CASE REPORT

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Unusual median nerve schwannoma: a case presentation

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Abstract

Peripheral nerve sheath tumors are common soft tissue neoplasms and their characterization is often challenging. Although the surgical pathology defines some typical entities, some degree of controversy regarding the classification of these tumors still exists. Newer imagistic and histopathological techniques are crucial for their accurate diagnosis and grading. We present an unusual case of median nerve schwannoma in a young patient, discussing the clinical, surgical and pathological elements, including immunohistochemistry.

Keywords: nervous tumors, schwannoma, immunohistochemistry.

Introduction

Schwannomas, also known as neurilemmomas, the most common benign tumors of the peripheral nerves' neural sheaths, are benign tumors originating from Schwann cells derived from the neural crest [1, 2].

Schwannoma usually affects patients aged 20–50 years without race or sex predilection and accounts for approximately 5% of all benign soft tissue tumors [3].

The most common sites of involvement are the head and neck, the flexor surfaces of the extremities, the mediastinum and the retroperitoneal space. Upper limb schwannomas (contributing 19% of all locations) [4] usually involve the ulnar nerve, only 6.8% of them being situated along the median nerve sheath [5].

Although they commonly appear as solitary lesions, multiple tumors can occasionally develop in schwannomatosis (one of the "candidate" genes is SMARCB1, a tumor-suppressor gene that regulates cell cycle, growth and differentiation, located on chromosome 22 a short distance from the neurofibromatosis type 2 gene) [6, 7] or in association with neurofibromatosis type 2 (bilateral vestibular schwannoma is pathognomonic of neurofibromatosis type 2) and neurofibromatosis type 1 [6]. They rarely undergo malignant transformation [8].

Solitary schwannoma is a slow-growing tumor and it can present as a painless swelling for years before the onset of pain and neurological symptoms caused by nerve compression. Clinically, the tumor is well circumscribed and mobile transversely to the course to the nerve, but immobile in the longitudinal plane [9, 10].

Tumors with a long evolution and/or relatively large dimensions can undergo degenerative changes such as cyst formation, calcification, hemorrhage and fibrosis and are described as ancient schwannomas [11].

Macroscopically, a schwannoma is an oval yellowish mass, typically eccentric to the nerve and enveloped in a true capsule, often covered by tortuous blood vessels. This capsule consists of the perineurium of the nerve bundle of origin, surrounded by an onion-like condensation of the deepest layers of the epineurium. As such, it usually allows excision of the tumor without damage to the parent nerve. The extratumoral fascicles are stretched, attenuated and displaced over the dome of the mass. The rare plexiform variant of a schwannoma may infiltrate between nerve bundles and thus make excision difficult [12].

Microscopically, the tumor contains a variable mixture of two distinctive areas: Antoni A (cellular areas with nuclei arranged in parallel rows termed "nuclear palisading", Verocay bodies in which two rows of palisading nuclei are separated by pink fibrillary material) and Antoni B (paucicellular, microcystic areas rich in macrophages and collagen fibers). Degenerative changes are frequent. Ectatic, hyalinised, thrombosed blood vessels with associated hemorrhage and deposition of fibrin are typically present. Cyst formation, hyalinization of the matrix and focal calcification are also described. An inflammatory infiltrate is usually present, including numerous histiocytes. The nuclei of the Schwann cells become hyperchromatic, enlarged and multilobed, but mitoses remain sparse [5].

By immunohistochemistry, schwannomas typically show diffuse, strong expression of S100 protein, given the neuroectodermal origin of Schwann cells similar with that of melanocytes [13, 14].

Folpe and Gowan (2001) have stated that immunostaining for this protein is so consistent and of such intensity that it serves as an important diagnostic tool [15].

Recent markers frequently used in the positive and differential immunohistochemical diagnosis of schwannoma include calretinin, CD34, neurofilament protein, Ki67, CD56 and factor XIIIa [16–18].

Here we report an unusual case of schwannoma of the median nerve that, despite the classical description as a well-defined tumor not including the patent nerve, entrapped nerve bundles with intraoperative motor response to electrical stimulation. We describe the anamnestic and clinical presentation, the MRI imaging, the surgical findings and therapy, the histopathological and immunohistochemical diagnosis and the functional outcome. The patient signed a full informed consent form. This presentation received the approval of the Scientific Research Ethics' Committee of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania.

