Low grade malignant peripheral nerve sheath tumor with mesenchymal differentiation: a case report

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Malignant peripheral nerve sheath tumor (MPNST) is an uncommon neoplasm. Rarely, MPNST may display focal mesenchymal differentiation and this is more frequently encountered in high than low grade lesions. Here we present an example of a low grade MPNST with osteoid, cartilaginous and probably smooth muscle components occurring in the subtemporal fossa of a 26-year-old male patient with no associated neurofibromatosis type 1. The tumor exhibited diffuse S-100 protein expression, whereas immunostainings for epithelial membrane antigen and smooth muscle actin were positive in a portion of neoplastic cells.

Key words: MPNST, mesenchymal differentiation.

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) comprise approximately 5% of all malignant tumors of soft tissue and typically arise from a neurofibroma or from a peripheral nerve. In extraneural soft tissue the MPNST diagnosis is confirmed by the presence of immunohistochemical or ultrastructural features of the nerve sheath differentiation. The majority of MPNSTs occur in adults, frequently in the setting of neurofibromatosis type 1 (NF-1). The most common localizations for MPNST are the buttocks, thigh, brachial plexus, upper arm and the paraspinal region. MPNSTs affecting nerves typically involve large and medium-sized nerves. Histological grade II, III and IV MPNSTs are distinguished according to the current WHO grading system [1]. The differential diagnosis between neurofibroma and low grade MPNST (WHO grade II) is based on increased cellularity, increased nuclear size and hyperchromasia in the latter. Presence of necrosis is required for the diagnosis of WHO grade IV lesion. According to the analysis of a large series of 134 MPNSTs, in high grade MPNSTs more than four mitoses per 10 high power fields are usually identifiable [2]. Apart from conventional MPNST a rare variant of MPNST with epithelioid morphology exists and accounts for about 5% of MPNST cases [3-5]. In another study of 116 MPNSTs, heterologous mesenchymal components were identified in 14.7% of cases [6]. Mesenchymal differentiation is more frequently encountered in high than in low grade MPNSTs [7].

Here, we report a case of a low grade MPNST showing focal osseous, cartilaginous and probably smooth muscle differentiation.

Case report

A 26-year-old male presented with progressive unilateral loss of visual acuity associated with exophthalmos and facial paresthesia on the left side. The neurological examination revealed the sixth cranial nerve palsy on the left side. The patient had no previous health problems and his family history for NF-1 was negative.

The tumor, demonstrated by CT and MR imaging, was located in the subtemporal fossa and infiltrated the superior and lateral wall of the orbital cavity as well as great wing of the sphenoid bone penetrating into the sphenoid and maxillary sinuses.

Extended left temporal craniotomy with the removal of the zygomatic arch was performed. At surgery, the tumor was found to be a cream-colored, friable, poorly vascularized mass, well-demarcated from the sur-

