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Nasal Epithelioid Malignant Peripheral Nerve Sheath Tumour: A Rare High-Grade Sinonasal Neoplasm and a Major Pathological Diagnostic Pitfall

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Abstract **Case Report**

Epithelioid malignant peripheral nerve sheath tumour (EMPNST) is an uncommon variant of MPNST defined by an epithelioid cytomorphology together with diffuse expression of S100 protein and SOX10. It is exceptional in the sinonasal tract, where its morphological and immunophenotypic resemblance to mucosal melanoma, a far commoner tumour at this site carrying the same neural-crest markers, makes it one of the genuine diagnostic traps of head and neck pathology. We report a 56-year-old man who presented with a recurrent nasal mass extending to the nasal floor, having been lost to follow-up before re-presenting with recurrence. The excision specimen showed a high-grade malignant proliferation of spindle and epithelioid cells arranged in short intersecting fascicles and sheets, with marked atypia, vesicular nuclei, prominent nucleoli, brisk mitotic activity and a Ki-67 index near 50%, without necrosis. The tumour expressed S100 with diffuse SOX10 positivity, whereas melanocytic markers (HMB45, Melan-A), cytokeratins, EMA, muscle markers (desmin, h-caldesmon) and neuroendocrine markers were all negative. The absence of melanocytic-marker expression, the fascicular–epithelioid architecture and the lack of any autonomous melanocytic proliferation favoured EMPNST. This case underlines that S100 and SOX10 positivity, however diffuse, cannot by itself separate EMPNST from melanoma, and that the diagnosis rests on integrated morphological, immunophenotypic and clinicopathological reasoning.

Keywords: Epithelioid malignant peripheral nerve sheath tumour; Nasal cavity; Mucosal melanoma; Immunohistochemistry; Case report.

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INTRODUCTION

Malignant peripheral nerve sheath tumour (MPNST) is a rare sarcoma showing nerve-sheath differentiation, and its epithelioid variant (EMPNST) is rarer still. EMPNST is defined by a predominantly epithelioid cytomorphology and, in contrast to conventional spindle-cell MPNST, by diffuse rather than focal S100 protein expression; in the largest series to date, comprising 63 cases, association with neurofibromatosis type 1 was infrequent, a minority of tumours arose in a pre-existing schwannoma, and loss of nuclear INI1/SMARCB1 was seen in only a subset of cases [1,2]. Occurrence in the sinonasal tract is exceptional, with only isolated reports involving the nasal cavity or the maxillary sinus.

The diagnostic problem is one of immunophenotypic convergence. S100 protein and SOX10 are sensitive markers of both Schwannian and melanocytic differentiation, because both lineages derive from the neural crest; neither is specific, and SOX10 in particular labels almost all melanomas as well as nerve-sheath tumours and even a proportion of myoepithelial neoplasms [3,4]. In the sinonasal region this overlap is clinically consequential, since mucosal melanoma is considerably more common than EMPNST at this site and shares the same S100/SOX10-positive profile. A diffusely SOX10-positive sinonasal malignancy therefore cannot be assigned to either category on that basis alone; the distinction turns on the presence or absence of melanocytic-marker expression, on

architecture, and on the demonstration of an autonomous melanocytic proliferation [5].

We report an exceptional case of EMPNST of the nasal cavity that closely simulated mucosal melanoma, and we use it to set out the morphological and immunohistochemical reasoning by which the two are separated. The report follows the CARE guideline for case reports.

Case Presentation

A 56-year-old man presented with a recurrent nasal mass extending to the nasal floor (Figure 1).

