

Schwannomatosis – first reported cases in Brazil

Schwannomatose – primeiros casos relatados no Brasil

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ABSTRACT

Neuropathic pain stems various sources including schwannomatosis (SCH), a disease that affects about five thousand Brazilians. SCH is characterized by multiple and intensely painful schwannomas. Differential diagnosis of SCH includes, especially, neurofibromatosis types 1 and 2. A typical case of SCH, possibly the first recorded in Brazil, is presented and discussed in detail and compared with two other subsequent cases with regards to selected clinical and radiological aspects. A 33 year-old female patient was admitted with pain and progressive loss of strength in the left lower limb for the past five years. These complaints were associated with the appearance of very painful nodules in the same region. She also had two light brown (café-au-lait) spots (<1 cm). MRI detected soft tissue tumors in the subcutaneous and intracavitary regions. Two distinct biopsies of different regions and microscopic examination of two nodules revealed Schwann cells surrounded by abundant myxoid stroma. Immunohistochemical examination showed strong and diffuse markers of S-100 protein. Ultrastructural examination showed Schwann cells in the core areas with traces of intracytoplasmic membranes and foci of redundant basement membrane. The pain symptoms, the pattern of intraneural neoplastic growth with marked peritumoral edema, vascular hyalinization, and immunohistochemical reactivity for S-100 protein in Schwann cells in lesion cores suggested the diagnosis of schwannomatosis. Pharmacological pain treatment achieved partial remission of pain.

Key words: Facial Pain; Peripheral Nervous System Diseases; Schwann Cells; Neurilemmoma; Neurofibromatosis; Neurofibromatosis 1; Neurofibromatosis 2.

RESUMO

A dor neuropática pode ser decorrente de diversas causas, entre elas a schwannomatose (SCH), uma doença que acomete cerca de cinco mil brasileiros. A SCH é caracterizada por schwannomas múltiplos e intensamente dolorosos. O diagnóstico diferencial de SCH inclui especialmente as neurofibromatoses do tipo 1 e 2. Um caso típico de SCH, provavelmente o primeiro registrado no Brasil, é apresentado e discutido em detalhes e dois outros casos subsequentes são comparados quanto a determinados aspectos clínicos e radiológicos. Paciente feminina de 33 anos de idade foi admitida com queixas de dor e diminuição progressiva da força no membro inferior esquerdo, havia cinco anos, associadas ao surgimento de nodulações muito dolorosas naquela região. Apresentava também duas manchas café com leite (<1 cm). A RNM detectou tumores de partes moles em região subcutânea e intracavitárias. Foram realizadas duas biópsias em regiões distintas e o exame microscópico de dois nódulos revelou células de Schwann envoltas por abundante estroma mixóide. O exame imuno-histoquímico mostrou marcação forte e difusa para proteína S-100. O exame ultraestrutural demonstrou nas áreas centrais células de Schwann, com restos membranosos intracitoplasmáticos e, focalmente, membrana basal redundante. A sintomatologia algica, o padrão de crescimento neoplásico intraneural, com acentuado edema peritumoral,

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hialinização vascular e reatividade imuno-histoquímica para proteína S-100 nas células de Schwann no centro das lesões possibilitaram o diagnóstico de schwannomatose. O tratamento farmacológico para a dor foi a opção possível, obtendo-se remissão parcial da dor.

Palavras-chave: Dor Facial; Doenças do Sistema Nervoso Periférico; Células de Schwann; Neurilemoma; Neurofibromatoses; Neurofibromatose 1; Neurofibromatose 2.

INTRODUCTION

Neuropathic pain has many causes, among them Schwannomatosis (SCH), a disease that affects around 5,000 Brazilians (1:40,000 births) and is characterized by multiple schwannomas and absence of vestibular nerve tumor. The differential diagnosis of SCH should include neurofibromatoses types 1 (NF1) and 2 (NF2). The diagnostic criteria for SCH were listed by MacCollin *et al.*¹ For the diagnosis of SCH, anatomicopathological confirmation of at least two schwannomas is necessary, and the absence of tumors in the vestibular nerve should be verified through imaging examination for patients older than 18 years. Some peculiar characteristics of schwannomas in schwannomatosis are the peritumoral edema in the adjacent nerve, prominent myxoid transformation and intraneural growth pattern.¹

OBJECTIVE

The objective of this study is to report on and discuss in detail a typical case of SCH, probably the first one recorded in Brazil, in its clinical, radiological and histopathological aspects. This case is then compared to certain clinical findings from other two cases diagnosed subsequently.

