Lumbar region intra-spinal primitive neuroectodermal tumour (PNET) combined with neurofibromatosis type 1

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Primitive neuroectodermal tumours (PNET) are aggressive neoplasias that are diagnosed, usually, in infancy. Their appearance in adulthood is rare and, exceptionally, in association with neurofibromatosis type I (NF-1). We present a case of a 37 year-old man with NF-1 combined with PNET in the intra-arachidial lumbar region. Diagnosis was by Nuclear Magnetic Resonance (NMR) and biopsy of soft tissue mass which showed a PNET with undifferentiated round cells and immunohistochemically positive for CD99, neurone-specific enolase, synaptophysin and LEU-7. Surgery was performed with spine decompression and resection of 80% of the tumour, with symptoms improvement. Radiotherapy was administered on the lumbosacral column, but only up to 30 Gy because of severe actinic enteritis and pan-cytopenia grade III. Six months later, the patient was hospitalized with deterioration in his overall clinical status with multi-organ involvement. The patient died and an autopsy was performed.

The initial treatment of the PNET is surgery and, if possible, the radical extirpation of the tumour. Administration of radiotherapy and chemotherapy appears to increase survival.

We comment on the clinical, histological, cytological and immunohistochemical aspects together with a review of the literature. To the best of our knowledge this is the first documentation of such a case.

Key words: PNET, neurofibromatosis type 1.

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INTRODUCTION

The primitive neuroectodermal tumours (PNET) are tumours composed, mainly, of nondifferentiated cells but which show some evidence of neural differentiation. They can be located in the cerebrum, cerebellum, brainstem, pineal gland, spinal cord and peripheral nerves. Primary location at an intra-spinal site is rare and can have its origin at an intra-or extramedulla or extradural site at any level of the spinal cord. A PNET of the corda equina is less frequent[1].

Neurofibromatosis is an autosomal dominant disease that affects cell growth of neural tissues and is classified in two variants: type 1 and type 2. For its diagnosis, neurofibromatosis type 1 (NF-1) requires the presence of six or more "café au lait" patches on the skin, the presence of two or more neurofibromas of any type, or one or more plexiform neurofibroma, and axillary or groin frecking[2]. The gene locus for NF-1 encodes a protein named neurofibromin. Inactivation of the gene leads to loss of function and subsequent development of different types of tumours seen in the disease[3]. Its association with PNET in infancy has been described[4] but, in the adult, this combination is extremely rare and, to-date, there are no detailed descriptions in the literature.

We present the first case of a lumbar region intrarachidial PNET in an adult patient with NF-1. We comment the clinical, radiological, histological, cytological and immunohistochemical findings, with a review of the literature.

CLINICAL CASE

A 37 year-old Caucasian male had NF-1 diagnosed in infancy and had a family history of NF-1 in his mother, and in 2 of his 3 children of 7 and 4 years of age. In December 2002 he was admitted to the hospital for right lumbo-ciatalgia with loss of power in the ipsilateral lower limb. His body showed innumerable "café au lait" patches and multiple neurofibromas of varying sizes. The left foot had a non-painful, fixed tumour of 3 cm in diameter. There was hypo-aesthesia in the perianal

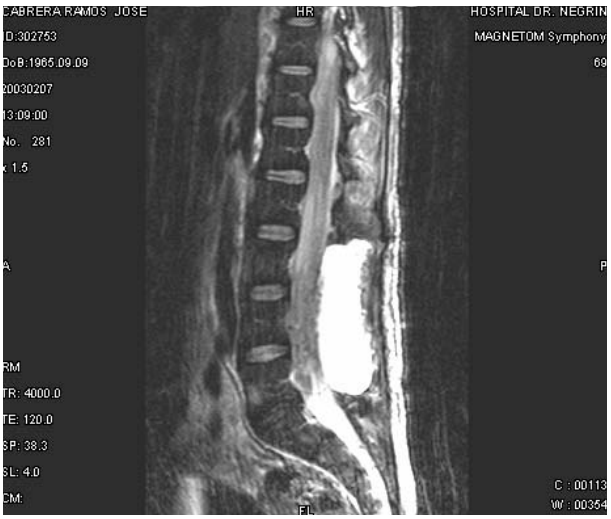

Fig. 1. Lumbar region intra-spinal PNET combined with neurofibromatosis type I. Sagital section T2-lumbar: epidural and paravertebral mass that is bilateral between L3-L5 that has invaded the foramen, the lateral and posterior faces of the dural sac, and producing severe bilateral compression affecting the right L4 lamina.

