Metastatic neuroendocrine tumour of the orbit

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Abstract

A 64-year-old patient presented with a tumour of the orbit. A biopsy showed an infiltrative tumour with coarse "salt-and-pepper" chromatin, showing strong expression of AE1/3, CD56, synaptophysin, chromogranin, and CDX2 on immunohistochemistry. The Ki67 proliferation index was low (<1%). The diagnosis of metastatic neuroendocrine tumour, most likely of gastrointestinal origin was favoured over a primary neuroendocrine tumour of the orbit.

Keywords Head and neck pathology; immunohistochemistry; neuroendocrine tumour; ocular pathology; orbital tumour

Case report

A 64-year-old lady presented with right eye pain and ocular restriction. No significant abnormalities were detected on baseline blood tests including thyroid function, auto-antibodies, and CRP. CT and MRI scans revealed enlargement of the lateral rectus muscle. The favoured clinical diagnosis was of an atypical presentation of an orbital myositis. A degree of symptomatic improvement was achieved with oral steroids, although progressive enlargement of the lateral rectus was noted on a repeat MRI 6 months later, prompting a biopsy to exclude a neoplastic cause.

The biopsy showed fibrous connective tissue and skeletal muscle focally infiltrated by a malignant neoplasm predominantly composed of irregular islands and cords of cells with round, relatively monomorphic nuclei and granular chromatin forming flat honeycomb-like clusters. Scattered irregular, ill-defined nests of pleomorphic cells with hyperchromatic nuclei were also noted. The cells contained variable amounts of eosinophilic cytoplasm. No definite small cell component was identified. Mitotic activity was low (around 1 mitosis per 10 high-power fields) (Figures 1 and 2).

On immunohistochemistry the neoplastic cells diffusely and strongly expressed AE1/3, CD56, synaptophysin (Figure 3) and chromogranin A. They were negative for CK5, p40, S100, HMB45, SMA and desmin. No definite sustentacular network was identified with S100. The Ki-67 proliferation index was less than 5% (Figure 4). Further immunohistochemistry showed the cells to have nuclear positivity for CDX2 (Figure 5). They were negative for CK7, CK20 and TTF-1.

The morphological features and immunoprofile were in keeping with infiltration by a metastatic neuroendocrine tumour, favoured to represent the low grade or well differentiated end of the spectrum. The expression of CDX2 raised the possibility of the gastro-intestinal tract as a primary source of origin. Negative expression of TTF-1 suggested that an origin from the lung was less likely.

CT and PET-CT scans showed no obvious lesions in the colon, distal small bowel, or elsewhere in the abdomen and pelvis. The PET CT did identify a slightly enlarged ileocolic lymph node, and the report suggested a dedicated somatostatin receptor scan (68-Gallium Dotatate PET CT) to rule out a low grade small bowel neuroendocrine tumour.

Discussion and conclusion

The literature contains numerous reports of neuroendocrine tumours of the orbit, and suggests that while can rarely represent primary orbital disease, they more often represent metastasis, most commonly from the gastro-intestinal tract or lung.[1]

At the point of presentation, the patient's primary may not have been discovered, so patients diagnosed without prior diagnosis of a neuroendocrine tumour should be investigated for a primary site.[2]

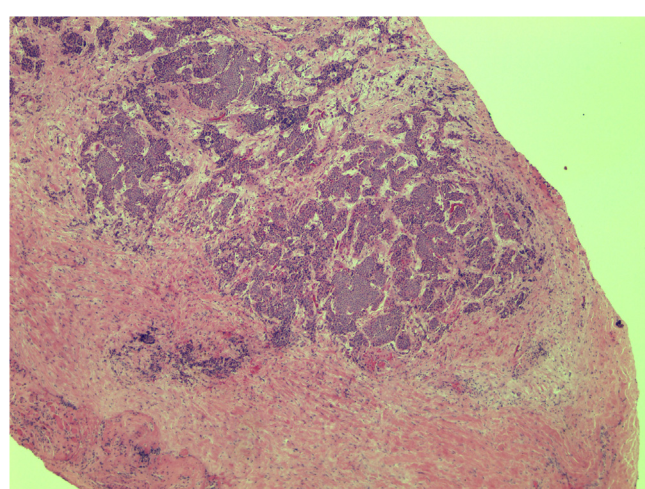

Figure 1 This orbital biopsy is infiltrated by a neoplasm predominantly composed of irregular islands and cords of cells. Haematoxylin & eosin, low power.

