Malignant peripheral nerve sheath tumour of the paranasal sinuses and the anterior skull base

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Malignant peripheral nerve sheath tumour represents 10% of all soft tissue sarcomas, only 10% of which occur in the head and neck, which makes it a rare entity.

Keywords:
head and neck neoplasms, malignant peripheral nerve sheath tumours, neurofibromatosis type 1, paranasal sinus, skull base

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Introduction

Malignant peripheral nerve sheath tumour (MPNST) has been defined as any malignant tumour arising from or differentiating towards cells of the peripheral nerve sheath, with the exception of tumours originating from the epineurium or the peripheral nerve vasculature [1,2].

According to Enzinger and Weiss, the term MPNST is preferred for these tumours because they may recapitulate the appearance of any cell of the Schwann cell and also the perineural fibroblast or fibroblast [3,4].

MPNST represents ~10% of all soft tissue sarcomas. This tumour is usually found in the lower extremities, and only 10–12% of all lesions occur in the head and neck region, which makes it a rare entity [5].

Various misleading synonyms including the term neurofibrosarcoma, neurogenic sarcoma, malignant neurilemmoma and malignant schwannoma have all been applied previously to this neoplasm and thus indicate the controversial clinicopathologic classifications of this rare tumour [6,7]. Malignant schwannoma was first described by Lewis and Hart [8]. The term 'Malignant Peripheral Nerve Sheath Tumour' was adopted in the beginning of 1990s, by the WHO committee for the classification of soft tissue tumours, after advances in electron microscopy and immunohistochemistry contributed towards the histological diagnosis of MPNST [9,10]. However, the diagnosis and management of MPNST continue to challenge pathologists and surgeons [6,7].

In many respects, MPNSTs in general, and MPNSTs of the head and neck in particular, represent exceptional neoplasms: MPNSTs are one of the most aggressive malignant tumours, with the highest local recurrence rate of any sarcomas, and a marked propensity for dissemination and metastatic spread [11,12]. Despite multimodal therapy including radical surgical resection and adjuvant radiochemotherapy, the prognosis of MPNSTs is believed to remain dismal, particularly in the head and neck. However, prognostic factors and treatment modalities have not been identified consistently in the literature as yet [13–15].

As MPNSTs are rare neoplasms, with only a few reported cases of MPNST affecting the paranasal sinuses and the anterior skull base, the biological and clinical behaviour of this aggressive tumour is poorly understood [6,15,16]. In an effort to further elucidate the natural history and prognosis of this rare neoplasm in the head and neck, we present a further case of MPNST of the anterior skull base.

Illustrative case history

In November 2011, a 62-year-old man was admitted to our department of Otorhinolaryngology Head/Neck & Skull Base Surgery with a 5-month history of recurrent right-sided epistaxis and increased nasal obstruction with persistent headache.

He had a history of a right facial swelling, which was initially small, and had rapidly increased in size over the past 5 months.

The swelling was associated with intermittent, dull aching pain.

Patient also had a history of difficulty in speech, chewing, breathing and numbness in the roof of the mouth and over the right cheek.

Past dental, medical and drug histories were unremarkable.

Family history was negative for von Recklinghausen's neurofibromatosis.

Two months before presentation, the patient has undergone a surgical biopsy from a mass in the right nasal cavity, at another institution, and the histopathology was misdiagnosed as a chronic nonspecific inflammatory reaction with no malignancy.

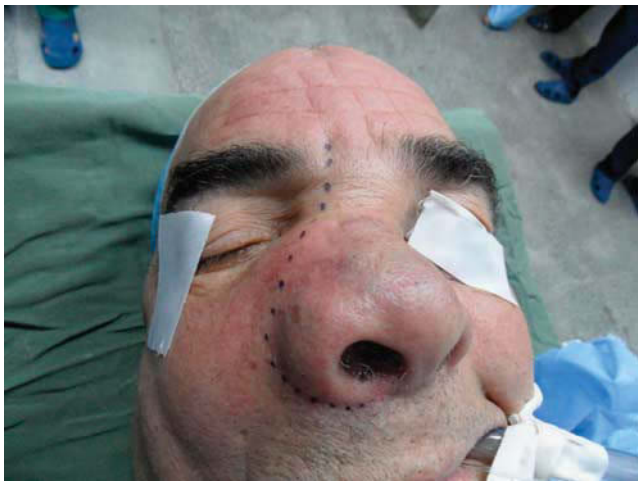
On general physical examination, the patient was moderately built and nourished with satisfactory vital signs. There were no signs of any wasting disease.