METHOD, SAMPLE, AND RESULTS

This study was approved by the Ethics Committee of the Association of Social Pioneers, and the informed consent was obtained. There is no conflict of interest.

The first patient, JVLM, female, 33 years-old, was admitted into the Rede Sarah on March 30 2009 reporting pain in the inguinal region, radiating to the left lower limb and associated with progressive loss of muscle strength in this limb in the past five years. Coinciding with these symptoms, the patient noticed the emergence of multiple nodules in the inguinal region,

gluteus and left thigh, and some small nodules on the right gluteal region. No other relevant information was available besides use of tobacco and hypertension treated with irregular use of hydrochlorothiazide 25 mg. Family history showed no cases of anything similar neurofibromatosis. The examination revealed hyperesthesia and grade-4 muscle weakness (MRC), almost homogeneously, and gait with monoparesis of the left leg. She underwent a magnetic resonance imaging (MRI) of the entire spine, which found multiple asymmetric and well delimited nodules, some septate, slightly heterogeneous, with a hypersignal on T2-weighted sequences and an intermediate signal on T1 involving thoracolumbar extraforaminal and foraminal nerve roots on the left (T11, T12, L1, L3 and L4), with intracanal component in the sacral segment and accompanying the sacral plexus, mostly on the left. These nodulations were also found in the anterolateral paravertebral region, starting from close to T10 down to the pelvis, involving the iliopsoas muscle and the gluteal adipose tissue on the left (Figure 1A).

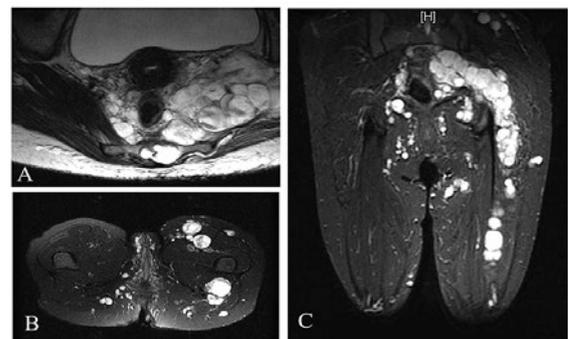


Figure 1 - Nuclear magnetic resonance images: (A) of the lumbosacral column in the axial plane, weighted in T2 with suppression of fat; (B) of the pelvis in the coronal STIR planes, and (C) of the pelvis and thighs in the T2 weighted axial plan with suppression of fat and thighs.

Abdominal ultrasound and computed tomography of the abdomen showed multiple, confluent, expansive, intra-abdominal lesions in the paraaortic, lateral pararectal and retro-rectal retroperitoneal spaces and on the left in iliac fossa, flank, inguinal, femoral, gluteal, and dorsal subcutaneous regions. The lesions had dimensions varying between 12x9 mm and 75x50 mm and the ultrasound revealed them to be hypoechogenic and heterogeneous, with a close relation with the peripheral nervous system.

Brain MRI did not show significant changes, only non-specific hyperintensities in the cerebral hemi-

spheres. Pelvis and thighs MRI showed multiple, expansive, grossly lobulated lesions isointense to the muscles, with a more heterogeneous aspect which are impaired due to impregnation by the paramagnetic contrast. The lesions are located in a topography of the left lumbosacral plexus, lower portion of the right lumbosacral plexus, in pelvic nerve branches (mainly the obturator and pudendal nerves), left femoral nerve and in its branches, as well as the left sciatica. The MRI also showed round, elongated structures, with similar characteristics in terms of signal intensity and contrast pattern, forming location chains mainly in the subcutaneous tissue along the cutaneous branches of the femoral nerve (Figures 1B and 1C).

