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NEUROFIBROMATOSIS TYPE 2 – CASE REPORT OF A PATIENT WITH ONLY SPINAL LESIONS

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NEUROFIBROMATOSIS TYPE 2 – CASE REPORT OF A PATIENT WITH ONLY SPINAL LESIONS. (Abstract): Neurofibromatosis type 2 is an autosomal dominant disease with an incidence of 1 to 33,000 – 40,000, characterized primarily by development of tumors at the level of the central nervous system due to a mutation in the NF-2 gene on chromosome 22q12. The authors present the case of a 49-year-old male patient, with an 8-year history of cervical, dorsal and lumbar spine tumors that were totally excised and relapsed. The patient is known for multiple admissions into the Neurosurgical and Neurological Departments, for multiple investigations. Neurosurgical intervention was performed, the biopsy of the tumor mass as well as the decompression of the nerve roots being accomplished via the interlaminar approach at L4-L5. After the surgery the patient's status has improved. The particularity of the case demonstrates the rare existence of spinal NF-2 without being associated with cerebral injury such as schwannomas located bilaterally at cerebral level and no family history commonly encountered in NF-2.

Keywords: Neurofibromatosis type 2, Spinal lesions, Neurofibroma, Neurosurgery.

INTRODUCTION

Neurofibromatosis type 2 (NF 2) is an autosomal dominant disease with an incidence of 1 to 33,000–40,000, characterized primarily by development of tumors at the level of the central nervous system due to a mutation in the NF-2 gene on chromosome 22q12[1]. NF-2 encodes a protein that is called merlin and belongs to the protein 4.1 family that includes myosin, radixin and ezrin[2]. Schwannomas are specific lesions, affecting 95% of patients, being characterized by bilateral localization. These tumors give the patient a high degree of disability due to hearing loss, visual disturbances, walking and balance disorders, pain or epileptic seizures[3]. Mortality is caused by respiratory arrest when medulla oblongata is compressed over the limit. The diagnosis of this pathology is based on clear criteria that include: the presence of schwannomas, a first-degree relative diagnosed with NF-2, or evidence of mutation on chromosome 22q12[4].

CASE REPORT

49-year-old male patient, with an 8-year history of cervical, dorsal and lumbar spine tumors that were totally excised in the past is admitted to the Neurological Department. His past clinical examination revealed good overall status, painless abdomen and tegmental lipofibromas at the level of upper limbs bilaterally. The neurological evaluation demonstrated normal orthostatic posture and spastic walking, spastic quadriplegia with predominance of paraplegia (3/5 MRC in left lower limb, 4/5 MRC in upper limbs bilaterally and right lower limb). Patient also was presented with urinary sphincter defect.

These symptoms were evaluated in the context of the myeloradicular compression given by an

expansive intramedullary lesion at the level of cervico-dorso-lumbar spine, as it was demonstrated on the imaging evaluations (Fig. 1). These nervous tissue alterations have recently evolved, considering the fact that the past investigations showed nothing.

