SEÇÃO ANATOMO-CLÍNICA/CASOS CLÍNICOS

Tumor de nervo periférico, diagnóstico diferencial com hanseníase neural primária: relato de cinco casos.

Peripheral nerve tumor, a differential diagnosis with primary neural leprosy; five case reports.

Almeida JEM, Kirchner DR Filho MC, Soares CT, Garbino JA. Tumor de nervo periférico, diagnóstico diferencial com hanseníase neural primária: relato de cinco casos. 2018;43:e-2367.

RESUMO

No período de dezembro de 1999 a maio de 2015, foram encaminhados ao Instituto Lauro de Souza Lima (ILSL) cinco pacientes com tumoração em nervos suspeitos de hanseníase neural primária (HPN) da forma clínica tuberculoide, uma prevalência de 4,5/10000 entre os casos novos atendidos nesse período. Todos os pacientes apresentavam quadro clínico semelhante caracterizado por mononeuropatia com tumoração do nervo associada à dor, ausência de lesões de pele e reação de Mitsuda positiva. Os autores relatam as principais características clínicas e os exames complementares: investigação imunológica da reação de Mitsuda e o teste do antígeno Glicolípideo-Fenólico-1, índice baciloscópico, avaliação neurofisiológica e estudos de imagem. Todos os pacientes foram submetidos a ressecção cirúrgica do tumor e estudo Anatomo-patológico. Dentre os cinco pacientes, quatro foram diagnosticados como tumor de nervo periférico (um Schwannoma maligno, dois Schwannomas benignos e um fibrolipoma neural) e um como hanseníase tuberculoide.

Palavras-chave: Hanseníase Tuberculoide; Neoplasias da Bainha Neural; Neurilemoma

ABSTRACT

From December 1999 to May 2015, five patients with nerve tumors were sent to Lauro de Souza Lima Institute. It was suspected that they suffered from primary...
neural leprosy towards the tuberculoid clinical form, a prevalence of 4.5:10000 among the new patients assessed during the study period. All of the patients had similar clinical conditions characterized by mononeuropathy with nerve tumor associated with pain, absence of skin lesions and positive Mitsuda reaction. The authors report the main clinical characteristics and complementary tests: immunologic investigation of Mitsuda’s reaction and the antigen Phenolic GlicoLipid-1 test (PGL-1), bacilloscopic index, neurophysiologic study and image procedures. All patients were submitted to tumor resection and anatomopathological study. Four out of the five patients were diagnosed with peripheral nerve tumor (one of them with malignant schwannoma, two of them with benign schwannomas and the other with neural fibrolipoma), whereas the fifth patient was diagnosed with tuberculoid leprosy.

Keywords: Neurilemmoma; Leprosy; Neoplasms, Nerve Tissue

INTRODUCTION

Peripheral nerve tumors affecting neural trunks are uncommon and rarely identified in the initial phase. Symptoms and signs of neural tumors are triggered by direct or indirect involvement of the nerve: directly due to neoplasms of the neural elements and secondary alterations due to malignant neoplasia, i.e., paraneoplastic syndrome or infiltration and direct compression of the neural structures, secondary to the development of the neoplasia. Neural neoplasms may be focal, producing local tumors or conditions associated to the development of generalized injuries, such as neurofibromatosis. Among the tumors of neural elements, hereditary etiology is the most frequent.

Neurofibromatosis type 1 (Von Recklinghausen disease) and type 2 are associated with the increase of peripheral nerve tumors. Besides tumors, the peripheral nerve system may also be affected by several inflammatory and hyperplastic processes, and malformations which may be clinically similar. In endemic countries, leprosy must be included as an important differential diagnosis.

Nerve tumors may be divided in the ones originated in the nerve sheath, which are the most frequent of them, and the tumors that originate in other structures of the nerve. Chart 1 summarizes the main benign and malignant neoplasms arising from or secondarily affecting the nerves, and Chart 2 list the tumor-like conditions according to the World Health Organization.