Clinical examination was negative for von Recklinghausen's neurofibromatosis.

Nasal examination indicated a large polypoid mass, of variable consistency, filling the right nasal cavity.

External examination showed an oval-shaped well-defined swelling measuring $\sim 4 \times 5$ cm on the right middle third of the face extending from the zygomatic arch to the level of angle of the mouth, and from the nasolabial fold (which was splayed by the swelling) to the level of the outer canthus of the right eye (Fig. 1).

Figure 1



Clinical picture of the swelling.

The skin over the swelling was stretched and the surrounding tissues appeared normal. No scars, sinuses, ulcerations and discolorations were detected over the swelling. Mouth opening was found to be adequate.

Movements of both eyes were normal.

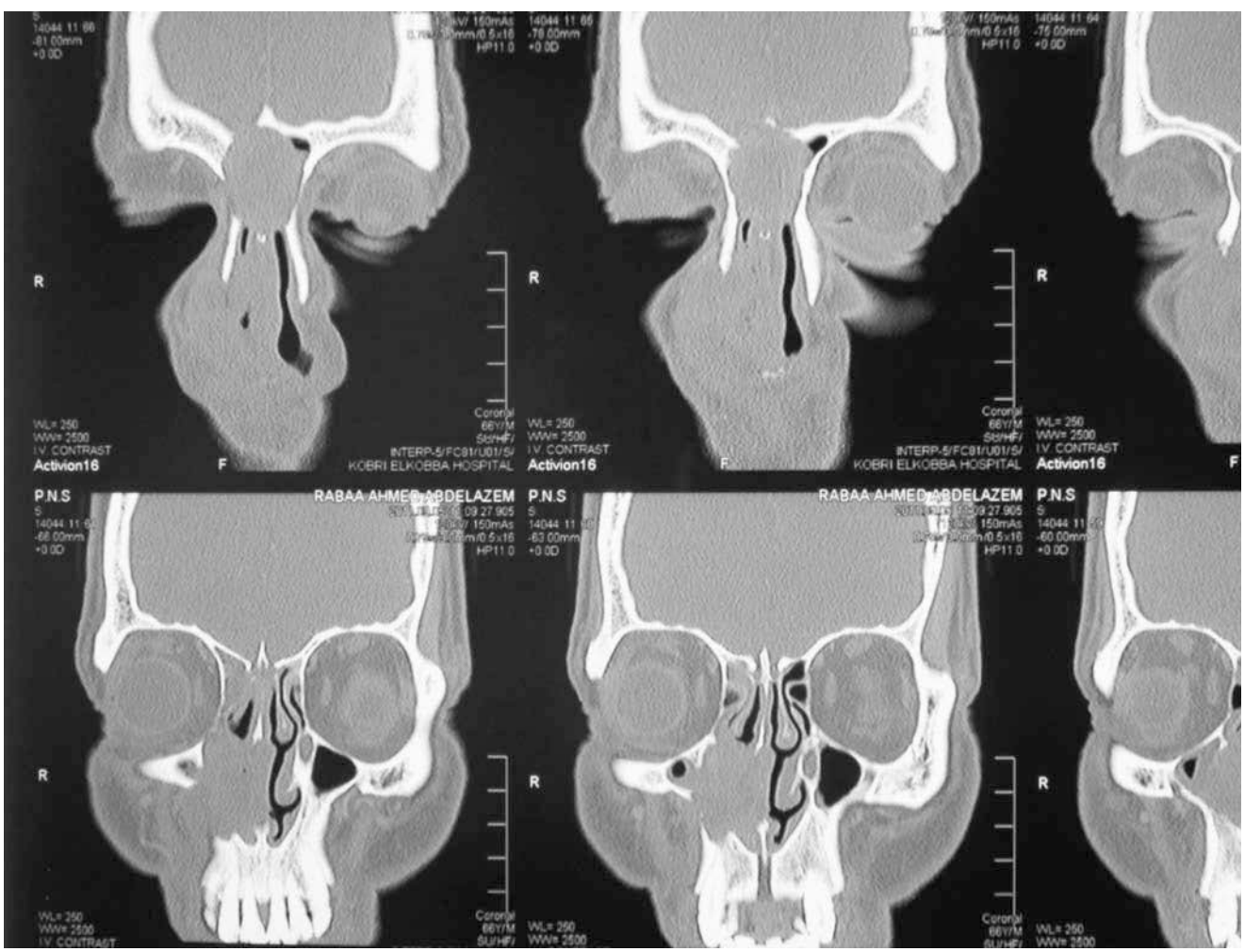
Pupillary reaction to light was normal.

