# Primary sinonasal neuroendocrine carcinoma invading the orbit

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## Abstract

Primary sinonasal neuroendocrine carcinoma (SNEC) is a rare aggressive sinonasal malignancy which typically occurs in the ethmoidal or maxillary sinuses, with or without nasal cavity involvement, of middle-aged patients (median age 53 years), with a slight male preponderance. No risk factors have been identified. Most patients present at advanced stages due to the lack of significant symptoms.[1,4,5,8] Advanced tumours may invade the skull, orbit or brain. Staging is of limited value in predicting prognosis and recent literature clearly highlights the importance of histological diagnosis, particularly differentiation grade, in determining the prognosis and predicting treatment response. Nomenclature has been ambiguous, but broadly SNECs can be classified as well-, moderately- or poorly differentiated. The latter group includes sinonasal undifferentiated carcinoma and sinonasal small cell carcinoma. On histological examination, well-to-moderately differentiated tumours show medium-sized cells with large nuclei containing stippled or 'salt/pepper' chromatin and scant cytoplasm. Nuclear moulding, increased mitoses and apoptotic bodies are commonly seen. Immunohistochemistry reveals expression of neuroendocrine markers.[1,4–7] Poorly-differentiated tumours may lose expression of neuroendocrine markers and differentiation from other poorly differentiated malignancies can be extremely difficult.[1,4–7] Due to the limited number of reported cases, there is no clear consensus on management, although oncologists now advocate multimodal therapy. Combined surgery and radiotherapy is thought to beneficial in moderately and poorly-differentiated subtypes.[1,4–8] We describe a classical case of SNEC with secondary orbital involvement, with a review of the current literature.

**Keywords** Ethmoid; orbital metastases; orbital tumours; sinonasal neuroendocrine carcinoma

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## Case report

A 62-year-old female patient was referred for rapid growth of a left peri-orbital soft tissue lesion with proptosis. Her past medical history included hypertension, hyperlipidaemia and bipolar disorder, all of which were controlled by medication. She had never smoked.

On examination, vision in the affected eye was hand movements and in the right eye was 6/9 aided. There was a palpable mass left peri-orbital mass, marked anterolateral proptosis (Figure 1) and a fixed globe with no extraocular movements.

An MRI scan of the head and orbits with contrast (Figure 2) showed a left orbital tumour (white arrows) measuring 7 × 5.4 × 6 cm displacing the globe anterolaterally and extending to the paranasal sinuses, left nasal cavity with bifrontal extradural extension.

A left lateral canthotomy with upper and lower lid cantholysis was performed and an incisional biopsy of the lesion was sent for ophthalmic pathology assessment.

Macroscopic examination showed a gelatinous pale mass measuring 12 × 8 × 6 mm.

Histological examination revealed extensive infiltration of lesional tissue with medium-sized cells with a high nuclear:cytoplasmic ratio, stippled chromatin and scant cytoplasm. There were numerous mitoses and apoptotic bodies (Figure 3).

The neoplastic cells demonstrated strong positive staining for CD56 and synaptophysin, 'dot-like' cytokeratin positivity and a very high Ki67 growth fraction (~85%) (Figure 4). Lymphoma markers were all negative. The morphological and immunohistochemical features were consistent with a neuroendocrine carcinoma – possibly metastatic to the orbit.

Full systemic investigations were undertaken, including CT scanning of the neck, thorax, abdomen and pelvis, to locate the primary tumour, the extent of disease and staging. The patient was referred to oncology and to the neuro-oncology MDT for discussion. CT scan revealed possible submandibular lymph node and T9 vertebral metastases but no other primary lesion – in particular, no lesions were found within the bronchopulmonary or gastrointestinal tracts. Furthermore, there was no evidence of liver metastases. It was concluded that the tumour most likely originated in the ethmoid sinus and represented a primary sinonasal neuroendocrine carcinoma which had locally invaded the orbit. The patient is currently receiving chemotherapy.