Primary neural leprosy (PNL) symptoms are firstly manifested in peripheral nerves, without identifiable skin injury, neither clinical nor laboratorial. Ridley and Jopling (1966) proposed a subgroup system within the spectrum of leprosy, dividing the intermediate group into subgroups: tuberculoid (TT), borderline-tuberculoid (BT), mid-borderline or borderline-borderline (BB) and borderline-lepromatous (BL). The primary neural form and the indeterminate leprosy are not part of such classification.
Objective: To present clinical, laboratorial and histological cases with suspicion of nerve tumors or non-neoplastic tumor-like conditions aided in the ward of Clinical Neurophysiology of Lauro de Souza Lima Institute (LSLI).

Patient and Method: A retrospective study of patients admitted to LSLI throughout December 1999 to May 2015. Among 55.454 new cases, only five had nerve tumors for a prevalence of 4.5:10000. The patients were submitted to a clinical history; skin and neurologic examination; immunologic investigation of Mitsuda’s reaction and the antigen Phenolic GlicoLipid–1 test (PGL-1), bacilloscopic index, neurophysiologic study and image procedures. All patients were submitted to tumor excision and anatomopathological study.

RESULTS

Case 1:
A 13-year-old male patient with a diagnosis of lower limb neuropathy, and a four-year progress, that had been treated as leprosy for a year. As there was no improvement of his condition, he was submitted to an evaluation at LSLI, a reference center.

His physical examination showed atrophy of his left calf, longitudinal...
thickened knotted cord, which was painful to palpation and with positive Tinel’s sign. He did not have skin lesions, was submitted to the Mitsuda test (6.5 cm) and bacilloscopy index (negative). Neurophysiologic study revealed axonal mononeuropathy in the left tibial nerve. Ultrasonography (USG) of his left calf showed a mass involving a third of his right soleus muscle, distorting it and dividing it in two halves measuring 47.7 x 57.8 x 36.8 mm, with a volume of 53 cm³. The anatomopathologic study after surgical resection showed neoplasia consisting of atypical and pleomorphic spindle cells, numerous mitosis figures, signs of tumor necrosis and strong expression for S-100 protein. The diagnosis indicated malignant schwannoma tumor (malignant peripheral nerve sheath tumor), Figure 1, A and B.

**Figure 1:** Case 1: Malignant epithelioid schwannoma infiltrating neural branch (1A, HEx4). Histological detail of neoplastic cells presenting atypical and prominent nucleoli (1B, HEx40).

**Case 2:**

A 34-year-old male presented paroxysmal pain with neuropathic characteristics in his left sole and 1/3 distal to the left foot, which radiated proximally throughout the entire lower limb. The patient reported pain with a four-year progress and increased intensity a year before. He had skin alteration on his left foot and was sent to LSLI with suspected tarsal tunnel syndrome and leprosy.

Dermatological examination and skin biopsy of the plantar region were negative for leprosy, and a 15 mm Mitsuda was observed. Routine neurophysiological study of the lower limbs revealed mild chronic neurogenic impairment, distributed in L5 root in the left side. Motor conduction of the left tibial nerve in the medial and lateral plantar branches through the tarsal tunnels did not show alterations. As most of the symptoms were located in the sole, a magnetic resonance imaging was requested. The resonance exam revealed a mass in the plantar region of the midfoot on the left side measuring 1.8 x 2.8 cm. The patient was subjected to a tumor resection on the left foot – the nodule measured 1.8 x 1.5 x 2.7 cm in the largest
dimensions, with smooth, shiny, whitish surface and firm consistency. Anatomopathology showed neoplasia, consisting of fusiform cells without atypia, forming wavy bundles, nuclei arranged in palisades, presence of focal myxoid alterations, absence of mitotic figures and strong expression of S-100 protein, Figure 2. The diagnosis was benign schwannoma tumor.