On palpation, the swelling was not hot, not tender, firm in consistency, nonfluctuant, nonreducible and noncompressible.

He had no palpable neck nodes.

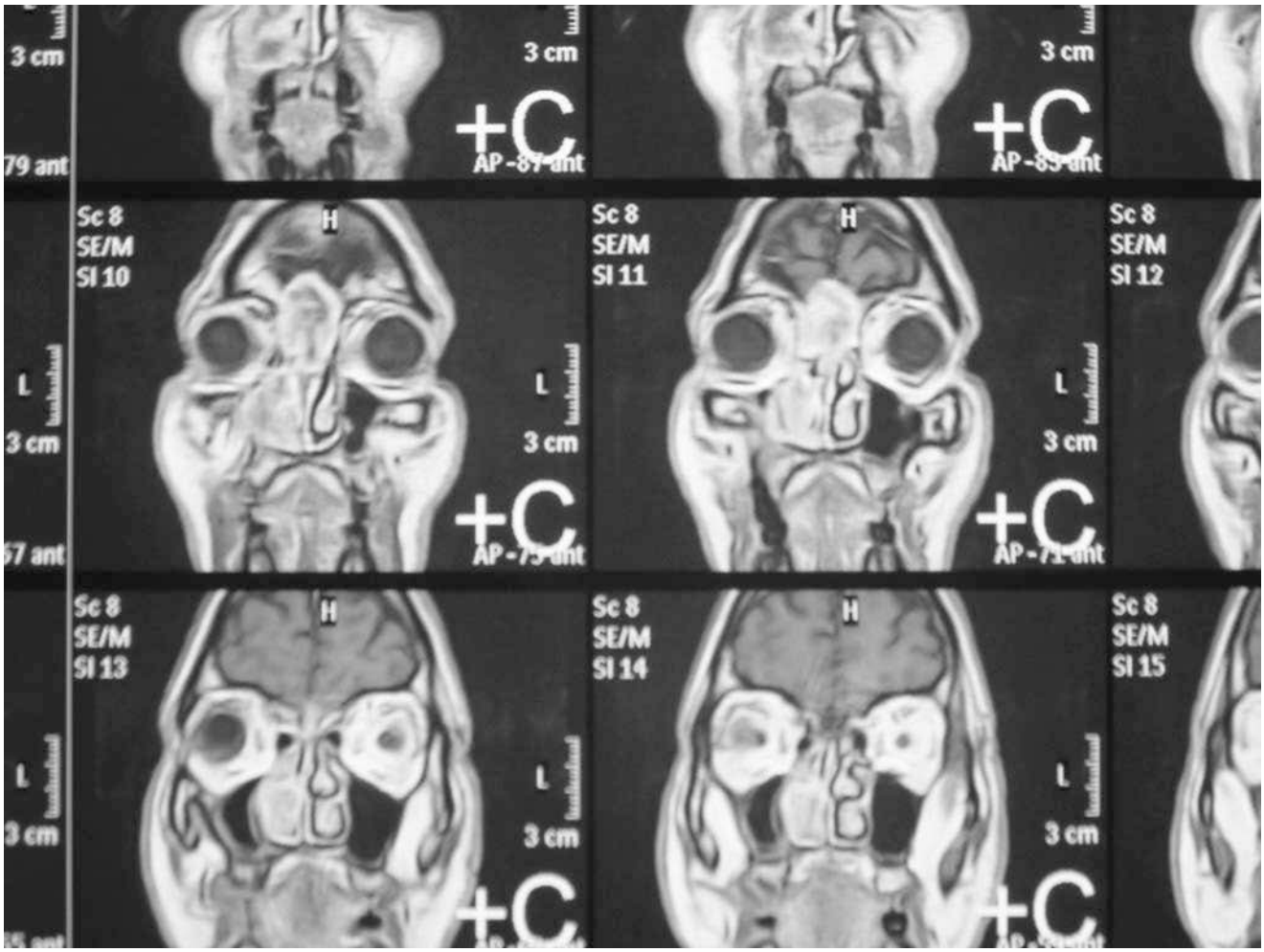
On the basis of the history and clinical examination, a provisional diagnosis of antral malignancy was made and differential diagnosis included squamous cell carcinoma, mucoepidermoid carcinoma, adenoid cystic carcinoma, fibrosarcoma, neurogenic sarcoma, chondrosarcoma and osteosarcoma.