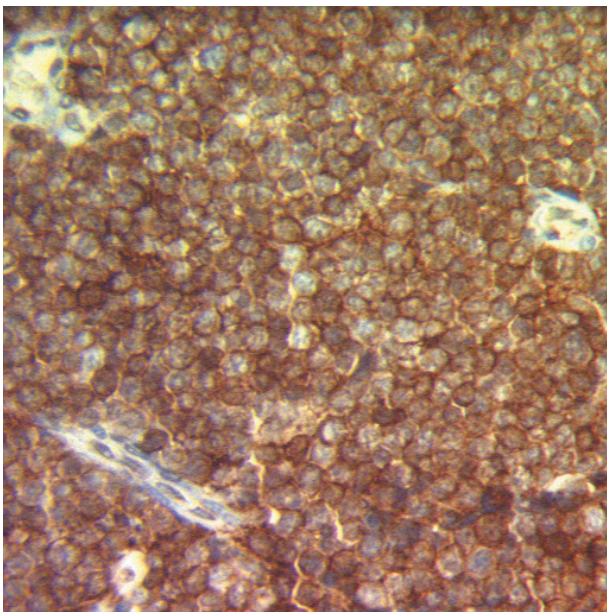

Fig. 2. Photomicrograph of small non-differentiated cells of primitive neuro-ectodermal tumour that expresses strong immuno-reactivity for the surface glycoprotein CD99.

area and deficient sensitivity at the right L5-S1; no bilateral soleus stretch reflex, with symmetrical hypoactive patellae; paraparesia 4/5 left and 4/5 right; bilateral Lasègue's sign of 50º and positive lateral Bragard's sign. Cranial nerves were normal. Thoracoabdominal CT scan was normal and Nuclear Magnetic Resonance (NMR) with gadolinium of the neuroaxis showed epidural and bilateral paravertebral mass that affected the right L4 lamina. The lesion extended from L3 up to L5 while invading the foramens, the lateral and posterior faces of the dural sac, and producing severe bilateral compression (fig. 1). An urgent L3-L5 right laminectomy was performed with bilateral resection of the paravertebral tumour as well as a complete tumour resection from posterior epidural L3-L5. The lateral and foraminal epidural mass was partially resected (80%). The anatomopathological findings showed paravertebral mass, epidural tumour and, in the spinal apophysis of L3-L5 a PNET that had infiltrated extensively into the fibromuscular, epidural and bone tissue. Optical microscopy showed that the tumour was composed of a uniform population of small non-differentiated cells with a high nucleocytoplasmic content and with elevated mitotic and apoptotic activity. The nuclei were oval, some with irregular outline. Superstructure was rich in eucromatin with heterochromatin in clusters and frequently nucleated. The cytoplasm contained ribosomes and polyribosomes, occasionally lysosomes, mitochrondria and some rough endoplasmic reticulum, but very few organelles. Intermediate filaments were observed. Rudimentary cellular junctions could be identified and some cytoplasmic processes. The accumulation of intracytoplasmic glucogen was present in several cells. Neither microtubules nor granules with electrodense centres were observed. Immunophenotype assay was positive for CD99 (fig. 2), vimentin, enolase, neurofilaments, synaptophysine and LEU 7 (CD57) and negative for GFAP, S100, EMA, AE1-AE3, LCA and chromogranine. After surgery the clinical condition improved. The sphincters were conserved and there was improved bilateral motor response to 4+/5 and partial recovery of sensitivity L5-S1, without changes in the perineal sensitivity. A new NMR with gadolinium of the neuroaxis was performed, and which showed a persistence of lesions occupying the nerve canal from the foramen holes to the level of L4-L5 and L5-S1 compatible with tumour infiltration. Radiotherapy was administered on the lumbosacral column (2cGy/day) reached only 30 Gy because of severe actinic enteritis and pancytopenia grade III-IV without enough medular recovery to give the standard chemotherapy regimen. Six months later the patient was hospitalized because a progressive deterioration in his general clinical status with elevation of hepatic enzymes, jaundice and hepatic encephalopathy. He died and the autopsy was performed.

