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CASE REPORT

A Small Intraneural Epithelioid Malignant Peripheral Nerve Sheath Tumour of the Median Nerve Simulating a Benign Lesion. Description of a Case and Review of the Literature

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Abstract The epithelioid variant of malignant peripheral nerve sheath tumours (MPNSTs) is a very rare malignancy. We describe the case of a 30-year-old man complaining of acute pain in his right elbow, mild distal paraesthesias, and some motor deficiencies. He was discovered as having a small fusiform swelling of the median nerve. In view of its very small size, shape, and nonspecific MRI signal, it had initially suggested a benign lesion. The diagnosis of epithelioid MPNST was made only at the histopathological examination. This malignant neoplasm recurred locally fourteen months after surgery. In addition to describe the above very rare case, we have reviewed the literature on epithelioid MPNSTs clearly involving deep major nerve trunks. This case serves as a warning that, even in major nerve trunks, tiny lesions may in reality be early intraneural MPNSTs which, due to their deep location, must be treated adequately with wide margin surgery since the resection margin status represents one of the major parameters influencing the local control of disease and its clinical outcome.

Keywords Malignant peripheral nerve sheath tumour · Epithelioid variant · Surgical margins · Outcome · Immunohistochemistry

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Introduction

Malignant peripheral nerve sheath tumours (MPNSTs) encompass malignant neuroectodermal tumours arising either from a peripheral nerve or located in extraneural soft tissues, but displaying differentiation along one or more cell lines belonging to the nerve sheath (e.g. Schwann cell, perineural cell, fibroblast) [1]. The general term MPNST (which embraces the entire spectrum of malignant tumours reproducing the nerve sheath cell phenotypes) has progressively replaced some outdated appellations such as "neurofibrosarcoma", "malignant schwannoma", and "neurogenic sarcoma" [2]. They are typically highly malignant large bulky tumours [3].

In this report, we describe the case of a young man who developed an epithelioid variant of MPNST which, at the time of diagnosis, was small in size and entirely intraneural. In addition, we have reviewed and discussed the English-language literature on deeply located epithelioid MPNSTs clearly involving major nerve trunks.

Case Report

An otherwise healthy 30-year-old man went to his General Practitioner because of acute pain in his right elbow which had begun about one month before. Additional signs and symptoms were mild distal paraesthesias and some motor deficiencies. Ultrasonography revealed a fusiform swelling of the median nerve situated at the distal third of his right upper arm suggestive of a schwannoma. The magnetic resonance imaging (MRI) images demonstrated a small round mass with an elongated spindle-type morphology that was in anatomic contiguity with the median nerve in the arm (Fig. 1a, b, c). The orientation of the mass along the long axis of the nerve was highly suggestive of a mass of neural origin. Although small in size, the mass had nonspecific signal characteristics with heterogeneous signal on T1 and T2, slightly irregular margins and a heterogeneous pattern of enhancement. The differential diagnosis for a mass with these imaging features would include a benign or malignant peripheral nerve sheath tumour (PNST) or, less likely, a focal nonspecific inflammatory process.

The lesion was surgically excised sparing an outwardly unaffected nerve fascicle. Grossly, it was a yellowish nerve swelling (2×0.8 cm) apparently confined to the endoneurium (Fig. 1d).

After surgical excision, this lesion was immediately fixed in a 10% formalin-buffered solution for 48 h and embedded in paraffin. The paraffin tissue blocks were cut into 5-μm sections and stained with haematoxylin and eosin. Additional 5-μm histological sections were kept for the immunohistochemical analysis.

Histopathologically, serial sections revealed the presence of isolated neoplastic foci— of different shape and size (from 0.5 to 3 mm)— within a mild-to-moderate fibrotic endoneurial compartment (Fig. 2a). None of these foci either involved or extended beyond the perineurium layers. The neoplastic cells displayed epithelioid appearance with abundant eosinophilic or amphophilic cytoplasm and a large nucleus with a prominent nucleolus (Fig. 2b). These elements were organised into small nodules and groups, short cords, or isolated single elements. From the immunohistochemical standpoint (Fig. 2c–f), the neoplastic cells were strongly positive for S-100 protein, and focally for EMA (which, in addition, diffusely stained the peripheral perineurial cells). An anti-collagen IV antibody highlighted the presence of basal membrane material around both single and small nests of tumour cells. On the contrary, cytokeratin, melan-A, HMB45, tyrosinase, and desmin stains were negative. The MIB-1 labelling index throughout the tumour was nearly 30%. No areas of necrosis were detected. The above morphological and immunohistochemical findings supported the diagnosis of "intraneural MPNST, epithelioid variant". The surgical margins, as evaluated on the resected specimen, were negative with a minimal free-from-disease distance of 3 mm.