Figure 2



Computed tomography coronal cuts showing the extent of the tumour.

Figure 3



MRI of the mass showing intracranial extradural extension.

Computed tomography (CT) showed a large soft tissue mass lesion in the right nasal cavity infiltrating the right ethmoidal air cells and the frontal sinus.

The lesion extended upwards, eroding through the roof of the frontal bone and the cribriform plate, with extension into the anterior cranial fossa (intracranial extension).

The lesion was also seen eroding through the right maxilla and the nasal bones (Fig. 2).

MRI confirmed infiltration of the anterior skull base, but without dural involvement (Fig. 3).

Suggestive features of angiofibroma (moderate arterial contrast enhancement) were observed.

MRI angiography indicated normal results.

Routine blood and serum chemistry panels indicated no abnormality.

Chest radiograph and ECG were also normal.

The patient underwent a craniofacial resection of the mass.

The mass was infiltrating the nasal floor, nasal septum, the medial wall of the right maxillary sinus and both the anterior and the posterior walls of the right and left frontal sinuses.

The dura was exposed along the entire rhinobase and no intradural infiltration was observed (using high magnification of the microscope).

Total wide resection and clearance of both intracranial and extracranial portions of the mass was carried out (Fig. 4).

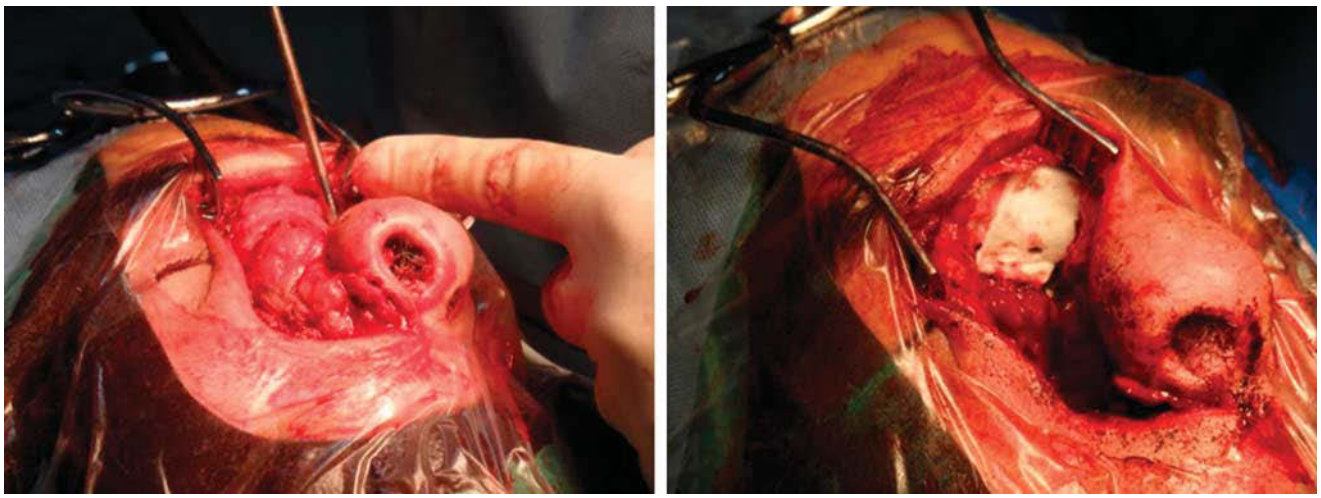
One week later, a second examination under general anaesthesia with removal of the pack was carried out.

The excised mass measured about $5 \times 4 \times 2$ cm and had a greyish-white cut surface (Fig. 5).

The mass was sent to two different histopathology institutions and indicated a highly cellular, focally polymorphic, spindle cell tumour with a low proliferation rate.

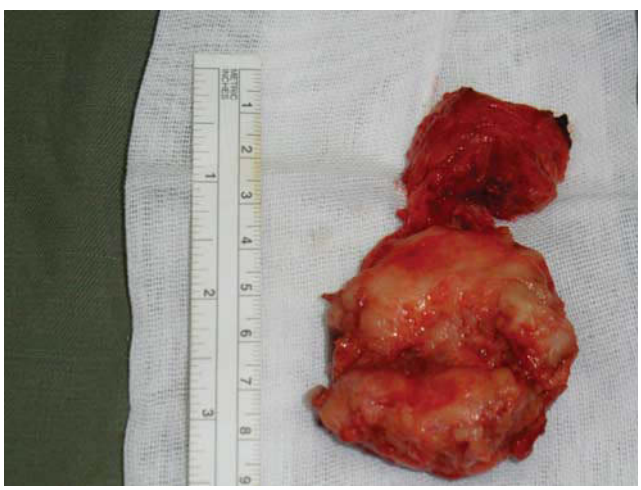
Immunohistochemistry showed focal expression of S-100 protein (i.e. positive for schwannoma), negative CD34 (i.e. negative for hemangiopericytoma), negative cytokeratin