**Case 3:**
A 45-year-old male patient mentioned painful nodules in his right leg starting 20 years before. He underwent three surgeries, the last one a year before the examination reported here. After the surgeries, he complained of numbness and pain in his right foot, which progressed to clawed fingers. The patient also noted the presence of two painful and little movable fibroelastic nodules in his right leg, near the heel. He did not have skin alterations and his bacilloscopy was negative, Mitsuda of 7.0 mm. Neurophysiologic study evidenced a moderate chronic impairment of the sciatic nerve, compromising the fibular portion of his thigh and tibial nerve. It was also observed a pronounced lesion on his calf. The patient was submitted to surgical exploration and excision of the calf nodule. The anatomopathology revealed neoplasia with characteristics similar to case 2, a benign schwannoma tumor.

**Case 4:**
A 14-year-old female patient was examined due to a nodule on the left palmar region which had been progressively growing for two years. Pain to
palpation in the thenar region and night tingling for a year. Examination showed softened lesion in the left middle thenar region. Ultrasonography revealed a lesion characterizing lipoma or tendon cyst. An aspiration biopsy exposed a cytological condition compatible with lipoma.

**Case 5:**

A 38-year-old male patient reported torsion of the left foot in 2013 which had progressed with sensory loss and sensitivity alteration in the left plantar region. During examination, he had pain to palpation of the left tibial nerve, which radiated to the hallux. The left tibial nerve was thickened, although the other nerves showed no alterations. The resonance of the left foot revealed small subcortical cysts, which did not justify the symptomatology. Ultrasonography of the left leg showed thickened posterior tibial nerve in its distal path in the leg and ankle with elongated hypoechoic nodules. Neurophysiologic study was performed three months before the surgical procedure and revealed only asymmetry of the left H reflex. Surprisingly, electromyography did not show significant alterations. Magnetic Resonance Image (MRI) showed expansive fusiform lesion in the tibial nerve in the popliteal fossa, associated with other foci of thickening of the tibial nerve in the distal third of the loss. The MRI findings suggest a neoplastic nature: either schwannomas or neurofibromas. The patient did not have skin lesions suggestive of leprosy; the skin biopsy did not show alterations, Mitsuda of 7.00 mm, non-reactive Phenolic Glycolipid-1 (PGL-1). After these results, surgical procedure was performed. The anatomopathology revealed neural segments with granulomatous inflammatory process associated with caseous necrosis and negative baciloscropy staining by Faraco-Fite, **Figure 4**. The diagnosis was tuberculoid leprosy.

**Figure 3:** case 4, nerve fibrolipoma characterized by epineural infiltration by fibroadipose tissue, separating the nerve fascicles (3A, HEx10). Bands of collagenated mature fibroadipose tissue evidenced by Masson’s trichrome stains (3B, x10).
DISCUSSION

The ILSL, a national reference institution for leprosy, assists cases of putative primary neural leprosy, without cutaneous lesions with clinical conditions indicating mononeuropathy or multiple mononeuropathy. Among the studied patients, there were some with mononeuropathy, nerve thickening or nodosity, indicating nerve tumors. Dermatological clinical examination, bacilloscopy index, Mitsuda reaction, Phenolic Glycolipid-1 (PGL-1) test and eventual biopsy of the skin in the anesthetic area are currently the routine exams to confirm leprosy. If skin lesions are not confirmed, specific investigation of neurological impairment is carried out. The focal loss of nerve function is the epicenter of the clinic. Therefore, due to its specificity for the function and topography of peripheral nerve disorders, neurophysiologic studies differentiate mononeuropathies (focal neuropathy) from multiple mononeuropathies and polyneuropathies and classifies the compromise of axonal and demyelinating lesions\textsuperscript{5,6}. In the four evaluated cases, the examination was decisive to confirm focal impairments and to rule out multiple mononeuropathy or polyneuropathy.