On postmortem showed multiple metastatic lesions in the rib cage, soft tissue, liver, lung, spleen, testicles and bone marrow. Neurofibromatosis type 1 was evidenced by multiple cutaneous neurofibromas and multiple "café au lait" patches on the skin; plexiform neurofibromas in the mediastinum and retroperitoneum; neurofibroma of 3.5 cm in soft tissue of the left perineal region (fig. 3). Macrocephalia; folicular ade-

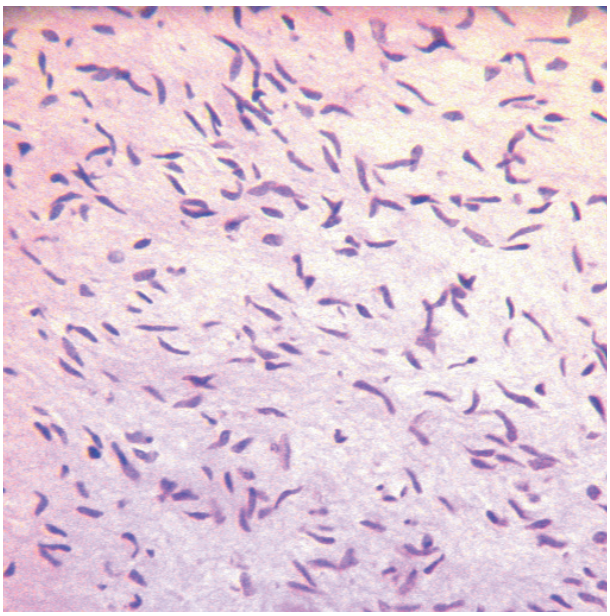

Fig. 3. Neurofibroma: Photomicrograph that shows the fusiform cells with sharp points typical of a neural tumour (magnification x 400).

noma in the right thyroid lobe; subpleural bullae; emphysema in the superior lobes of the lungs and dilated urinary bladder.
The anatomo-pathological diagnosis was PNET of the lumbar spine with multiple metastases combined with (NF-1).

DISCUSSION

An intrarachidial PNET is extremely rare. It is thought that the origin may be in pluri-potential cells of the neural crest with different grades of differentiation. Its histogenesis is unknown and, possibly, multifactorial. It can originate in the extra or intradural space with a predisposition towards the cauda equina[1-5].
The gene locus for NF-1 has been mapped at chromosome 17q11.2. It encodes a protein named neurofibromin, which has a role in tumour suppression (inhibits the ras oncogene). Inactivation of the gene (through mutation or allelic loss) leads to loss of function and subsequent development of many different types of tumours seen in the disease. The mutation of a "controller" gene migth lead to the development of a CNS as neurofibromas, malignat peripheral nerve tumour and astrocytomas or Non CNS malignancies as a pheochromocytoma, rhabdomyosarcoma, Will´s tumor and neuroblastoma[3].
The known propensity of NF-1 patients to develop CNS and Non CNS tumours supports the theory of the association of PNET and NF-1. The possibility of an association between NF-1 and PNET is based on their common origin in the neural crest[6,7].
In the literature there have been 14 cases of a primary intraspinal PNET described, in 8 of which, the tumour was located within the spinal cord and 5 with extramedullar extensions. In the majority of the cases described, there was a complete resection, radiotherapy was administered after surgery and in some cases standard chemotherapy was given, with the improvement in the prognosis and, in some cases, an extended survival[5,8]. In the current case, epidural tumour mass was extended exteriorly and compromised its lamina from L3 up to L5 and with involvement of soft tissue that was partially (80%) resected. Radiotherapy was the only adyuvant treatment administered because of severe actinic enteritis and haematopoietic toxicity grade III-IV without a quick recuperation, with partial recovery of the neurological symptoms. There is a controversy about the benefit of chemotherapy given to patients with PNET. Some authors[7, 9] have showed much better outcome in patients with Typical Ewing Sarcoma than patients with PNET treated with chemotherapy, but some other ones[10,11] have not found any statistical differences between this two diseases. The authors believe that chemosensitivity is related with neural differentiation and indicate that it should also be considered when allocating risk-adapted treatment to patients with PNET tumours of bone.
The postmorten findings showed an aggressive tumor of small non-differentiated cells with a high capacity of spread with short survival.
The differential diagnosis needed to exclude other tumours of small, non-differentiated round cells such as lymphomas, rhabdomyosarcoma, small cell tumour and Ewing sarcoma[12,13].
The diagnosis of PNET requires the presence, in the cytology investigation, of small undifferentiated cells and, on immunohistochemistry, to be positive for CD99, neurospecific enolase, synaptophysine and LEU-7[1], all of which criteria are fulfilled in our present case.
The treatment of choice for a PNET tumour is radical surgery followed by radiotherapy and chemotherapy, if it is possible[8].
In our survey of the literature, there was not a lumbar intra-spinal PNET and NF-1, described in an adult.

Palabra clave: PNET, neurofibromatosis tipo 1, asociaciones.

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