus cords bilaterally (Figure 1a); intradural lesions and alterations in the thoracic, lumbar, and sacral roots were not observed. By CT scan, these tumors were shown to extend into the ulnar and radial nerves bilaterally (Figure 1b). PET-CT scanning failed to show fluorodeoxyglucose radiolabeling of the neurofibromas, ruling out a malignant nature. An MRI of the brain was normal, in particular acoustic neuromas, ependymomas, and meningiomas were not detected.

A biopsy of the left supraclavicular mass showed histological features of plexiform neurofibroma, with diffuse S-100 immunoreactivity. A molecular test, performed as previously described on blood mononuclear cells by PCR amplification and DHPLC analysis on the 60 exons of the Nf1 gene, failed to show mutations or deletions. Causative mutations in the SMARCB1 gene, responsible of Schwannomatosis, were also not detected. The patient was unavailable for performing gene analysis on a second tissue specimen.

To better define the features of the lower limbs neuropathy, histological and ultrastructural studies of sural nerve biopsy were carried out as described before. Light microscopy of sural nerve semi-thin sections evidenced normal-sized fascicles surrounded by epineural tissue and perineural sheaths with a grossly normal appearance. In all the fascicles there was an important loss of myelinated fibers together with abundant clusters of axonal regeneration (Figure 2a-b). Sporadic examples of remyelinated fibers and rudimentary onion bulb formations were present. Endoneurial mast cells were unusually frequent. By electron microscopy, the most impressive feature was represented by marked and diffuse endoneurial fibrosis, with an altered relationship between SC and collagen fibrils, which were densely packed around nerve fibers (Figure 2c-d-e-f). Moreover, both myelinating and non-myelinating Schwann cells were characterized by the presence of various types of cell degradation products such as lipofuscin granules (Figure 2d-e), II granules (Figure 2g), and myelin figures (Figure 2h). A teased fiber preparation showed a large prevalence of medium/small caliber fibers with rare remyelinated internodes.

Morphometric analysis revealed a decrease (5956/mm², normal mean value 8800/mm²) of myelinated nerve fibers (MNF), with a preferential and severe loss of large caliber MNF (Figure 3). Active axonal regeneration was documented by the presence of 173 axonal clusters/mm². The mean axonal/total MNF diameter (g ratio) was 0.515 (normal mean value...
indicating a prevalence of axonal atrophy over demyelination/remyelination.

**Discussion**

Some of these histopathological findings have been previously described in a few cases of NF1 associated polyneuropathy. However, these changes were reported to be present mainly in areas of perineural disruption, hypercellular epineurium, and disorganized sub-perineurium, that are features of neurofibroma.

As a whole, the ultrastructural changes we describe indicate that, in this neuropathy, SC
present a pathological phenotype not confined to neurofibromas but diffused throughout peripheral nerves.

This altered phenotype seems to induce perturbations of both SC-axons and SC-fibroblast cell signaling, further inducing axonal degeneration and collagen overproduction, possibly mediated by mast cell degranulation, as happens for other neuropathies. Similar features have been described in neurofibromas of NF1 animal models. In NF1, SC show an abnormal behavior, which is probably due to overexpression of the neuregulin (NRG1) receptor ErbB1. Similarly, in Charcot-Marie-Tooth disease type 1A, SC display overexpression of other NRG1 receptors (ErbB2 and 3) and show an aberrant phenotype. In the present case, the coexistence of multiple cervico-brachial plexiform neurofibromas with a diffuse peripheral neuropathy, strongly suggests a diagnosis of NF1 even without fulfillment of clinical criteria. In the absence of Nf1 gene mutations in peripheral blood cells, neurofibroma and neurofibromatous neuropathy are suggestive of NF1 due to a somatic mosaicism, previously described in a minority of patients. In alternative, the present case may represent a sporadic occurrence of plexiform neurofibromas, accompanied by a “neurofibromatous neuropathy,” a so far unreported association. Further ultrastructural studies of peripheral nerve independent from neurofibroma are needed in NF1 patients, to verify if the SC perturbations we found in our patients are unique to “neurofibromatous neuropathy” and could be considered a hallmark of this disease as happens for cytological alterations in other hereditary neuropathies.

In conclusion, we propose that in the presence of plexiform neurofibromas, electrophysiological studies should be performed also in asymptomatic patients, in order to detect the existence of a subclinical neuropathy and to prompt molecular analysis of the Nf1 gene in peripheral blood or other tissues.

Acknowledgments

The authors are indebted to Mr. Graziano Bonelli for excellent technical assistance.

Author contribution

Chiara Terracciano: study concept and design, analysis and interpretation of data, manuscript preparation.

Christa Pachatz: study design and collection of data.

Emanuele Rastelli: collection and analysis of data.

Francesco S. Pastore: collection and analysis of data.

Mariarosa Anna Beatrice Melone: study supervision, data interpretation, revising the manuscript for intellectual content.

Roberto Massa: study concept and design, manuscript preparation, data interpretation, revising the manuscript for intellectual content.

Author Disclosures

Dr. Chiara Terracciano reports no disclosure.

Christa Pachatz reports no disclosure.

Emanuele Rastelli reports no disclosure.

Francesco S. Pastore reports no disclosure.

Mariarosa Anna Beatrice Melone reports no disclosure.

Roberto Massa reports no disclosure.

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