Figure 4



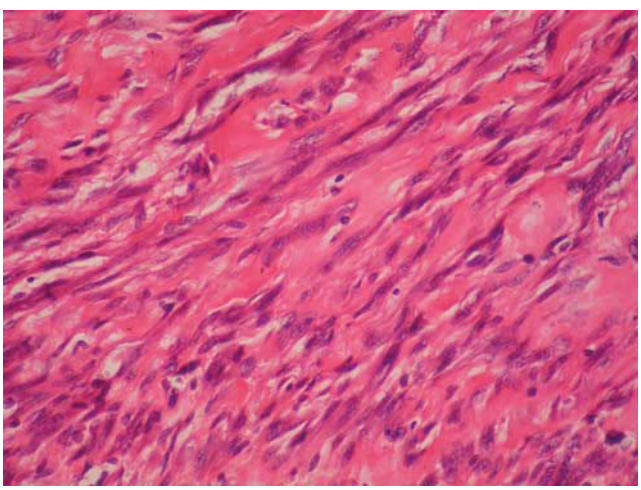
Wide surgical excision carried out by craniofacial resection.

Figure 5



Picture of the mass after excision.

Figure 6



High magnification of malignant spindle cell tumour enclosing nerve fibres.

(i.e. negative for carcinoma) as well as negative smooth muscle actin.

Higher magnification showed spindle cells with a serpentine shape arranged in a palisade manner and whorl distribution separated by abundant oedematous tissue, indicating malignant transformation of schwannoma.

These studies were consistent with an MPNST (Figs 6–11).

Postoperative CT indicated no residual mass (Fig. 12).

The patient had not received external beam radiation or chemotherapy during the first 45 days postoperatively.

Six weeks later, during the follow-up period, the patient returned with an external swelling in the right cheek and the skin over it was stretched with red discoloration.

Both eye movement and visual acuity were normal.

New CT indicated mass recurrence, but with infiltration to the medial orbit at the right side.

The patient was referred to a regional oncology institute for further evaluation and management.

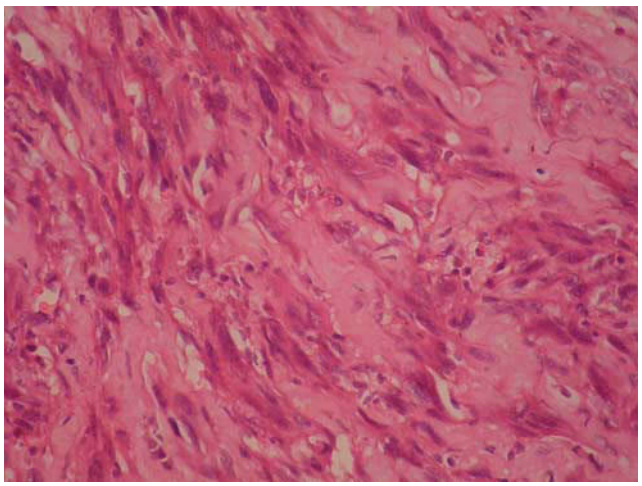
Discussion

MPNSTs are rare neoplasms, with an estimated incidence of 0.1/100 000/year in the general population.

They account for ~5–10% of all soft tissue sarcomas and have a strong association with neurofibromatosis type 1 (NF-1), also known as von Recklinghausen's neurofibromatosis [9,15,17].

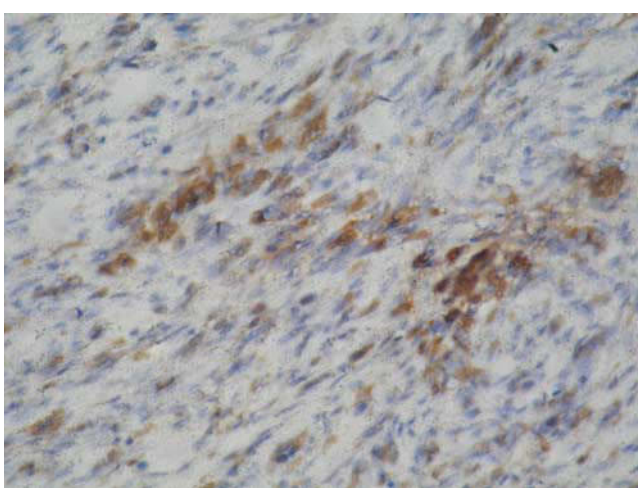
Up to 30–50% of all MPNSTs are found in association with NF-1, with a reported incidence of MPNST in this subgroup ranging from 2 to 29% [15,16,18].