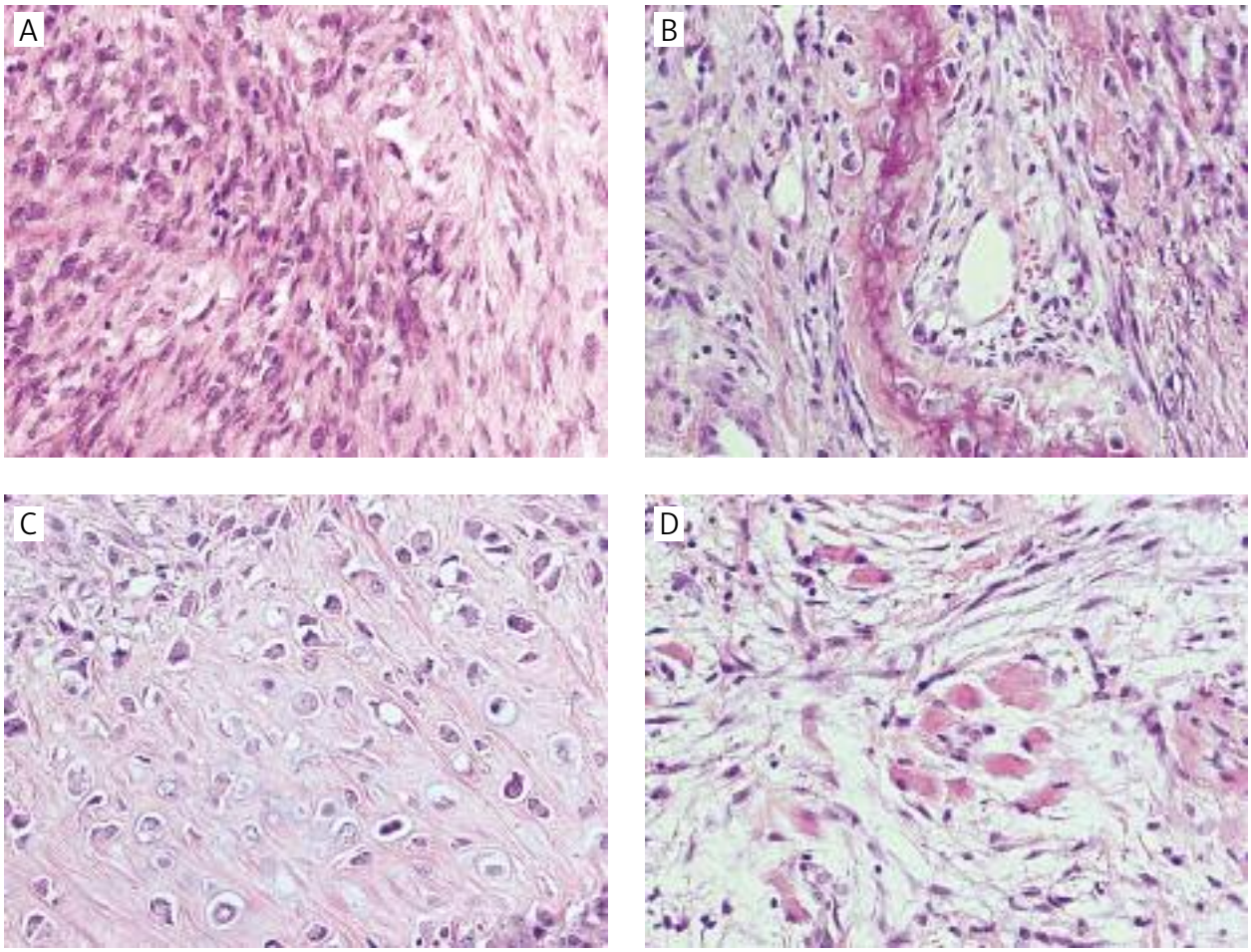

Fig. 1. Hypercellular zones (A) with areas of osteoid (B) and cartilage (C) differentiation. Tumor cells infiltrating skeletal muscle (D). HE staining. A, B and D original magnification 200×, C 400×

rounding soft tissue. The lesion was infiltrating the bones of the skull base and meninges.

The postoperative course was complicated by rhinorrhoea. The exophthalmos resolved and improvement of visual acuity was observed. Subsequently, the patient received a course of radiotherapy.

On follow-up, 6 months after surgery, the signs of local recurrence and new neoplastic loci in the meninges as well as the left parietal and left occipital region were demonstrated on MRI. The patient was referred for further oncological treatment.

Material and methods

Soft fragments of tissue with 6 cm maximal dimension were received for histopathological examination. Hematoxylin and eosin staining and immunohistochemistry were performed on 5 μm-thick sections of formalin fixed paraffin embedded tissue. Immunohistochemical analysis of S-100 protein (1 : 400, Dako Cytomation, Denmark), desmin (1 : 100, Dako Cytomation, Denmark), smooth muscle actin (SMA, 1 : 100, Dako Cytomation, Denmark), CD34 (1 : 50, Dako Cytomation, Denmark) and epithelial membrane antigen (EMA, 1 : 100, Dako Cytomation, Denmark) expression was performed using horseradish peroxidase based method (EnVision, Dako Cytomation, Denmark).

Results

Hematoxylin and eosin stained tissue sections demonstrated a heterogeneous neoplasm with hypercellular and hypocellular zones. The hypercellular areas of the tumor contained pleomorphic cells with features of atypia (Fig. 1A) and mitotic activity up to four mitoses per 10 high power fields. Within the hypercellular zones areas of mesenchymal differentiation in the form of osteoid (Fig. 1B) and cartilage (Fig. 1C) tissues were seen. The hypocellular component resembled a neurofibroma and was composed of cells with wavy nuclei and scant eosinophilic cytoplasm, and contained some fibroblasts (Fig. 2A). Within the paucicellular zones areas of collagen formation were observed. No areas of necrosis were found. The tumor infiltrated skeletal muscle (Fig. 1D).