Patient, Methods and Results

We present the case of a 19-year-old male admitted in our department for a soft tissue tumor located antero-medially in the proximal third of the left arm. The tumor had started growing slowly three years before and it was painless, but it associated paresthesias and numbness on the volar aspect of the second and third phalanges of the index and middle finger for the last few months. The patient had previously suffered a sports accident, the impact area matching the exact localization of the tumor.

The patient's medical history showed a Wolff–Parkinson–White syndrome – posterior septal accessory fascicle – recently treated by radiofrequency ablation.

The clinical examination revealed a firm, painless subcutaneous soft tissue tumor of about 3×2.5×1 cm, placed antero-laterally on the proximal left arm. The tumor could be mobilized transversely, but not axially or on the deep planes. The percussion of the median nerve at this level generated a positive Tinel sign over the volar distal phalanges of the second and third fingers.

Magnetic resonance imaging (MRI) showed a nodular, well-demarcated tumor of the median nerve, with discreet T2 signal, T1 signal and STIR hyperintense signal (Figure 1, a–c).

The median nerve conduction studies were completely normal.

The patient underwent surgery under general anesthesia, the tumor being dissected and excised with microscope magnification. It entrapped two nerve fascicles on the antero-medial aspect of the median nerve, which were also resected. Since their electrical stimulation produced some degree of flexion of the proximal interphalangeal joint of the index finger, the resulted defect was grafted using the medial brachial cutaneous nerve (located in the same surgical field) as a donor (Figure 2, a–c).

No motor deficit was noted postoperatively. The numbness of the index and middle finger subsided progressively, with significant improvement 12 months later.

The excision specimen was formalin-fixed and paraffin-embedded samples were examined histopathologically and immunohistochemicaly at Oncoteam Diagnostic, Bucharest. Serial 3 μm sections had been cut from paraffin blocks and stained with Hematoxylin and Eosin (HE).

Histopathological evaluation

HE-stained sections showed the typical biphasic pattern of Antoni A (Figure 3b) and Antoni B (Figure 3a) areas, nuclear palisading (Figure 3c) and Verocay bodies, common vascular ecstasies, some blood vessels with thickened walls (Figure 3d), thrombosis and hyalinization with moderate chronic inflammatory infiltrate (Figure 3e).

Immunohistochemistry method

The immunohistochemistry (IHC) was performed on 3 μm sections from 10% formalin-fixed paraffin-embedded tissues according to the IHC method an indirect bistadial technique performed with a polymer-based detection system (EnVision™ Dual Link System-HRP, DAKO, Carpinteria, CA, USA). Tissue sections were spread on poly-L-Lysine-coated slides immersed in three changes of xylene and rehydrated using a graded series of alcohol. Antigen retrieval was performed in microwave oven. In each section, endogenous peroxidase was blocked by 20 minutes incubation in 3% hydrogen peroxide. The sections were incubated with primary antibody: S100 protein (DAKO, 1:400, polyclonal), Vimentin (Leica, 1:50, V9), Leu-7 (DAKO, 1:50, TB01), CD34 (DAKO, 1:50, QBend10) and Ki67 (DAKO, 1:100, Mib-1) at room temperature for one hour. The DAKO EnVision Detection System-HRP was then applied for 30 minutes. Finally, the sections were incubated in 3,3'-diaminobenzidine for 5 minutes, counterstained with Meyer's Hematoxylin and mounted. The slides was examined and photographed on Leica DM750 microscope. Negative controls were obtained by replacing the primary antibody with non-immune serum. As a positive control, a neural tissue section was used.

Immunohistochemically, the tumor cells presented a diffuse strong expression for S100 protein (Figure 4a) and Vimentin (Figure 4c) with focal positive immuno-staining for Leu7 (Figure 4d). CD34 was expressed only in blood vessels (Figure 4b) and Ki67 was positive in about 5% on the tumor cells (Figure 4e).

Discussion

Peripheral nerve sheath tumors include a spectrum of clinical and pathological entities, ranging from benign lesions such as schwannoma and neurofibroma to high-grade malignant neoplasms such as malignant peripheral nerve sheath tumors, but the main categories of solitary benign peripheral nerve sheath tumors consist of schwannoma and neurofibroma.