Figure 7



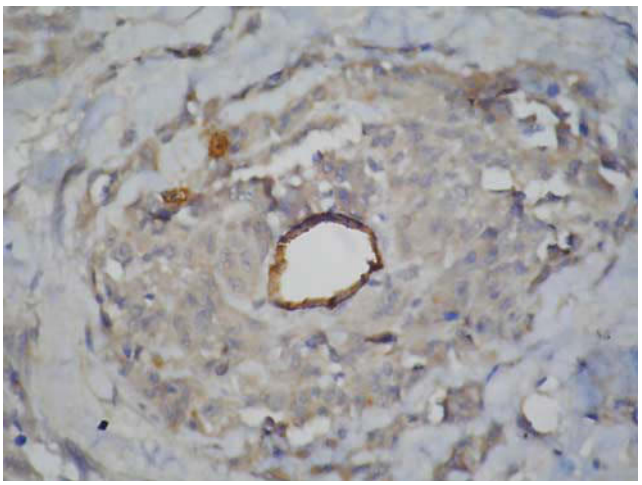
Malignant spindle cells with a serpentine shape arranged in a palisade manner and whorl distribution separated by abundant oedematous tissue (malignant transformation of schwannoma).

Figure 8



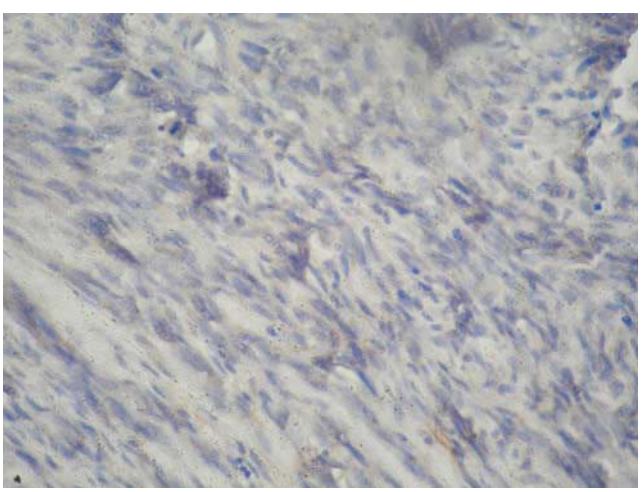
S-100 immunoreactivity positive for schwannoma.

Figure 9



CD34 vascular space stained with negative tumour cells around, indicating negativity for neurangiopericytoma.

Figure 10



Negative cytokeratin, that is, negative for carcinoma.

Besides von Recklinghausen's neurofibromatosis, radiation has been implicated as an aetiologic factor in the development of MPNST, with a latency interval of 10–20 years [19].

In previous series, up to 10% of MPNSTs have been considered to be postradiation malignancies [11]. Because of the risk of radiation-induced MPNST, several authors have recommended that caution be exercised when irradiating patients with NF-1 and that these patients should be observed closely for the development of MPNST [13,19]. MPNST can affect all age groups, but usually presents in adult life between 20 and 50 years of age, with no established predilection for sex or race.

However, the mean age of patients with NF-1-associated MPNSTs is approximately a decade younger [16,20]. The most common sites of involvement are the extremities, trunk, chest and retroperitoneum [18,21]

Although benign peripheral nerve sheath tumours such as benign schwannoma and neurofibroma have a propensity for the head and neck, fewer than 10% of MPNSTs affect this anatomic region [22,23]. MPNSTs comprise only 2–6% of head and neck sarcomas [19].

Primary neurogenic tumours of the nose and paranasal sinuses are uncommon, accounting for not more than 4% of all neural tumours of the head and neck [23,24]. The skull base is often affected even less. Therefore, the involvement of the paranasal sinuses or the skull base in MPNST is extremely rare [21].