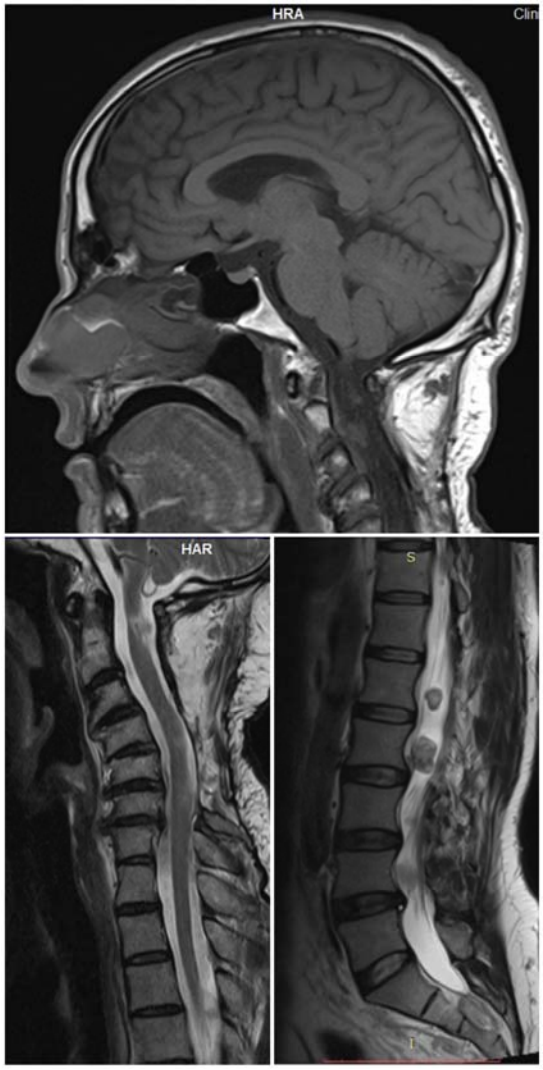

Figure 1a (up) – Cerebral MRI – Sagittal T1 section – no pathology revealed.
Figure 1b (down, left) – Cervical MRI.
Figure 1c (down, right) – dorsal – lumbar spine MRI – sagittal T1 section revealed multiple intraforaminal, perivertebral nodular formations in the medullary cord.

Since the patient responded unsatisfactory to the analgesic and muscle relaxant treatment (Gabapentin and Baclofen), doctors decided to perform a new neurosurgical intervention for decompression and to obtain a biopsy from one of the tumors. The surgical approach was at the L4-L5 site (with a Grade C on ASIA Impairment scale before the surgery and Grade B on ASIA Impairment scale after the surgery).

The histopathological examination of the biopsy specimen offered important information, as follows: tissue fragments consisted of fasciculated/ comb-like cellular arrangements including cells with oval/elongated nuclei, moderate hyperchromic and sharp-ended, with eosinophilic cytoplasm; multifocal red blood cell extravasation (lysed / old red blood cells); bundles of fusiform cells dissociate / surround ganglionic nerve cells and embed nerve fibers; fibro-conjunctive stroma; focal adipose / bone support. Three stains, namely Haematoxylin-Eosin, Masson and PAS-AA, were used – Figure 2.

The genetic test was also performed: a variant of NF-2 gene was identified – Exon 36, c5005A>C (p. Thr1669Pro), heterozygous. This sequence change replaces threonine with proline at codon 1669 of the NF1 protein (p. Thr1669Pro).

In terms of immunohistochemical reactions, the following were emphasized: S-100: diffusely positive in tumor cells (positive internal control); vimentin: diffusely positive in tumor cells (positive internal control); actin: negative in tumor cells (positive internal control); Ki-67: 2%. Both the histopathological examination and the immunohistochemical reactions concluded that the biopsy tissue samples suggested neurofibroma (Fig. 2). Nerve root decompression was performed, and patient's condition improved: relief of pain and ameliorated walking disorders (4/5 MRC). Postoperative MRI demonstrated tumors removal – Figure 3.

DISCUSSIONS

The authors have presented the case of a patient diagnosed with neurofibromatosis type 2, but with no cerebral pathology and no family history, as literature describes in most cases. Surprisingly to us, while for NF-2 the pathognomonic sign is the vestibular schwanomma, this patient presented just with the spinal lesion. It is known that patients diagnosed with NF-2 often experience symptoms such as tinnitus, facial paresis, hearing loss, caused by the schwannomas located bilaterally at cerebral level [5]. Although spinal tumors can occur relatively frequent in patients with NF-2, they are often associated with brain tumors, as well as, in very rare cases, the initial symptoms are those due to spinal pathology. Despite other types of tumors, NF-2-associated spinal tumors are asymptomatic (80%). Intramedullary spinal cord tumors usually are presented with back pain, weakness, or sensory disturbances [6].