The tumor exhibited diffuse S-100 protein expression (Fig. 2B). The S-100 protein immunopositivity was

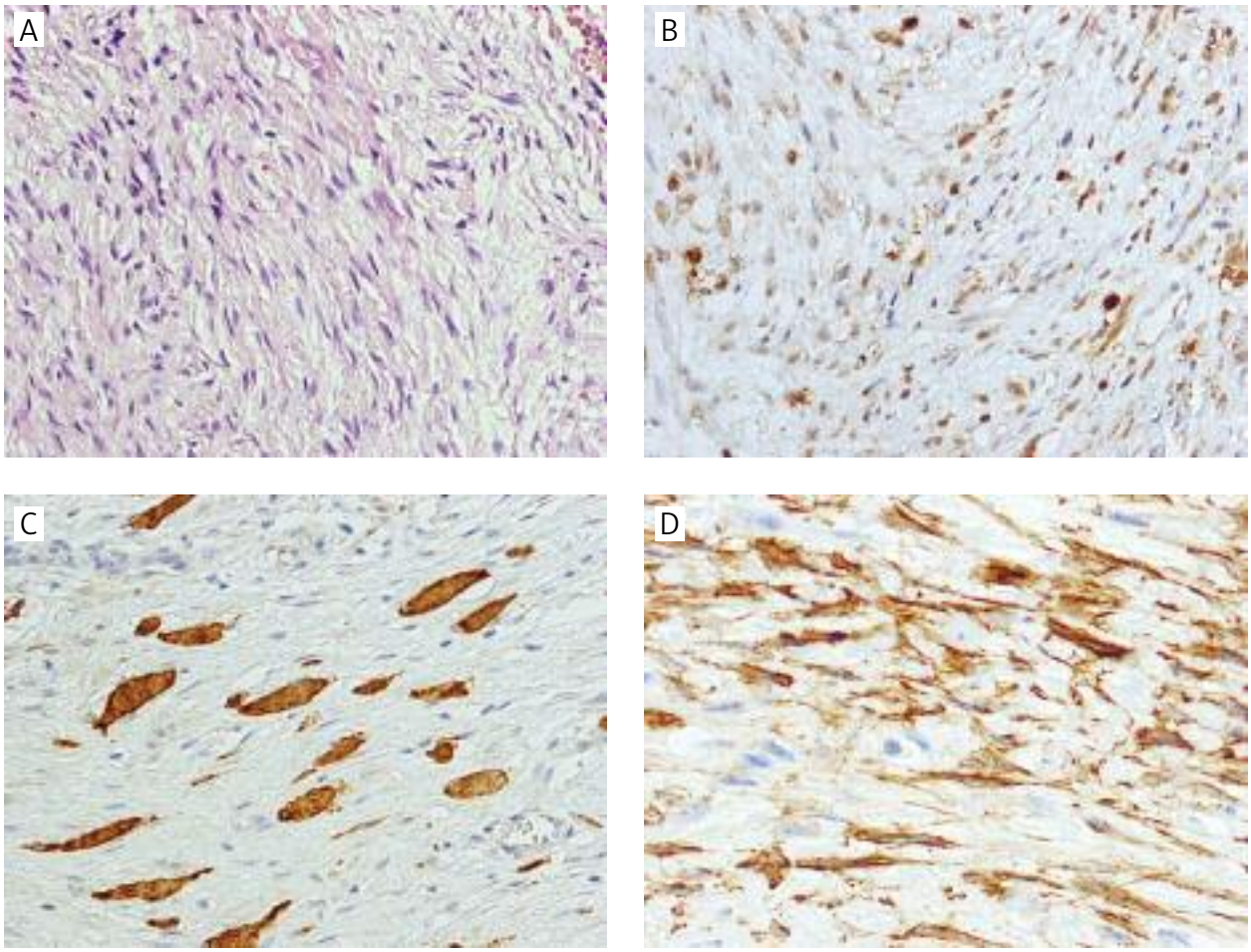

Fig. 2. Hypocellular component (A). HE staining. Original magnification 100×. Diffuse S-100 protein (B), focal desmin (C) and SMA (D) expression. Peroxidase immunohistochemistry. B and C original magnification 100×, D 200×

particularly intense in the areas with cartilaginous differentiation. The tumor showed focal SMA expression suggesting smooth muscle differentiation (Fig. 2D). Focal immunoreactivity for desmin was observed in some regions of the tumor but this was consistent with infiltration of the skeletal muscle by the tumor rather than muscle differentiation (Fig. 2C). Sparse EMA-positive cells were present. CD34 expression was limited to the vessel walls.

The described morphological and immunohistochemical findings support the diagnosis of low grade MPNST with osteoid, cartilaginous and probably smooth muscle differentiation.