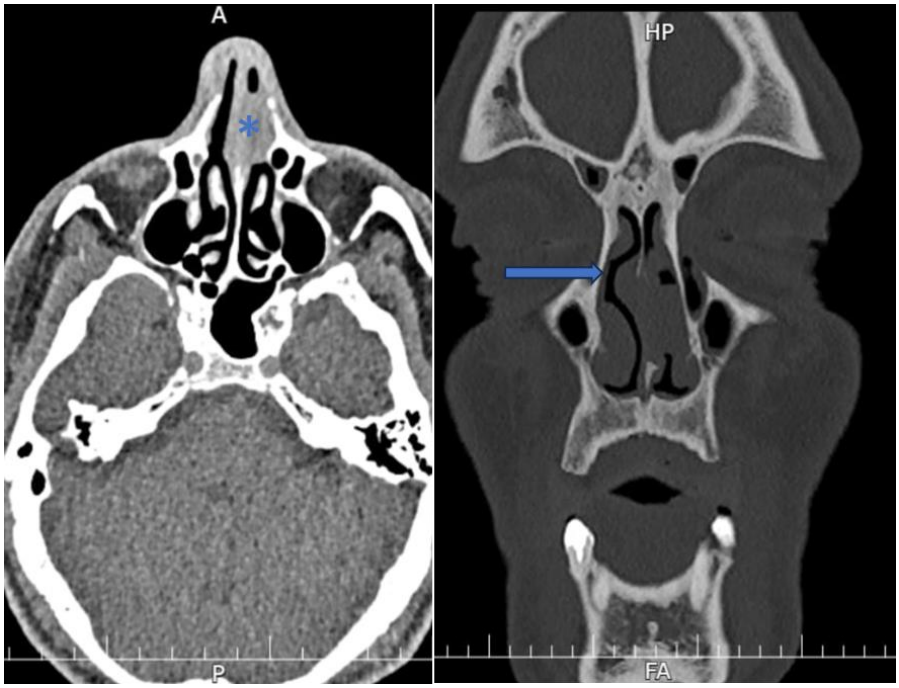


Figure 1: Computed tomography (CT) scan showing a polypoid neoplasm in the right nasal cavity (star), with deviation of the nasal septum (arrow)

The lesion had been managed initially elsewhere without definitive diagnosis, after which the patient was referred to the oncology department for further treatment but was lost to follow-up in March 2025. He re-presented to our institution in February 2026 with clinical evidence of tumour recurrence, and an excision specimen was submitted for histopathological examination.

On gross examination the specimen consisted of a firm, whitish, nodular mass measuring 2.5 × 2 × 1.5 cm.

Histological sections showed a malignant neoplasm composed of both spindle and epithelioid cells arranged in short intersecting fascicles and sheets (Figure 2). The tumour cells displayed marked cytological atypia, with vesicular nuclei, prominent nucleoli, and abundant eosinophilic to clear cytoplasm. Mitotic activity was high, estimated at approximately 12 mitoses per 10 high-power fields; tumour necrosis was absent.

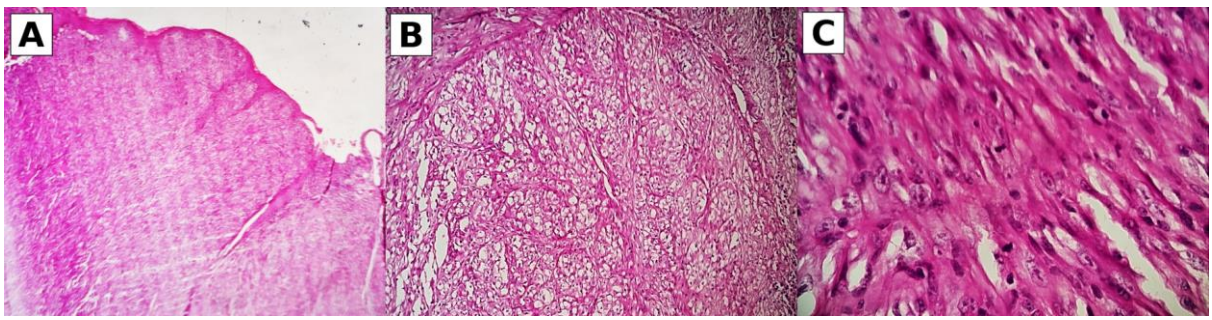


Figure 2: (A) Photomicrograph showing a high-grade submucosal malignant neoplasm composed of spindle and epithelioid cells arranged in short intersecting fascicles and sheets (haematoxylin–eosin, Gx10). (B) Fascicular–epithelioid architecture with cellular sheets and marked cytological atypia (haematoxylin–eosin, Gx20). (C) Vesicular nuclei with prominent nucleoli and brisk mitotic activity (approximately 12 mitoses per 10 high-power fields); no tumour necrosis (haematoxylin–eosin, Gx40)

Immunohistochemistry showed strong and diffuse expression of SOX10 (Figure 3) and expression of S100 protein. The tumour cells were negative for the melanocytic markers HMB45 and Melan-A. Epithelial

markers (cytokeratins, EMA), muscle markers (desmin, h-caldesmon) and neuroendocrine markers were all negative. The Ki-67 proliferation index was elevated, reaching approximately 50%.