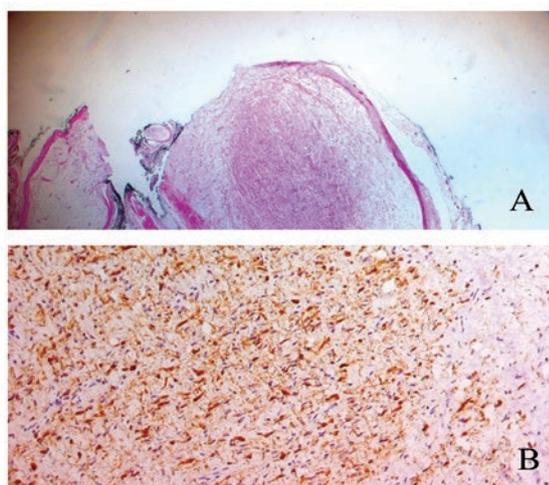


Figure 2 - A) Hyalinized blood vessels in the myxoid area (HE 200x); B) immunohistochemical examination with marking of Schwann cells for S-100 protein (HE 100x).

The patient then underwent a biopsy by excision of two nodes (Picture 2A). The first was on the lateral surface of the root of the left thigh and was 3.6 x 1.2 x 0.4 cm, while the second, in the left ankle, was 1.6 x 0.4 x 0.3 cm. Both nodules had shiny, white and yellowish surface with a soft, jelly-like consistency. Microscopic examination revealed a plexiform lesion formed by the proliferation of fusiform cells with elongated nuclei, with edges ranging between tapered and rounded, and evenly distributed chromatin. The cell population was concentrated mainly in the central areas and surrounded by abundant myxoid peripheral material. The cells were predominantly arranged perpendicularly to the lesion's main axis. A few vessels of the myxoid areas presented hyalinized walls. Delineation was good, with loose connective tissue and intraneural growth pattern.

Immunohistochemical examination showed strong and diffuse markers for S-100 protein. Collagen IV presented marking in more cellular central areas of the lesions, of intraneural growth and with myxoid transformation. The immunophenotype was compatible with Schwann cells. Rare positive structures were found for neurofilament protein. They were morphologically compatible with sparse axonal extensions. The cell proliferation marker Ki-67 showed an index of 3%.

Ultrastructural analysis of the lateral surface of the left thigh lesion revealed two distinct areas, one of which was compact and collagen-rich while the other was looser, showing a myxoid matrix. The compact area presented primarily with Schwann cells, with webbed intracytoplasmic remnants and redundant basal membrane foci. The extracellular matrix consisted of long bundles of collagen fibrils. In the looser areas, there were elongated cells of the fibroblast type and Schwann cells groups amid a myxoid matrix, with thin loose collagen bundles.

The cytogenetic study of the hip lesion fragments showed normal chromosome numbers and structure. The morphological and radiological findings described, associated with imaging and clinical data, especially the pain, allowed the diagnosis of schwannomatosis.

DISCUSSION

Neurofibromatosis is a group of conditions prone to the development of multiple nerve sheath tumors, among them the schwannomas, which are benign tumors of the peripheral nerve sheath found both in SCH and in NF2. Unlike NF2, however, in SCH there is no involvement of the eighth cranial nerve, no ocular changes, and no ependymoma or propensity for emergence of meningiomas. Moreover, in SCH only 15% of cases are familial, with changes in chromosome 22 near the NF2 gene region, with mutations in the tumor suppressor gene SMARCB1 (hSnf5/INI1).²

The diagnostic criteria of SCH were described by MacCollin *et al.*¹ and the diagnosis occurs when two or more schwannomas are identified and followed by anatomopathological confirmation. Absence of tumors in the vestibular nerve must also be confirmed by imaging examination conducted for ages 18+. A presumptive diagnosis of SCH is considered when two or more schwannomas are detected through biopsy, with or without symptoms of vestibular nerve dysfunction after 30 years of age or when there are

two or more schwannomas with demarcated anatomical distribution without symptoms of vestibular nerve dysfunction, at any age.

SCH is considered to be the third most common subtype of neurofibromatosis and as frequent as NF2.¹ The classic criteria for the histopathological differential diagnosis between schwannoma and neurofibroma consider the growth pattern of the two neoplasms.³ Schwannomas are encapsulated, formed almost exclusively by Schwann cells, arise eccentrically and expand compressing the peripheral nerve around its periphery. Neurofibromas expand the endoneural matrix and consist of various cell populations, including Schwann cells, axons, fibroblasts and perineurial cells, in abundant extracellular matrix, with expansion of the endoneural matrix, forming a tortuous plexus in the myxoid matrix.

Reports of schwannomas in schwannomatosis describe peritumoral edema in the adjacent nerves, prominent myxoid transformation, and intraneural growth pattern.¹ In this case, a pronounced peritumoral edema, extensive myxoid transformation inside the tumor and intraneural expansion were noted.