Discussion

The presented tumor is a low grade lesion that demonstrates cartilaginous, osseous and possibly smooth muscle differentiation. This is an example of a rare neoplasm as majority of MPNSTs are high grade lesions and mesenchymal differentiation is only rarely encountered in low grade MPNSTs.

Most MPNSTs are high grade tumors with aggressive clinical behavior. Low grade MPNSTs usually arise in a neurofibroma. In a large series of 120 MPNSTs published by Ducatman *et al*. low grade MPNSTs accounted for 18% of cases [8].

Conventional low grade MPNSTs are hypercellular, mitotically active lesions with enlarged, hyperchromatic cell nuclei. Yamaguchi *et al.* described clinicopathological features of four low grade MPNSTs with diverse cytological and histological patterns and discussed their differential diagnoses [9]. In their series atypical neurofibroma was included in the differential diagnosis of the MPNST exhibiting neurofibroma-like features, whereas in the case of MPNST showing fibromyxoid sarcoma-like morphology spindle cell sarcomas (low grade fibromyxoid sarcoma, low grade myxofibrosarcoma and fibrosarcoma) were considered. Metastatic carcinoma, sweat gland carcinoma and malignant melanoma were considered in the differential diagnosis of low grade MPNST with epithelioid appearance. The MPNST with hemangiopericytoma-like features was distinguished by Yamaguchi *et al.* from solitary fibrous tumor, hemangiopericytoma and pleomorphic hyalinising angiectatic tumor.

The present case exhibited marbled appearance with alternating hypocellular and hypercellular zones. In the

differential diagnosis neurofibroma was considered. The presence of areas with increased cellularity composed of polymorphic cells with hyperchromatic nuclei was in favor of the diagnosis of MPNST as these features are absent in a neurofibroma.

Normal nerve sheath consists of Schwann cells, perineurial cells and mesenchymal cells [2]. The origin of MPNSTs remains a subject of a debate but they are believed to arise from Schwann cells or pluripotent cells the of neural crest. Lack of a single immunohistochemical marker for nerve sheath tumors complicates the diagnosis in cases when the tumor is not associated with a nerve or is arising in a patient without NF-1. Currently, the S-100 protein staining is the most widely accepted means to demonstrate the neural differentiation [9]. Up to 70% of MPNST cases demonstrate S-100 protein expression with weak and focal immunostaining in conventional MPNSTs and strong and diffuse pattern of expression observed in epithelioid subtype [3-5, 10]. In our case cells exhibited diffuse S-100 expression.

Additionally, we observed expression of EMA in a proportion of neoplastic cells that reflects perineurial differentiation. It remains controversial whether and to what degree the perineurial cells contribute to the formation of MPNSTs [11]. A low grade MPNSTs derived from perineurial cells have been described previously [11]. The MPNSTs with perineurial differentiation are negative for S-100 protein and appear to have more favorable prognosis than conventional MPNSTs [2].

The differential diagnosis between MPNST and hemangiopericytoma requires immunohistochemistry for CD34. Both partial and pure hemangiopericytoma-like patterns in MPNSTs were reported. Our case had a different immunohistochemical profile than a hemangiopericytoma as it was negative for CD34 and showed S-100 protein immunoreactivity.

The MPNST must be also distinguished from leiomyosarcoma. In our case, the presence of numerous cells with wavy not blunt-ended nuclei, delicate stromal collagen, diffuse S-100 protein expression and focal immunostaining for SMA favored the diagnosis of MPNST.

In the case presented here immunopositivity for SMA could indicate smooth muscle differentiation. Rodriguez *et al.* presented a case of low grade MPNST with smooth muscle differentiation in a 62-year-old male with neurofibromatosis type 1 [7]. In their case however, the smooth muscle differentiation was confirmed not only by immunohistochemistry but also by electron microscopy.

The treatment of MPNSTs encompasses surgery (complete removal with tumor-free margins) followed by irradiation [2, 12]. The MPNSTs are highly aggressive tumors with a poor prognosis and the 5-year overall survival rate of 52% [8]. The results of studies evaluating tumor grade as a potential prognostic factor for patients with MPNSTs are inconclusive [2, 8]. High Ki-67 labeling index (> 25%), large tumor size, history of NF-1 have been established as unfavorable prognostic factors [2, 8, 13]. Complete resection is as a positive prognostic factor that also improves local control of the disease [2].

In summary, we report here histological and immunohistochemical findings in a rare example of a low grade MPNST with mesenchymal differentiation.

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