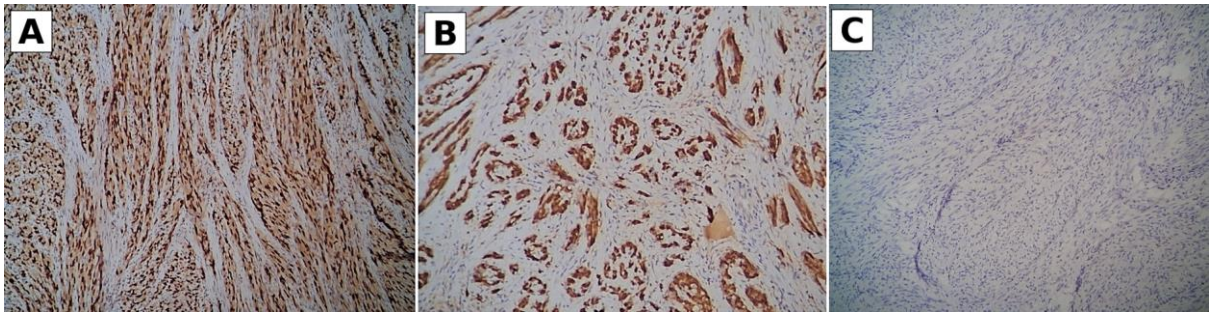


Figure 3: (A) SOX10 immunostain: Strong, diffuse nuclear positivity of the tumour cells. (B) S100 protein immunostain: Expression by the tumour cells, in keeping with neural differentiation. (C) Melanocytic markers (HMB45 / Melan-A): The tumour is negative, a key argument against mucosal melanoma

Based on these histological and phenotypic criteria, a diagnosis of EMPNST was established.

DISCUSSION

EMPNST falls within the spectrum of malignant peripheral nerve sheath tumours showing epithelioid differentiation and is typically marked by diffuse S100 and SOX10 expression, frequently though not invariably accompanied by loss of nuclear INI1/SMARCB1 [1]. The central difficulty illustrated by this case is that this immunoprofile is not specific. Because S100 and SOX10 reflect the neural-crest origin shared by Schwann cells and melanocytes, both markers are expressed by melanoma with very high sensitivity, and the distinction between EMPNST and melanoma cannot be made on the strength of S100 or SOX10 positivity, however diffuse [3]. In the sinonasal tract this is no academic point: mucosal melanoma is the commoner of the two and bears the identical neural-crest immunophenotype, so a diffusely SOX10-positive sinonasal malignancy demands that the question “nerve sheath or melanocyte?” be answered by other means.

In the present case the answer rested on three observations. First, the melanocytic markers HMB45 and Melan-A were negative, in contrast to the broad neural-crest markers; while melanomas may occasionally be amelanotic and show reduced HMB45, the complete absence of melanocytic differentiation markers in a tumour that is otherwise strongly SOX10-positive shifts the balance away from melanoma. Second, the architecture was fascicular and epithelioid, in keeping with a nerve-sheath neoplasm rather than the sheet-like or nested growth of mucosal melanoma. Third, and decisively, there was no autonomous melanocytic proliferation (no junctional component, no in situ melanocytic atypia of the overlying mucosa) that would anchor a diagnosis of primary mucosal melanoma. Taken together, these features favoured EMPNST [1,5].

Myoepithelial carcinoma deserved explicit consideration, the more so because SOX10 also labels a proportion of myoepithelial neoplasms [4]. Here the negativity of EMA and of epithelial markers, together with the overall neural immunophenotype, made that diagnosis unlikely. The negative muscle markers (desmin, h-caldesmon) and the absence of neuroendocrine expression similarly excluded the rhabdomyosarcomatous and neuroendocrine differentials that arise in the sinonasal region, and the negative cytokeratins argued against the SMARCB1-deficient sinonasal carcinoma that can enter this differential when rhabdoid cytomorphology is present. Sinonasal MPNST as a whole remains exceptionally rare and is generally diagnosed only after a broad immunohistochemical panel has excluded the commoner carcinomas, melanomas and other sarcomas of the region [6].