On the basis of this unforeseen diagnosis, a number of staging investigations were performed. The symptomatology remained unaltered after the tumour excision. The neoplasm

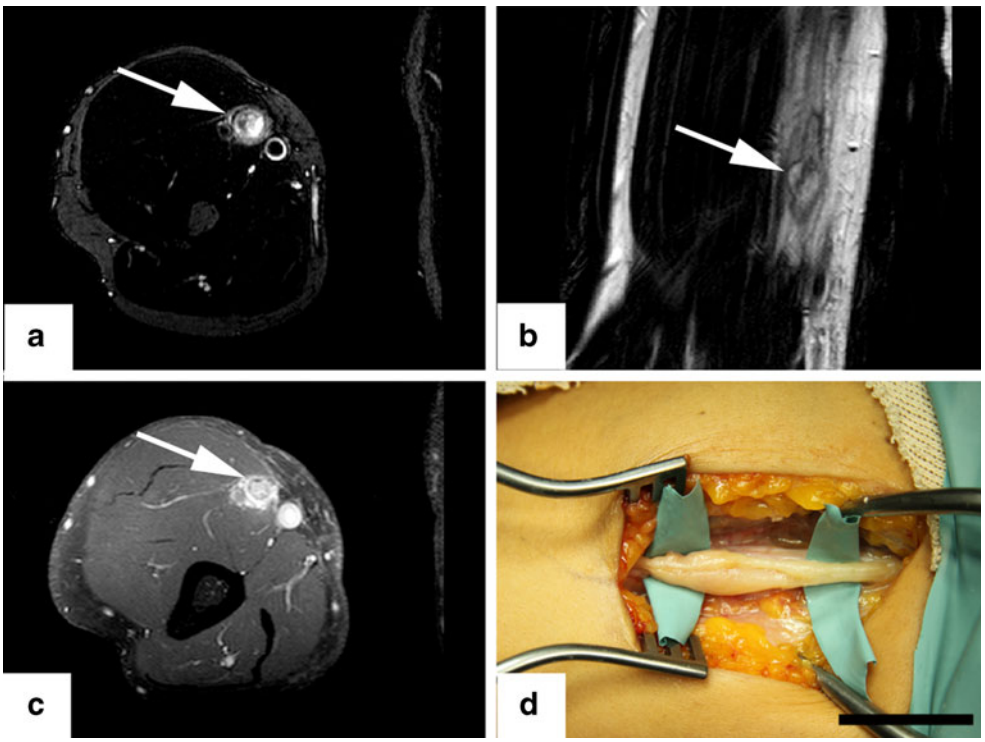

Fig. 1 Axial T2 with fat suppression (**a**), coronal T2 (**b**) and axial T1 with fat suppression and gadolinium (**c**) MRI images of the distal third of the right arm show a small mass with a round to spindle-type morphology (*arrows*) that affects the median nerve and is in anatomical contiguity with the brachial artery and vein. The mass is markedly heterogeneous with slightly irregular margins and enhances heterogeneously with gadolinium. Intraoperatively, this lesion appeared as a yellowish bulge of the median nerve (**d**). Scale bar. D: 2 cm