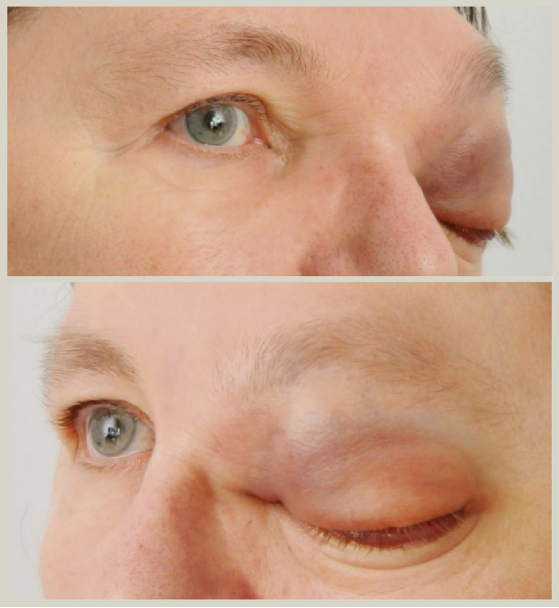

**Figure 1** Clinical photographs showing a left peri-orbital mass with marked anterolateral proptosis.

## Discussion

Primary sinonasal neuroendocrine carcinomas (SNECs) are rare and account for 3–5% of all sinonasal malignancies, with squamous cell carcinoma being the most common. It was first recognized as an entity by Silva et al. in 1982 and further described by Mills et al. in 2002 but the nomenclature in the literature remains ambiguous.[1–3]

SNECs are categorized by their differentiation grade into well-, moderately- and poorly differentiated. The latter group is further subdivided into small and large cell neuroendocrine carcinoma. Poorly differentiated large cell SNEC are in fact classified as 'sinonasal undifferentiated carcinoma' (SNUC) whereas poorly differentiated small cell SNEC is referred to as 'sinonasal small cell carcinoma'. Importantly, differentiation grade determines prognosis rather than TNM staging.[1] Well-to-moderately differentiated neuroendocrine carcinomas are associated with lower metastatic rates and better survival (5-year disease-specific survival ~70%) compared to the rarer poorly differentiated neuroendocrine carcinomas (5-year ~40%). The latter are rapidly growing, aggressive tumours with high propensity for recurrence and widespread dissemination. Poorly differentiated SNEC may lose their immunohistochemical

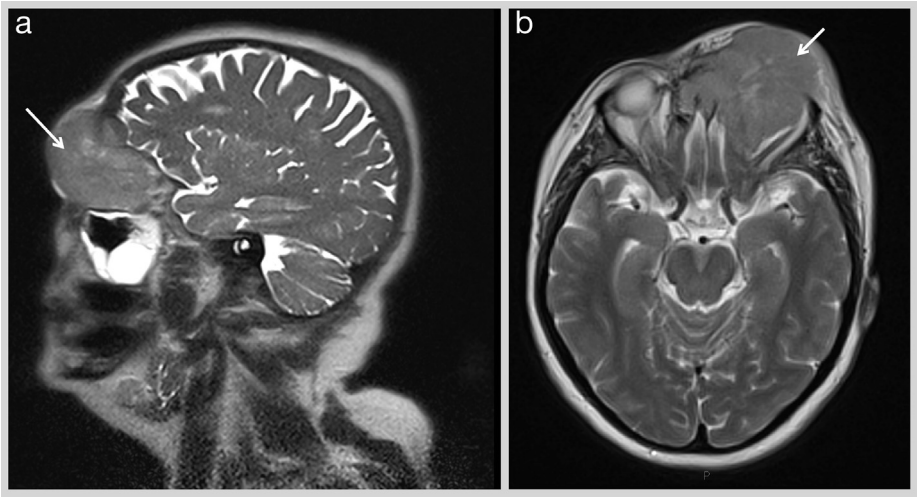


**Figure 2 (a)** Sagittal view and **(b)** axial view of MRI head and orbits with contrast demonstrating the left orbital tumour (white arrows) displacing the globe anterolaterally and extending to the paranasal sinuses and left nasal cavity.

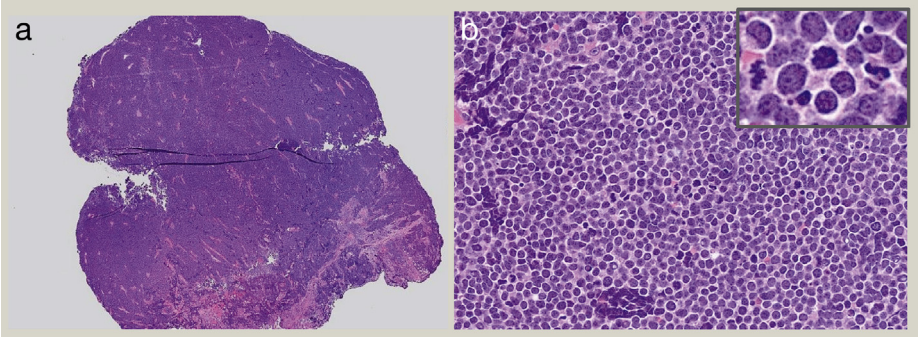


**Figure 3 (a & b)** Lesional tissue showing extensive infiltration with medium-sized cells with a high nuclear:cytoplasmic ratio, stippled chromatin and scant cytoplasm. **(b)** There are numerous mitoses and apoptotic bodies. (H&E; various magnifications).