Localized or solitary neurofibromas are slowly growing fusiform lesions with a centrally entering and exiting nerve. These lesions often lack a capsule and the tumor tissue cannot be separated from normal nerve fibers. Neurofibromas account for approximately 5% of all benign soft tissue tumors and are usually observed in younger individuals aged 20–30 years with no sex predilection [3].

The classical literature describes the schwannoma as a slow-growing, well-encapsulated tumor that develops eccentrically to the nerve fibers, allowing complete enucleation during excision. Despite these well-known descriptions, recent studies have revealed a significant possibility of fascicle entrapment (even up to 75%) in the schwannoma, possibility confirmed by the case depicted in this paper [19–21].

Schwannomas arise from neural sheaths and, especially in larger and/or longer history tumors [22, 23], the fascicles surrounded by this part of the sheath can become embedded and may have to be excised – particularly in tumors located in the proximal upper extremity and associated with preoperative sensory disturbances (positive Tinel sign), as in our case [24].

The literature shows controversial results regarding both the neurological deficit resulted after resection and the attitudes of various surgeons towards resection and repair of the entrapped nerve fascicles. Sturzenegger *et al.* reported six cases in which one or more fascicles disappeared in the tumor bulk and required resection, no additional neurological deficit being reported after excision [25]. On the other hand, Park *et al.* stated that larger tumors tended to have more fascicles entering the tumor bulk, thus being at a greater risk of major neurological deficits after surgery. Oberle *et al.* observed that schwannomas with long evolutions associated a greater number of postoperative neurological complications. Likewise, the study of Park *et al.* showed that 75% of patients had immediate neurological deficits that seemed to be determined by the transection of the fascicles that ran through the tumor [22, 23].

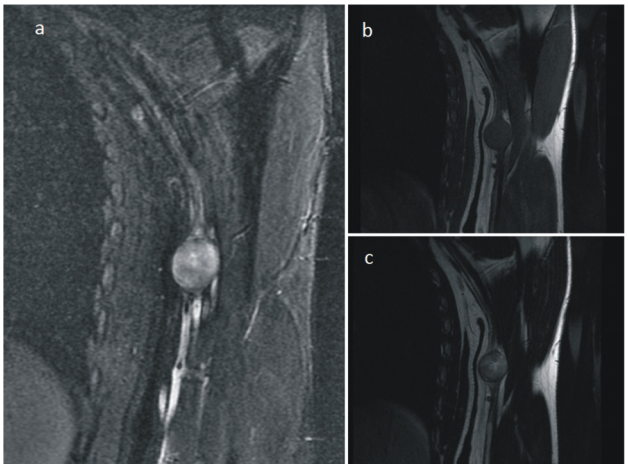

Figure 1 – ***Large nodular tumor of the median nerve, MRI: (a) STIR; (b) T1; (c) T2.***

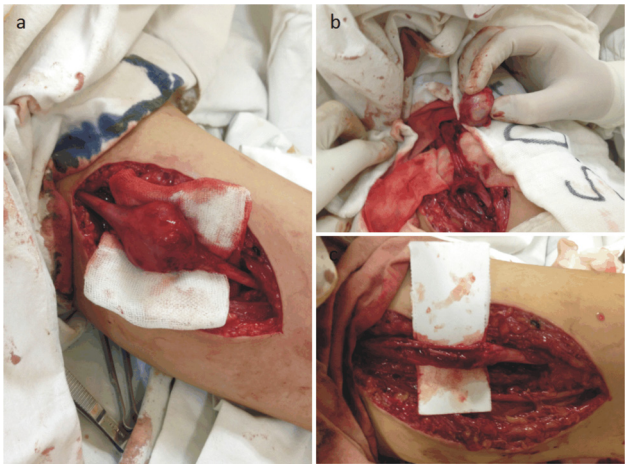

Figure 2 – ***Intraoperative aspects: (a) Pre-excision; (b) After partial excision of the tumor (distal end); (c) Nerve graft at the site of post-excisional nerve gap.***