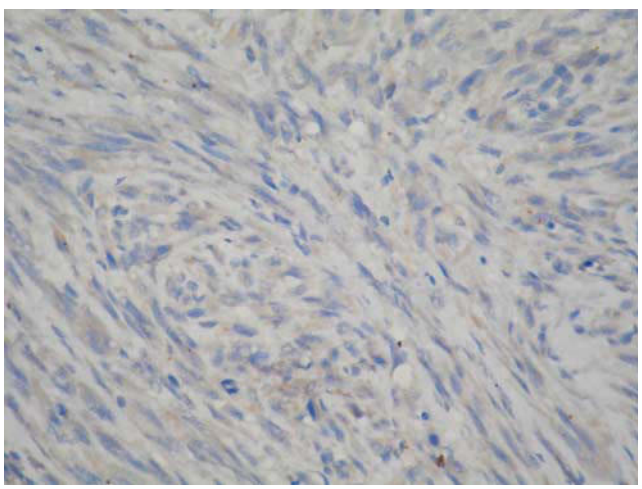
The origin of most MPNSTs of the nose, the paranasal sinuses and the anterior skull base is presumed to be the

ophthalmic and maxillary divisions of the trigeminal nerve and its terminal branches as well as autonomic ganglia, although identification of the nerve of origin is frequently impossible [18,24]. The olfactory nerve contains no Schwann's cells [23].

Clinically, MPNSTs generally present as a progressively enlarging painless mass [6,22,25]. As with any other paranasal sinus or anterior skull base neoplasms, MPNSTs in this anatomic region may become clinically apparent with unilateral nasal obstruction, hyposmia, epistaxis, atypical pain, hypoaesthesia or localized swelling of the facial and orbital region, mucopurulent rhinorrhoea and headache. Exophthalmus and impairment in the cranial nerve function may also develop [23,24].

The majority of MPNST arise either *de novo* or from pre-existing neurofibromas, with an estimated incidence of malignant transformation ranging from 3 to 30%.

Figure 11



Negative for smooth muscle actin.

Only very rare examples of MPNSTs arise in schwannoma, ganglioneuroma or phaeochromocytoma [1,6,26].

Despite advances in diagnostic techniques and ultrastructural analysis, controversies on the natural history of some of these uncommon neoplasms remain [9,22].

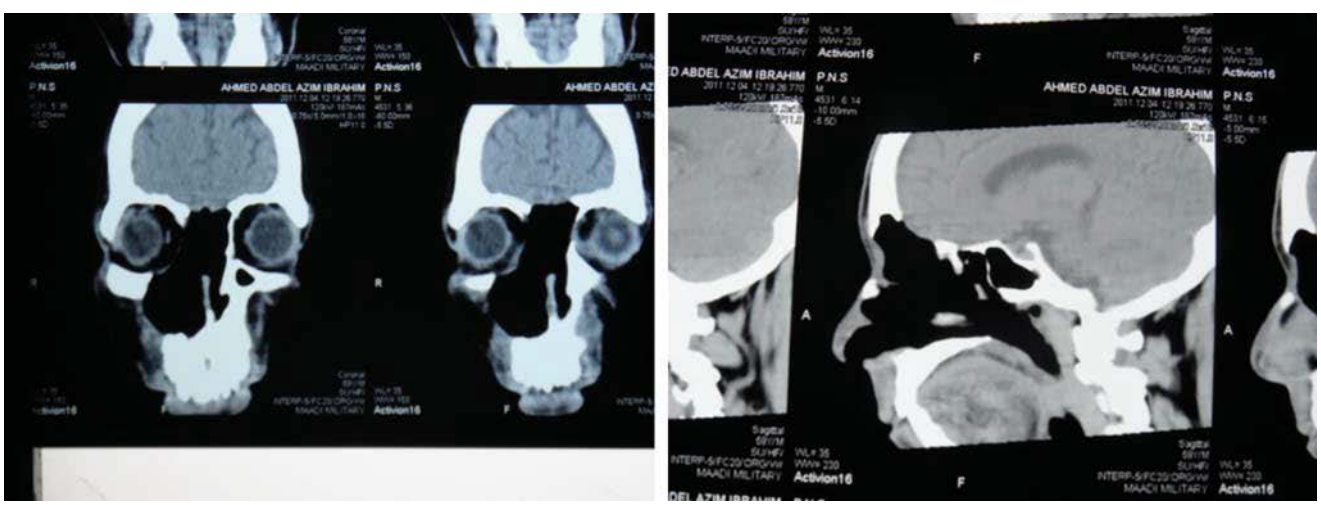
Therefore, the term MPNST is preferred, acknowledging the possibility that these tumours may be histologically diverse [1,7].