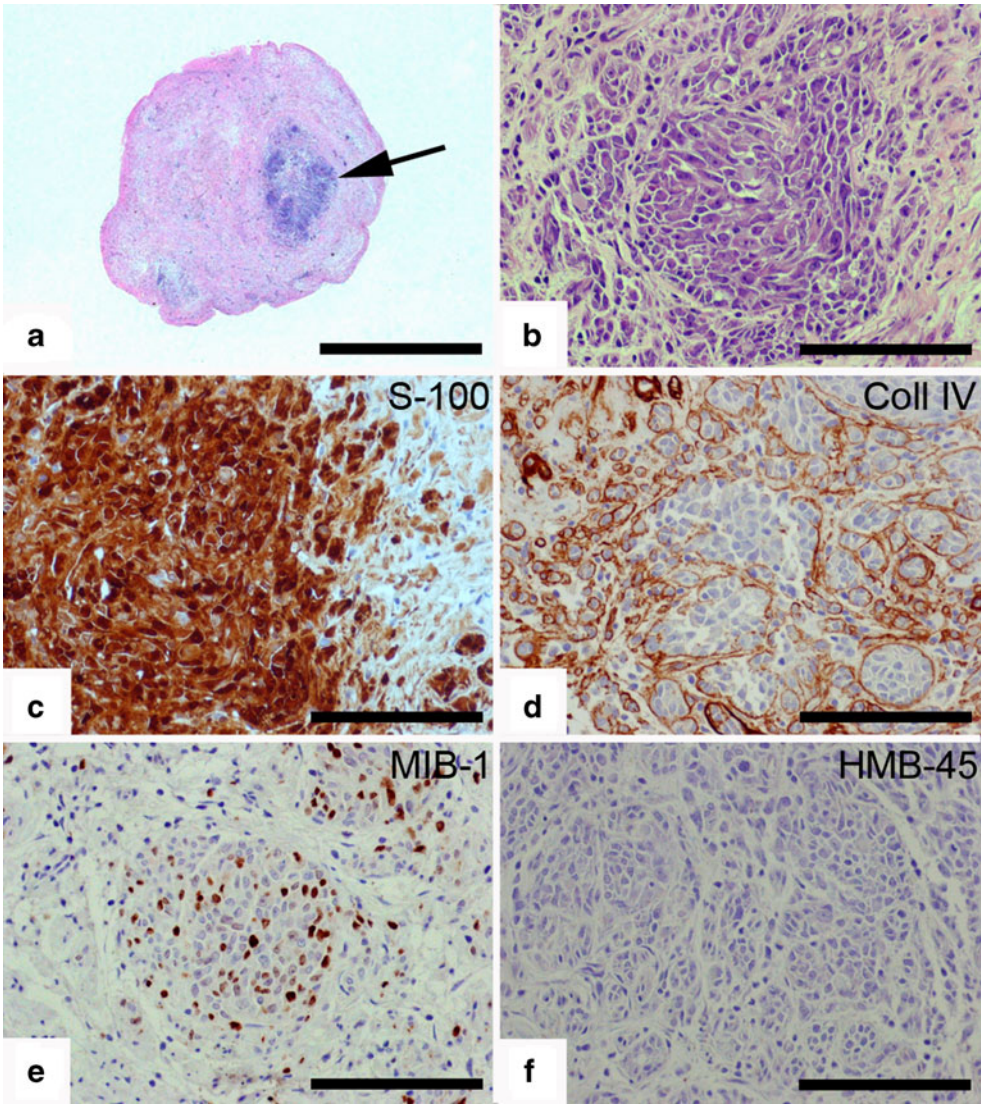

Fig. 2 Low-power histopathological view (**a**) of a transversal section cut along the middle portion of the tumour (the *arrow* indicates the largest MPNST focus). High-power field (**b**) showing the epithelioid MPNST cells arranged in nodules, small groups, rare cords, and single elements. These neoplastic cells are immunohistochemically positive for S-100 protein (**c**) while type IV collagen may be detected around both single and small nests of tumour cells (**d**). The MIB-1 proliferative index is highly significant (**e**). HMB-45 is negative (**f**). Staining. A, B: H&E; C–F: Mayer's haematoxylin counterstained. Original magnification. A: ×1.25; B–F: ×20. Scale bar. A: 0.5 cm; B–F: 150 μm

under discussion recurred locally 14 months after surgery and was treated with wide excision.

A complete English-language PubMed review between 1960 and December 2009 was performed in order to identify cases of epithelioid MPNST which had manifestly occurred in deep major nerve trunks. Among all of the cases identified, 14 fulfilled the above cited criteria and contained detailed clinico-pathological information (Table 1) [4, 5].

Discussion

The uniqueness of the present case lies in the fact that it combines the exceptionality of being a very small intraneural epithelioid MPNST with deceptively benign gross appearance.

MPNSTs are rare neoplasms which account for about 5–10% of all soft tissue malignant tumours. Twenty-five to fifty percent of these arise in the setting of neurofibromatosis 1 (NF1), while second in frequency are those MPNSTs affecting peripheral nerves [1]. Among these latter, large and medium-sized nerves are more frequently involved than small ones. In particular, the sciatic nerve, buttock, thigh, brachial plexus, median nerve, and paraspinal region are the anatomical sites most prone to MPNST involvement. On the contrary, cranial nerve MPNSTs are less common [1]. MPNST is primarily a neoplastic process affecting adults, the great majority occurring in subjects aged 20–50 years. As in the present case, local pain is the most common symptom [2]. In addition, the patient under discussion complained of mild distal paraesthesias and motor deficiencies which did not change after tumour excision, very likely in view of sparing a nerve fascicle.