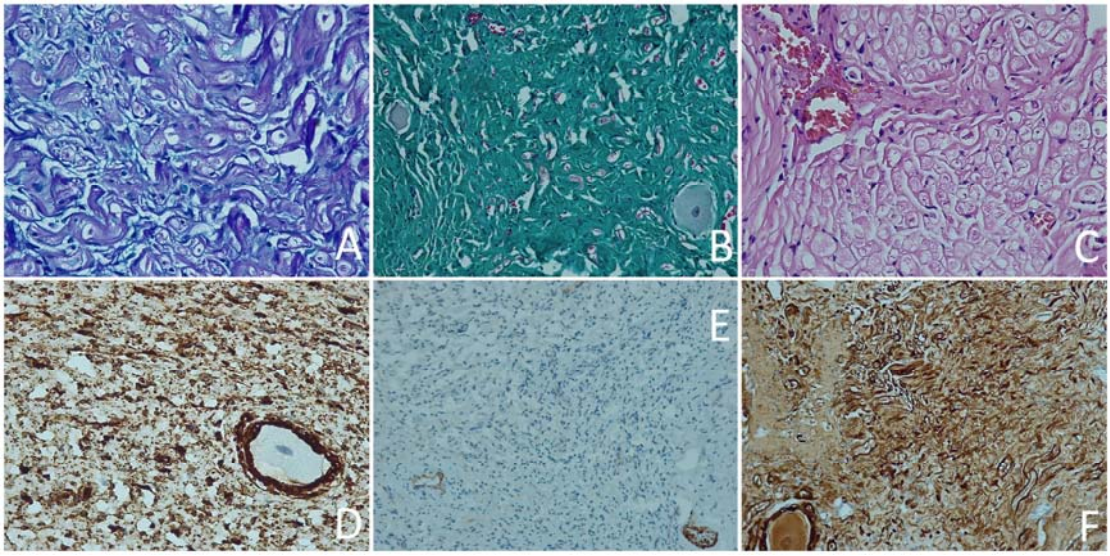

Figure 2. Histopathological examination and immunohistochemical reactions: A – PASS-AA staining, B – MASSON staining, C – HAEMATOXYLIN-EOSIN staining, D – ANTI-S100 imunohistochemical reaction, E – ANTI-ACTINE immunohistochemical reaction, F – ANTI-VIMENTINE immujnohistochemical reaction.

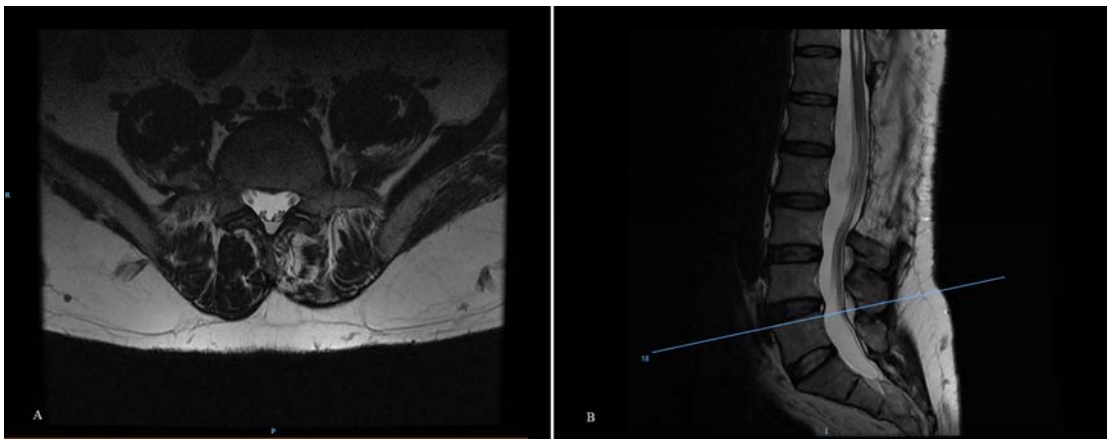

Figure 3 – Postoperative lumbar spine – a) transvers T1 section at L4-L5 b) sagittal T1 section demonstrates non-tumor lesion.