The histopathological differentiation between schwannoma and neurofibroma is not always clear, and some benign tumors of the hybrid peripheral nerve sheath have been described.⁴ The concept that axons are absent from schwannoma has recently been questioned with the description of intralesional axons.⁵ In the case described here, some axons positive for the neurofilament protein in the immunohistochemical analysis were noted. Furthermore, the vascular walls in the myxoid areas were hyalinized, which favors the diagnosis of schwannoma and is considered to be an important finding for the differential diagnosis between schwannoma and hybrid schwannoma-neurofibroma tumors.^{4,6}

The ultrastructural examination confirmed Schwann cell constitutions in the lesion's central areas and showed some collagen fibers in the loose areas of the schwannoma in the myxoid peripheral areas.

Neurofibromas are usually painless; however, about two-thirds of patients with SCH experience pain upon the growth of tumor masses, although there is no relationship between tumor volume and intensity of pain. In two other subsequent cases, both diagnosed at the Neurofibromatosis Reference Center at the UFMG Hospital das Clínicas, the disproportion between the size of the schwannomas and the pain is evident. While one of the patients (LECJ, male, 38

years old) presented multiple schwannomas smaller than 1 cm in diameter at the extremities of the upper limbs which unleashed intense neuropathic pain only reduced with surgical extirpation, the other patient (TRM, female, 24 years old) presented pain in just one of the several schwannomas located in the left upper limb and larger than 3 cm in diameter (Figure 3A), with no signs of vestibular schwannomas (Figure 3B).

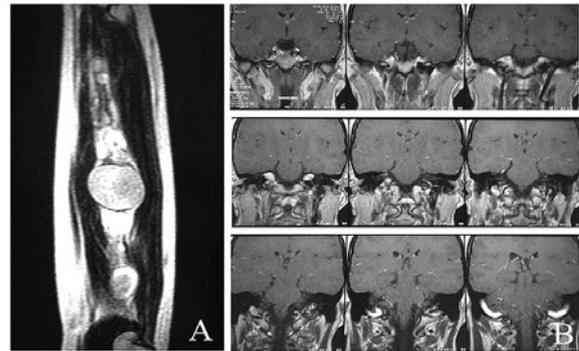


Figure 3 - Nuclear magnetic resonance imaging: A) of the left forearm, (showing multiple tumors – schwannomas according to biopsy) and B) of the encephalon (showing absence of tumors on the eighth cranial nerve) of another patient with schwannomatosis (TRM, female, 24 years old).

Half of the patients are reported to present changes upon neurological examination.⁴ The patient described here presented intense pain associated with monoparesis of the left lower limb. The two other patients, however, presented no neurological dysfunctions.

The treatment of SCH nodules is primarily surgical, according to the patient's clinical criteria and symptoms. The case was discussed with the neurosurgery, orthopedics, and plastic surgery teams and a conservative approach was chosen considering the lesions' extension and multiplicity. The patient achieved partial remission of pain upon prescription of gabapentin (600 mg in the morning, 300 mg in the afternoon and 300 mg at night), omeprazole (20 mg in the morning), amitriptyline (25 mg in the morning and 50 mg at night) and clonazepam (2 mg at night). In December 2012, patient JVLM suffered an episode of cerebral ischemia with sequelae (aphasia and hemiplegia). During the months before the episode, she had been showing persistent anemia of the spoliative type, which was attributed to frequent metrorrhagias, for which she received hormonal contraceptives and thereby recovering from anemia. She, however, was hypertensive and smoked, factors which, when

associated with the use of hormonal contraceptives, may have contributed to cerebral ischemia. A transesophageal echocardiography was performed (normal results) and tests for a possible study of thrombophilia were conducted because her sister (also young, smoker and obese) had died in 2012, likely of cerebral ischemia. The exams for C677T, Sickling, Protein C, Protein S, Lipoprotein A, Lupus anticoagulant, FAN, factor V Leiden, Rheumatoid factor, Prothrombin, Chagas disease and Anticardiolipin were all normal.

Surgical resection of the more painful tumors was possible for the two other cases of SCH, with complete remission of pain.

CONCLUSION

The present study shows that neuropathic pain is the main symptom of schwannomatosis, despite diversity in clinical expression in the first cases reported in Brazil.

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