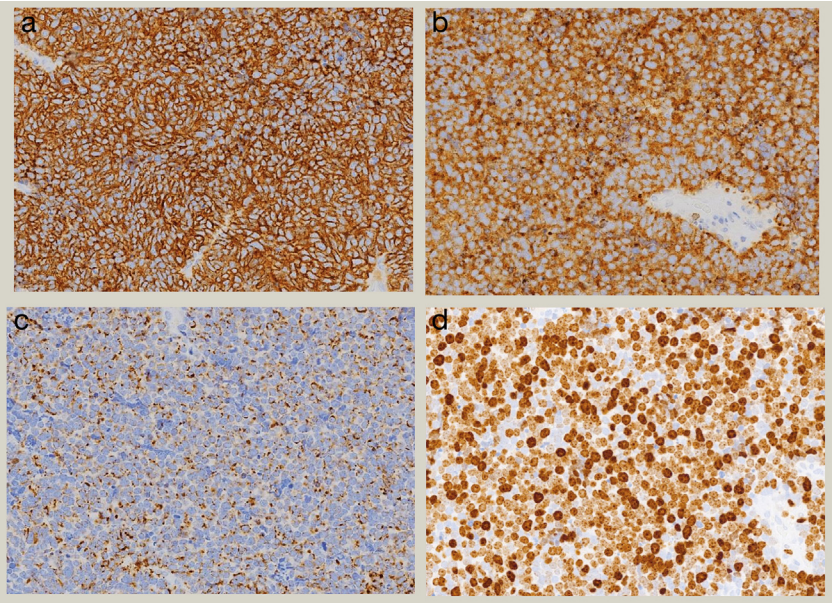


**Figure 4** Immunohistochemistry demonstrating the neoplastic cells expressing: **(a)** CD56, **(b)** synaptophysin, **(c)** AE1/3 'dot-like' positivity and **(d)** demonstrating a very high Ki67growth fraction.

expression of neuroendocrine markers (synaptophysin, CD56, neurofilament protein and chromogranin) and hence differentiation from other poorly differentiated epithelial and non-epithelial sinonasal malignancies, including metastases, is often extremely difficult, but paramount for further management. This may require a further comprehensive immunohistochemical panel.[1,4–7]

Unfortunately, most sinonasal malignancies present at an advanced stage due to the lack of any alarming symptoms. This reduces the importance of TNM staging in determining treatment and prognosis. They most commonly affect patients in their fifties, with a slight male gender predilection. No risk factors have been identified. SNECs typically arise in the nasal cavity and extend into the adjacent sinuses (ethmoid and maxillary) although primary involvement of the sinuses without nasal extension is also known to occur in ~45% of cases. Symptoms include nasal obstruction, epistaxis, headache, facial mass and/or facial pain. Advanced tumours may invade the skull base, orbit or brain. Ophthalmic manifestations, as in this case, include exophthalmos, reduced vision and restriction in ocular motility.[1,4,6–8] Ectopic hormone secretion has been described in a handful of cases.[1]

There are no clear treatment guidelines and the previous literature has been inconsistent in this regard. Previous management has included surgery with radiotherapy with/without chemotherapy; chemoradiotherapy; or radiotherapy or chemotherapy alone. Several authors, however, have advocated multimodal therapy with combined surgery and radiotherapy being especially beneficial in SNUCs. Well-differentiated subtypes may require a less aggressive treatment approach than their moderately-or poorly-differentiated counterparts.[1,4–8] ◆

## Practice points

- Primary sinonasal neuroendocrine carcinoma is a rare, aggressive sinonasal malignancy which typically occurs in the ethmoidal or maxillary sinuses, with/without nasal cavity involvement.
- No risk factors been reported.
- Classification is confusing but they can broadly be categorized as: well; moderately or poorly differentiated. The latter includes sinonasal undifferentiated carcinoma and sinonasal small cell carcinoma.
- Histopathological diagnosis and differentiation grade is paramount in determining prognosis and treatment planning.
- There are no clear management guidelines but a multimodal treatment approach is recommended.

## Self-assessment questions

**1. What risk factor is most strongly associated with primary sinonasal neuroendocrine carcinoma (SNEC)?**

**A. Smoking**
**B. Epstein Barr virus**
**C. Human papilloma virus**
**D. Radiation**
**E. None of the above**

**Answer: E**

**2. Which of the following is the most important prognostic indicator in SNECs?**

**A. Necrosis**
**B. Tumour size**
**C. Differentiation grade**
**D. Tumour staging**
**E. Recurrence**

**Answer: C**

**3. Sinonasal undifferentiated carcinoma will always immunohistochemically express which of the following?**

**A. Synaptophysin**
**B. S100 protein**
**C. Ki67**
**D. EMA**
**E. Chromogranin**

**Answer: C**

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