In Case 1, the patient was diagnosed with malignant schwannoma: anatomopathology was characteristic, showing atypical fusiform cells with signs of tumor necrosis and strong expression for S-100 protein, confirming malignant tumor of the peripheral nerve sheath. This diagnosis differs from leprosy, which is characterized by a granulomatous inflammatory process associated with caseous necrosis in advanced cases. Malignant schwannoma, also called malignant peripheral nerve sheath tumor (MPNST) is rare, representing up
to 10% of sarcomas. In approximately 50% of the cases, they are associated with type 1 neurofibromatosis. Malignancy is characterized by hyperchromatic nuclei with pleomorphism, high mitotic activity, vascular and surrounding tissue invasion, as well as presence of necrosis. About 15% of those tumors show several differentiations, allowing to classify them in distinctive subclasses: malignant glandular schwannoma, malignant epithelioid schwannoma and superficial epithelioid MPNST. Around 50-90% of the cases stain with S-100 protein, as in this Case 1, 50% for myelin basic protein and 40% for Leu-7 or (CD 57)\[^{10,11}\].

Case 2 led to a diagnostic delay due to the performance of routine examination instead of it being directed to the interdigital branches of the foot, that is, instead of the performance of nerve conduction studies in search of Morton’s neuroma. This more specific and sensitive test of the interdigital branches of the foot would have been a better procedure in this case. It was not considered at the time because it was an uncommon location for leprosy neuropathy, i.e., far from the compression sites. Ultrasonography and magnetic resonance imaging were essential to define or improve the definition of the expansive process and its location. Similar to Case 3, the anatomopathology presented neoplasia constituted by fusiform cells without atypia, absence of mitotic figures and strong expression for S-100 protein, leading to the diagnosis of benign schwannoma, which, due to its uniformity, was different from the malignant nerve neoplasia and the granulomatous inflammatory process of leprosy. Schwann cell tumors occur more frequently in places that are susceptible to traumas, as in the plantar region reported here. Differential diagnoses can be from pyogenic granuloma to carcinomas, showing the need for further investigation\[^7\].

The main benign schwannoma features are the microcystic areas, rich in macrophages and collagen fibers, semi-septal spindle cells in the capillary vessels and myxoid changes; and these alterations are restricted to the nerve limits. Whereas Antoni type B are hypocellular, microcystic areas, rich in macrophages and collagen fibers. Immunohistochemically, the tumor has strong and diffuse expression of S-100 protein, useful for a differential diagnosis, as schwannomas present more S-100 protein than neurofibromes. Another important differentiator is the CD-34. Neurofibromes typically have a significant subpopulation of CD-34-positive stromal cells, while schwannoma shows a more pronounced CD-34 stain in two areas: Antoni type B and blood vessels. Furthermore, the Ki-67 antigen is an indicator of mitotic activity that allows measuring the proliferation rate in these neoplasias that is usually very low or insignificant, whereas in malignant neoplasias the rate is usually high and prominent as in malignant schwannomas\[^8\].

In Case 4, the diagnosis was a rare benign neoplasia, fibrolipomatosis, characterized by abnormal growth of fibrolipomatous tissue of nerve sheath\[^8\]. The median nerve is the most frequently affected. However, there are reports of other nerves in the literature: ulnar, radial, cranial, sciatic, digital branches and
plantar branches. The anatomopathologic study shows noticeable infiltration of fibroadipous tissue impairing and surrounding neural branches.

Case 5 shows a patient with mononeuropathy in the tibial nerve, outside the tarsal tunnel, uncommon for leprosy, making it difficult to diagnose due to its neoplastic nature revealed in the imaging tests. The imaging tests are fundamental tools for diagnosis, even though it does not present the specific etiology, as in this case the imaging diagnosis suggested neoplastic nature, whereas the anatomopathology showed tuberculoid leprosy. However, tuberculoid forms of leprosy can have expansive process resembling tumors and nerve tumors can occur in patients with leprosy, which are a challenge for the diagnosis.

The anatomopathological examination of the resected nerve was definitive to establish the diagnosis in the five cases presented. Each case presented pathologies with distinct characteristics: nerve tumor versus tumor like condition, and benign versus malignant nerve tumors.

In the five cases presented here, all patients were submitted to surgical exploration for anatomopathologic study while were simultaneously treated. The suggestion to carry out surgical exploration in these specific cases is one of the final recommendations that the authors suggest.

REFERENCES