Parry *et al.*[7] supports this assumption in a study conducted on 49 patients diagnosed with NF-2 whereby 33 of them had spinal tumors. Only 21% of them had initial symptoms related to spinal pathology. Evans *et al.*[8] pointed out in a study that, although spinal tumors are relatively common in patients with NF-2, only 1% of patients reported symptoms related to the pathology and they mostly complained about paresthesia. In this case, there is a neuropathic pain treated with Gabapentin, non-responsive to treatment, rated with a score of 8 on the VAS.

Neurofibromatosis type 2 is a dominant autosomal disease characterized mainly by the occurrence of schwannomas, extending to vestibulocochlear nerve branches, or meningioma[9]. Genetically, patients with non-sense or frameshift mutations developed more often spine pathology than did patients with any other type of mutation. Spine tumors are usually encountered in the severe type of NF-2, depending on the age and mutation type.[10]

In our case, the patient has no cerebral pathology, but only pathology linked to spinal tumors.

Differential diagnostic includes brain tumours similar to oligoastrocytomas that can be described on MRI as tumors which lack the surrounding edema, with an infiltrative pattern sparring great vessels as they grow slowly.[11] The patient developed lipofibromas in the upper limbs and calcifications within the central nervous system, which are very rarely described in the clinical context of neurofibromatosis type 2.

Spinal tumors associated with NF-2 are meningiomas, neurofibromas and ependymomas.

Spinal ependymomas associated with NF-2 have a slow-evolution course and observation is the elective approach until the symptoms arise. Tumor approach depends on the tumor type and size. Gross-total removal is the elected treatment for increased disease survival rate[12]. In a study performed by Plotkin *et al.* 76% of the patients with spinal tumors had no symptoms at all.[13]. Spinal tumors usually don't recur and have a better outcome than the pontine tumors which are associated with severe neurological sequelae, high histological grade and deadly outcome[14]. Although spinal tumors can occur in NF-2 more frequent than in NF1, neurofibromas are known to occur rarely, literature mentioning ependymomas in most cases. Halliday *et al.*[9] suggested in a small study conducted on approximately 40 patients that schwannomas are the most common type of tumor present in NF-2, whereas neurofibromas are more common in NF1. This is a particular case after the study of Halliday et al when neurofibromas are confirmed in spine lesions. Neurofibromas are more often found in the cervical spine than in other regions and are often misdiagnosed with the hybrid schwannoma/neurofibromas[15]. Patronas *et al.*[10] demonstrated that in patient with spinal NF-2, intramedullary tumors are more often encountered than extramedullary lesions.

Although surgical intervention is known to aggravate neurological deficits, given the risk of exacerbation of neurological symptoms, the interdisciplinary team decided to perform the surgical decompression.

Even though they have a rare occurrence medullary tumors should be included in the array of tumors associated with NF-2. Surgery is applicable when symptoms get worse.

Although less likely, radiation and chemotherapy can also be applied[16,17]. Microsurgical resection is an effective treatment for spinal nerve sheath tumors. Intramedullary tumors have less favorable evolution being a sign for the severity of the disease, while extramedullary tumor could recover completely. Growing tumors should be excised before symptoms appear[18].

CONCLUSIONS

The case presented is a particular form of NF-2 (confirmed by clinical, brain imaging investigations and histopathological examinations) which has exclusively spinal manifestations. Surgery is the recommended treatment for symptomatic NF-2, leading to relief of pain and improvement in gait. Cervical lesions are more often encountered than other tumors in NF-2. Patient's evolution should be monitored over time as the recurrence rate is high.

Conflict of interests

The authors have nothing to declare. Original case report. No financial support.

Abbreviations

NF-2 – Neurofibromatosis type 2
MRC – Medical Research Council (scale)
ASIA – American Spinal Injury Association (Impairment Scale)
VAS – Visual Analog Scale

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