Loss of INI1/SMARCB1 is a supportive finding when present but is neither sensitive nor required: nuclear expression is lost in roughly 50% to 80% of epithelioid MPNST according to the series considered: 12 of 24 tumours (50%) in the first systematic survey, 35 of 52 (67%) in the largest historical series, and 81% in a recent cohort of 78 primary tumours [1,7,8]. Retained INI1 expression therefore does not exclude the diagnosis. Loss of H3K27 trimethylation, by contrast, is a marker of conventional MPNST and helps to separate it from histological mimics [9], but it is of little assistance in the epithelioid variant: complete loss is found in approximately 53% of high-grade MPNST overall (95% CI 42–64%), yet its pooled incidence in the epithelioid subtype is 0% (95% CI 0–7%), every epithelioid tumour reported so far having retained nuclear labelling [10,11]. Retained H3K27me3 associated with loss of SMARCB1 is therefore the expected profile of EMPNST rather than an argument against it [8,11].

In the present case neither INI1/SMARCB1 nor H3K27me3 immunostaining was performed; the diagnosis accordingly rests on morphology and a conventional immunohistochemical panel. While the absence of ancillary studies reflects a real constraint, it does not invalidate the diagnosis, which the morphological and immunophenotypic profile supports

on its own terms. SMARCB1/INI1 immunostaining, whose loss would have provided direct positive support for the epithelioid variant, together with molecular characterization where available, would nonetheless have strengthened the case, and both are recommended whenever the platform is accessible [1,8].

Several practical lessons follow. A diffusely S100/SOX10-positive sinonasal malignancy should not be equated with melanoma by reflex; the melanocytic markers must be assessed and weighed against architecture and the search for an autonomous melanocytic component [3]. The immunohistochemical panel should be constructed to interrogate the principal differentials in parallel (neural, melanocytic, epithelial, myoepithelial, myogenic and neuroendocrine) rather than to confirm a single favoured diagnosis. Where the morphology is epithelioid and the lineage uncertain, SMARCB1/INI1 immunostaining and referral for expert or molecular assessment should be pursued. Above all, this case is a reminder that in rare high-grade sinonasal neoplasms morphology retains its primacy and that no single marker substitutes for integrated clinicopathological reasoning [1].

MPNST is an aggressive sarcoma and the head and neck constitute an unfavourable site: in a registry series of 374 head and neck MPNST, 5-year overall and disease-specific survival were 51% and 67% respectively, tumour size and stage at presentation being the main adverse determinants, while smaller institutional series of skull-base and sinonasal tumours report considerably poorer figures, with 2-year and 5-year disease-specific survival of 50% and 20% [12,13]. Complete resection with negative margins remains the cornerstone of treatment and the strongest modifiable prognostic factor; adjuvant radiotherapy is generally added to improve local control, particularly for large, high-grade or incompletely excised tumours, whereas conventional chemotherapy has a limited impact on survival [12,13]. Whether the epithelioid variant behaves differently remains unsettled: a recent series of 78 primary EMPNST reported a longer median progression-free survival than conventional MPNST (34 versus 19 months), although the difference did not reach statistical significance [8]. In the present case the interrupted clinical course and the recurrent presentation preclude any inference on outcome.

Conclusion

Epithelioid MPNST of the nasal cavity is an exceptional and high-grade neoplasm whose diffuse S100 and SOX10 expression places it in direct diagnostic competition with the far commoner sinonasal mucosal melanoma. This case adds to the very limited literature on sinonasal EMPNST and reiterates the diagnostic value of morphology in rare head and neck sarcomas.

We demonstrated that neural-crest marker positivity, however diffuse, is uninformative for the distinction between these two tumours, and that the diagnosis depends on the disciplined integration of architecture, the absence of melanocytic-marker expression and of an autonomous melanocytic proliferation, and the exclusion of epithelial, myoepithelial, myogenic and neuroendocrine differentials. EMPNST should be kept firmly in the differential diagnosis of S100/SOX10-positive sinonasal malignant neoplasms.

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Ethical Approval: Ethical approval is not required at our institution to publish an anonymous case report.

Competing Interests:
The authors declare that they have no competing interests.

Data availability: The data supporting this case report are available from the corresponding author on reasonable request.

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