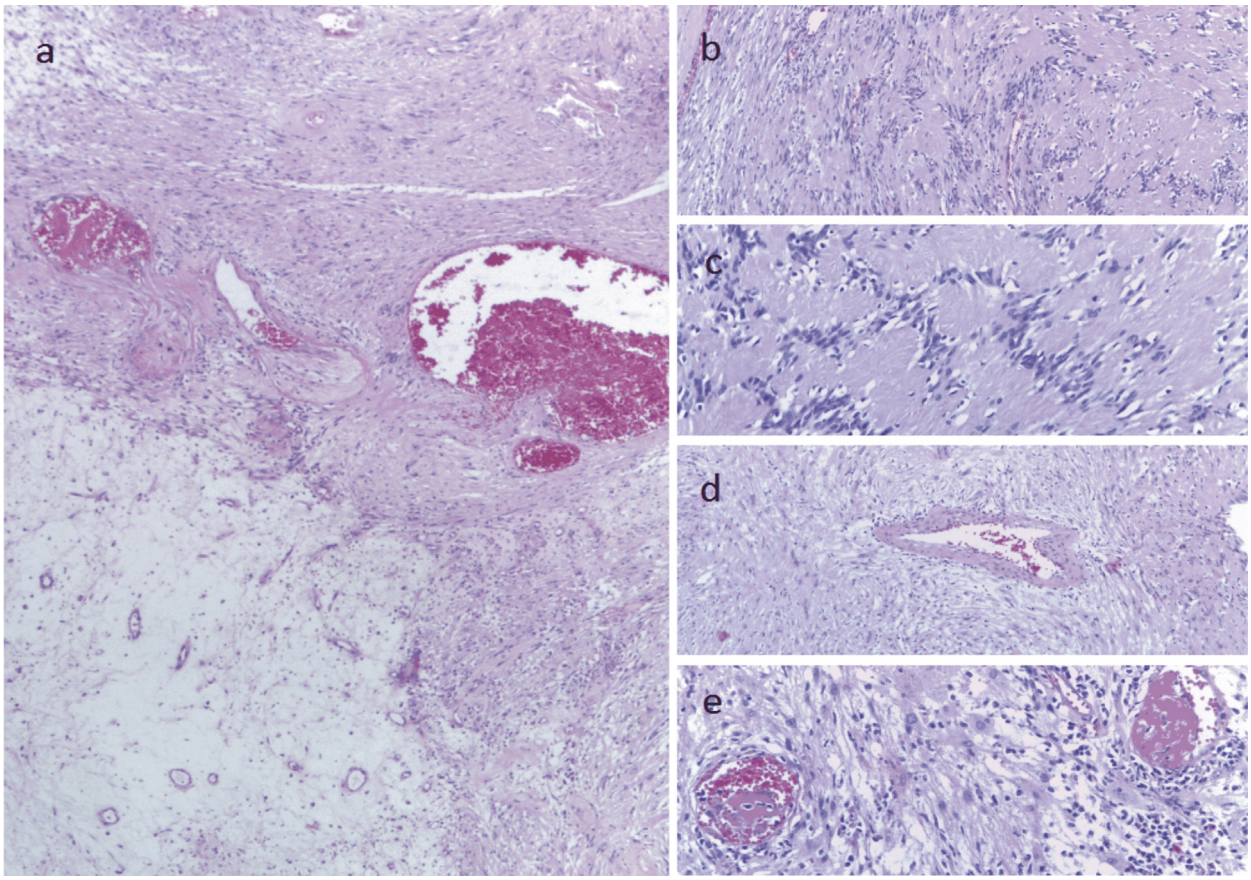

Figure 3 – ***HE staining: (a) Antoni B areas (ob. 4×); (b) Antoni A areas (ob. 10×); (c) Nuclear palisading (ob. 20×); (d) Blood vessels with thickened walls (ob. 10×); (e) Ectatic, hyalinized, thrombosed blood vessels and chronic inflammatory infiltrate (ob. 20×).***