The epithelioid variant of MPNST is a very uncommon malignancy (about 5% of all MPNSTs) either predominantly or exclusively composed of neoplastic Schwann cells with rounded/polygonal cytoplasm and epithelioid appear-

ance [4]. This variant shares the same age range and anatomical distribution with ordinary MPNSTs, while it seems slightly more common in men than in women. Interestingly, the epithelioid MPNST occurs less frequently in NF1 than its ordinary counterpart [2, 4].

The nonspecific MRI findings deserve special mention in this case. MRI is the imaging modality of choice for the detection and characterization of soft tissue PNSTs. The MR imaging features of PNSTs have been investigated extensively and correlated with histopathologic findings [6–9]. The imaging features that are suggestive of the diagnosis of a PNST include an ovoid to spindle-type shape, anatomic contiguity with a specific peripheral nerve, and a peripheral rim of fat (the "split fat" sign). However, the latter finding is not specific for PNST, but indicative of a lesion originating from an intermuscular location from the region of the neurovascular bundle and is more common with benign than malignant PNSTs [4]. There is significant overlap in the signal intensity of benign and malignant PNSTs, with the majority isointense with muscle on T1, hyperintense on T2 and a variable pattern of enhancement. Therefore, the signal intensity alone is not a reliable feature to differentiate many benign from malignant PNSTs. However, some benign peripheral tumours may reveal a target sign on T2 weighted imaging, with low-to-intermediate signal intensity centrally and a peripheral rim of high signal intensity. This finding has been shown to correlate pathologically with more cellular Antoni type A regions centrally and a more myxoid Antoni type B region peripherally [6, 7]. The target sign is nearly pathognomonic for neurofibroma, but can be seen with schwannomas and is rarely seen in MPNST [6].

Imaging features that favour the diagnosis of a benign PNST include a mass that is small in size with a smooth well-defined margin, a "split fat" sign on T1 and a target sign on T2. Features that are more suggestive of MPNST include a mass with irregular margins and associated abnormal signal in the surrounding soft tissues, both features suggestive of a more aggressive infiltrative lesion [9]. The signal intensity of the tumour is not a reliable indicator for differentiating benign and malignant PNST. Although the mass in this case is small in size, it has irregular margins and demonstrates nonspecific signal characteristics and is therefore, radiographically indeterminate, with the possibility of both benign and malignant PNST considered on the differential diagnosis. The radiological differential diagnosis for such a mass would also include an infectious or inflammatory process and other soft tissue sarcomas, but the latter would be considered less likely given the distinct anatomic distribution along the course of a peripheral nerve. Soft tissue masses with indeterminate imaging features on MRI can be biopsied with image guidance (either ultrasound or computed tomography) for definitive histological diagnosis.

In regard to its histopathological differential diagnosis, epithelioid MPNST must be distinguished primarily from malignant melanoma and carcinoma. Distinction between melanoma and MPNST may occasionally be very difficult, even though this latter, as a rule, does not express melanoma-associated antigens such as HMB-45 or melan-A. Carcinoma may be ruled out on the basis of the strong and diffuse positivity of epithelioid MPNSTs for S-100 and absence of immunoreactivity with epithelial markers (cytokeratins) [2].

Our review of the literature has yielded 14 cases of epithelioid MPNST clearly affecting major nerve trunks [4, 5]. There were 8 male and 6 female, and their average age at the time of diagnosis was 35±18 years (range 12–74). All of the lesions occurred in the extremities with brachial plexus and sciatic nerve the most frequent tumour locations. In 50% of the cases, patients either died from disseminated disease or experienced local recurrence, whereas in the remaining 50% patients were alive without any signs of disease. Lungs, adrenal gland, and, curiously, lymph nodes were the most common metastatic sites. Tumour size was larger in subjects with worse prognosis than in those with no evidence of neoplasm (mean values 7±2.7 cm versus 4.6±2.4 cm, respectively, see Table 1).

According to the very few studies which have clinically explored patients suffering from MPNSTs, their cumulative 5-year survival varies from 34% to 52% [10–13]. Prognosis of epithelioid MPNSTs is highly dependent on the extent/depth of invasion, the clinical course of deep lesions being worse than suprafascial ones. In a previous study by Laskin *et al*, the superficial lesions were smaller than the deeper ones, so that most of them could be treated with wide excision. Local recurrences occurred only in a fraction of cases in which this surgical approach had not been achieved. On the contrary, prognosis of the MPNSTs in deep soft tissues was not so favourable. Unlike superficial MPNSTs, there were patients who died from the disease with metastatic disease mainly affecting the lung.