Microscopically, MPNSTs are highly cellular, focally polymorphic tumours of spindle cells arranged in bundles or fascicles with high mitotic rates, indistinct cytoplasmic borders and a variable degree of nuclear pleomorphism [24,26]. Heterologous elements are often observed in MPNSTs, such as epithelial, cartilaginous, bony, adipose tissue and rhabdomyoblasts (malignant triton tumour) [18,21].

MPNST can histologically resemble other malignant tumours, particularly malignant melanoma and other spindle cell sarcomas. Currently, especially immunohistochemical analysis but also the recognition of Schwann cells by electron microscopy aid the identification of MPNSTs. Immunohistochemically, the majority of MPNST express the neuroectodermal marker S-100 protein and the mesenchymal marker vimentin, whereas cytokeratin and desmin are rarely identified. Protein expression of the p53 tumour suppressor is frequently observed and has been shown to be a marker for tumour aggressiveness. Ki-67 (MIB-1) immunoreactivity is used to evaluate the tumour growth fraction, and ranges from 5 to 65% [6,12,18].

Despite these technical advances, MPNSTs tend to be under-recognized, both clinically and histologically, and the initial diagnosis is often missed [27]. Thus, any recurrent mass in the site of an excised neurofibroma or a rapidly expanding mass in a patient with neurofibromatosis or previous recipients of radiation to the symptomatic area should increase the suspicion of MPNST [14,22].

Figure 12



Postoperative computed tomography showing total clearance of the mass.

Management of MPNST has often been reported to be challenging, especially in the head and neck. Early tissue diagnosis is indispensable and should not be delayed, bearing in mind that obtaining a biopsy can be complicated by severe bleeding secondary to the extensive vascularization of these tumours [18,23].

Once the diagnosis is confirmed, wide surgical excision is the mainstay of treatment and prolongs survival [14,22]. In the head and neck, wide surgical excision implies en-bloc resection of the involved soft tissue, muscle and bone. Involved nerves should be followed proximally in an attempt to obtain clear margins [6,18]. As regional lymph node metastases are notably rare, prophylactic neck dissection is generally not recommended [20,26].

Local recurrence depends on radical resection and therefore on tumour location, and follows in up to 50% of cases, often on multiple occasions. Distant metastases appear in up to 80% of patients with MPNSTs and primarily develop in the lung [12,18].

The role of radiotherapy and chemotherapy in the treatment of this tumour is still controversial [20,24]. MPNST has traditionally been described as being highly radioresistant.

However, some recent reports recommend the use of postoperative radiotherapy, but there is no clear evidence of a definite benefit [15,16,21,24].

Despite aggressive multimodal therapy, the long-term prognosis for this lesion remains poor, with reported 5-year survival rates ranging between 30 and 65% [15,18]. According to the literature, patients with MPNST have some of the worst clinical outcomes. The most important prognostic factors affecting the survival of patients have been reported to be tumour size and location. High-grade and large MPNST seem to have particularly aggressive behaviour.

Many studies have reported reduced survival rates for those cases with MPNST complicated by NF-1, but some other reports do not reflect this [2,7,15]. Overall, prognostic factors have not been identified consistently in the literature as yet.

It has often been reported that the prognosis of MPNSTs of the head and neck is relatively poorer than that of MPNSTs of the extremities and the trunk, with documented 5-year survival rates ranging from 15 to 35% [2,15,26]. This difference was related mainly to a difference in local control.

Particularly for MPNSTs of the paranasal sinuses and the skull base, this observation is likely to be true, because these tumours have even closer proximity to vital structures, making local control by radical resection more critical. Because of the anatomical location, en-bloc resection is often impossible and fractional excision is common [2,15,23].

This case highlights the importance of an early diagnosis of MPNSTs, especially those in the head and neck region, because radical excision with free margins seems to be the best therapeutic option.

Conclusion

The literature review presented shows that despite advances in surgical techniques, the prognosis of MPNST located in the paranasal sinuses and the anterior skull base is still dismal, particularly in NF-1 patients.

However, when compared with other locations, MPNST of the paranasal sinuses and the skull base seems to be relatively uncommon in NF-1 patients and relatively often affects the non-NF-1 population.

The management of this aggressive neoplasm in this anatomical location remains an interdisciplinary challenge. Outcome is mainly a function of local control by means of surgical resection. Unlike some recent reports on MPNSTs located elsewhere, adjuvant radiotherapy and chemotherapy seem to have no benefit for MPNSTs of the paranasal sinuses and the anterior skull base.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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