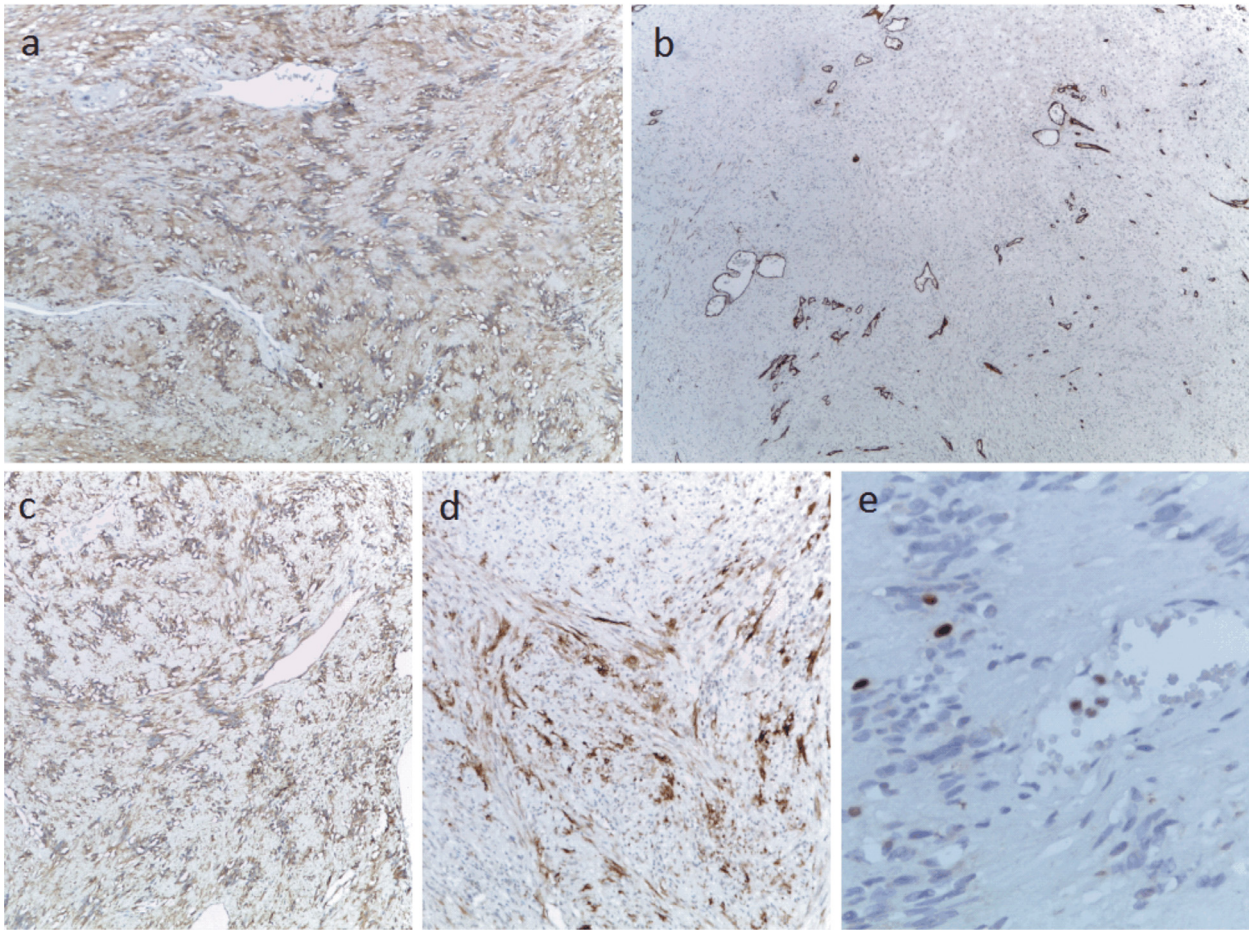

Figure 4 – ***Immunohistochemistry: (a) S100 staining (ob. 10×), diffuse positive; (b) CD34 (ob. 4×) in the blood vessels; (c) Vimentin (ob. 10×); (d) Leu-7 (ob. 10×), zonal positive; (e) Ki67-positive in about 5% of the tumor cells (ob. 40×).***

As mentioned above, the repair of resected nerve fibers in schwannomas is somewhat controversial, too. Donner *et al.* stimulated the intratumoral fascicles and recorded the action potentials across the tumors, resecting only the fascicles that did not transmit nerve action potentials [26]. Holdsworth opted for sural nerve grafts to repair the fascicles post-excision and achieved good results [27]. New or worsening pain after excision has been reported in 7.7–9.5% of cases and motor weakness in 7.7–10.5% [26, 28, 29]. Intraoperative electrical stimulation of the involved fascicles can help in directing the surgical attitude towards excision and/or repair of these fascicles [19]. When motor function loss is expected – after intraoperative nerve fascicle stimulation – nerve grafting is recommended [30].