Due to its extreme rarity, additional information on prognostic factors in epithelioid MPNSTs is not yet available. However, some of these factors might be gathered from larger investigations into ordinary MPNSTs [3]. According to a recent single-institution analysis, tumour size, location and surgical margin involvement greatly influence the clinical outcome. In particular, MPNSTs located at the extremities would be characterised by more favourable prognosis in comparison with those lesions situated in the trunk, head and neck regions [3]. In another study, performed by investigating a similar patient population, both diagnosed and treated at the Mayo Clinic [14], on multivariate analysis, prognostic factors affecting clinical outcome were a history of NF-1, prior irradiation, and positive surgical margins. These latter were also an

Table 1 Review of the literature on deeply located epithelioid MPNSTs occurring in a major nerve

Reference	Age	Gender	Anatomical location	Tumour largest dimension (cm)	Treatment	Outcome and follow-up duration
4	36	M	Knee, femoral nerve	1.5	Wide excision	ANED; 1 year
4	40	F	Forearm, radial nerve	4.9	Complete excision	ANED; 5 years
4	12	F	Forearm, median nerve	5	Complete excision	Lymph node and lung metastases, died of disease; 1 year
4	64	M	Thigh, sciatic nerve	7	Complete excision	Lymph node, adrenal, and rib metastases, died of disease; 1 year
4	19	M	Shoulder, brachial plexus	7.5	Wide excision	Metastases (NOS), died of disease; 1 year
4	47	M	Thigh, sciatic nerve	8	Wide excision	ANED; 7 years
4	34	M	Thigh, sciatic nerve	7.5	Wide excision	ANED; 5 years
5	20	M	Proximal part of left median nerve	2.5	Local excision followed by amputation of left scapula and arm	ANED; 5.5 years
5	74	F	Left brachial plexus	4	Local excision followed by wider do including nerve resection	Dead from myocardial infarction, at that time ANED; 18 years
5	33	F	Proximal part of right sciatic nerve	10	Local resection of right sciatic nerve followed by amputation of right leg	Lung, pleura, liver, adrenals, pancreas, peritoneum, and lymph node metastases, died of disease; 1.2 years
5	40	M	Proximal part of right peroneal nerve	4	Local excision followed by amputation of right lower leg and resection of right sciatic nerve distal of hip	ANED; 4 years
5	17	M	Left brachial plexus	7	Amputation of left arm	Lung & pleural metastases, died of disease; 13 yrs
5	21	F	Left peroneal nerve popliteal fossa	2.5	Wide local excision followed by radiation and chemotherapy	Lung & pleural metastases, died of disease; 1.8 yrs
5	37	F	Right brachial plexus	10	Local excision followed by radiation and chemotherapy	Large local recurrence after 3 years, radically removed by extended thoraco-scapular amputation; 1 year

Abbreviations. M: male; F: female; ANED: alive with no evidence of disease; NOS: not otherwise specified.

unfavourable prognostic factor for local control of disease. As regards the MPNST anatomical site, on univariate analysis, tumour location at the extremities negatively affected both survival and local control of the disease, while this significance was lost on the multivariate analysis which included the prognostic factors which were significant on the univariate tests. On this basis, wide excision of MPNSTs affecting major nerves is recommended in order to greatly improve both the local control of disease and survival.

Adjuvant irradiation (with a cumulative dose of $\geq$ 60 Gy), brachyterapy or intraoperative electron irradiation (IOERT) may be beneficial in the management of cases with either positive or close surgical margins [14].

The patient under discussion experienced MPNST local recurrence 14 months after surgery. This time is beyond the median time for relapse reported in major clinical studies dealing with MPNST [3, 14]. Interestingly, in this study, the 5-year distant control rate was found to be influenced by the MPNST histological subtype, by ranging from 79% in the perineurial type to 26% in the epithelioid type. The disease distant failure was also correlated with the tumour size, <5, >5, >10, and >15 cm being the reference sizes which were investigated [11, 12, 14]. There is no full agreement as to how higher histological grades can be related to a worse prognosis [1].

In conclusion, the case under discussion may serve as a warning that, in major nerve trunks, even small lesions which, on the basis of their size and shape appear benign, may in reality be early intraneural MPNSTs. Especially in deep locations, the possibility of malignancy should always be considered and planning for intraoperative consultation

is key in order to achieve the major goal of surgery in MPNSTs and improve the patient's clinical outcome.

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