In the case presented above, even if the MRI showed at least one nerve bundle entering the tumor and the surgery revealed that the tumor (localized in the proximal third of the arm, along the anterior aspect of the median nerve) entrapped two fascicles which produced a motor response at intraoperative electrical stimulation–flexion of the proximal interphalangeal joint of the index finger, both the histopathological exam and immunohistochemistry confirmed the diagnosis of median nerve schwannoma. The classical histopathology description shows the typical biphasic pattern of Antoni A and Antoni B areas, Verocay bodies, common vascular ecstasies, some blood vessels with thrombosis, moderate polymorphic inflammatory infiltrate and fibrosis with peripheral focal hyalinization.

Immunohistochemically, the tumor presented a diffuse, strong expression of S100 protein, a characteristic feature of schwannomas, given the neuroectodermal origin of Schwann cells similar with that of melanocytes [13, 14]. This protein is expressed by a great variety of human cells and tissues including glial cells, neurons, chondrocytes, Schwann cells, melanocytes, macrophages, Langerhans cells and different epithelial tissues (especially those in the breast, sudoral glands and female genital tract) [16], but not by perineurial cells and endoneurial fibroblasts. It is therefore useful for the differential diagnosis of schwannomas that express S100 more than neurofibromas, but not sufficient because of some overlap in the expression of this marker between the two tumors.

Because the predominant cells found in a schwannoma are the Schwann cells, while the neurofibroma presents some additional types (endoneurial fibroblasts, perineurial-like cells, etc.), CD34 or the human hematopoietic progenitor cell antigen is also a useful stain in the differential diagnosis of these tumors. Neurofibromas typically demonstrate a significant subpopulation of CD34-positive stromal cells, while schwannomas show CD34 immunostaining most marked in Antoni B areas and in the blood vessels (as in our case), given that CD34 is typically expressed by the embryonic cells of the hematopoietic system (endothelial cells and lymphoid/myelogenous elements), but also by embryonary fibroblasts, endoneurial fibroblasts [16, 31, 32].

The tumor cells of our patient presented also focal

positive immunostaining for Leu-7. Being a myelin-associated glycoprotein present on Schwann cells (as well as on around 10 to 20% of lymphocytes, some epithelial and chromaffin cells), Leu-7 – also designated CD57 or HNK-1 – is part of a panel for identification of neuroendocrine cells and neural cells and therefore for differentiating neuroendocrine tumors from others [32, 33].

Vimentin is a 57-kD protein and is considered the most ubiquitous of the intermediate filaments, being part of the cytoplasmic cytoskeleton. Vimentin is expressed by the great majority of mesenchymal cells (fibroblasts, endothelial cells, etc.), by many mesoderm-derived epithelial cells (*e.g.*, Bowman capsule in kidney, endometrium, myoepithelial cells of the breast, salivary and sweat glands, thyroid gland epithelium – in coexpression with cytokeratin) and by cells from the neural crest and tumors derived from these (malignant melanoma, schwannoma, glioma – in coexpression with glial fibrillary acidic protein) [16, 32, 34].

Finally, the immunostaining for Ki67 (a nuclear antigen expressed during the proliferating phases G1, S and G2 of the cell cycle), an indicator for the mitotic activity of the cells and a measure for the tumor growth fraction, was assessed in our case and it was positive in approximately 5% of the tumor cells. This percentage is somewhat borderline to malignancy, given that Kindblom *et al.* reported a Ki67 index ranging from 5% to 65% in malignant peripheral nerve sheath tumors, as opposed to benign peripheral nerve sheath tumors in which the Ki67 index was lower than 5% [16]. If we consider the idea that this marker may contribute to an earlier detection of malignant transformation of benign neural tumors and that in our case the index Ki67 was 5%, the resection of the whole tumor (including the entrapped functional nerve bundles) becomes justified, even imperative.

Conclusions

Hereby we add another case of schwannoma that, despite the classical description of this type of peripheral nerve sheath tumor, involved the bundles of the patent nerve and its treatment required complete excision and nerve grafting. At present, no clinical or imagistic method can reliably predict the occurrence of fascicular involvement. The histological and immunohistochemical exams are the ultimate diagnostic tools for the atypical cases.

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