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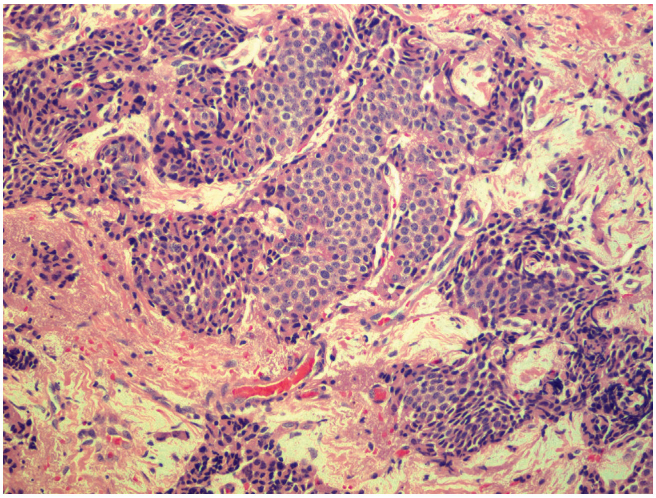

Figure 2 This higher power image demonstrates cells with round nuclei with salt-and-pepper chromatin, as well as other cells with more irregular and hyperchromatic nuclei. Haematoxylin & eosin, higher power.

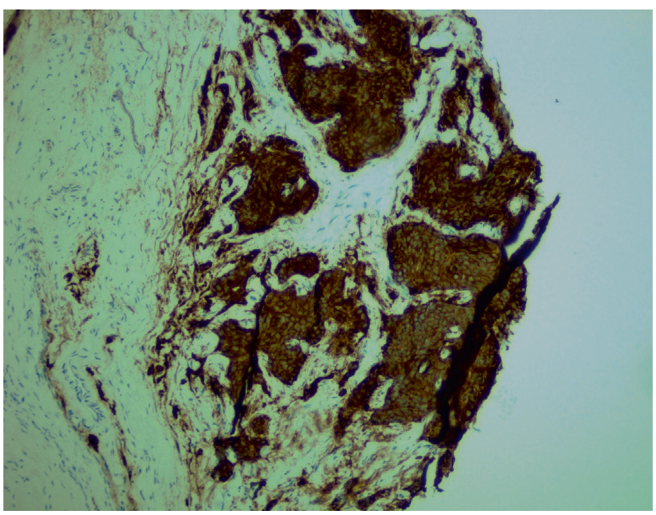

Figure 3 All of the infiltrating cells show strong and diffuse cytoplasmic positivity for synaptophysin, suggesting a possible neuroendocrine differentiation. Synaptophysin immunohistochemistry.

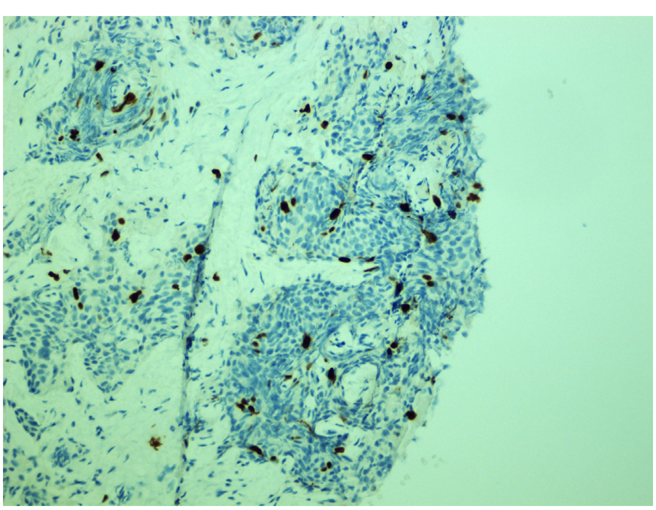

Figure 4 Ki67 immunohistochemistry shows a proliferative index of less than 5%.

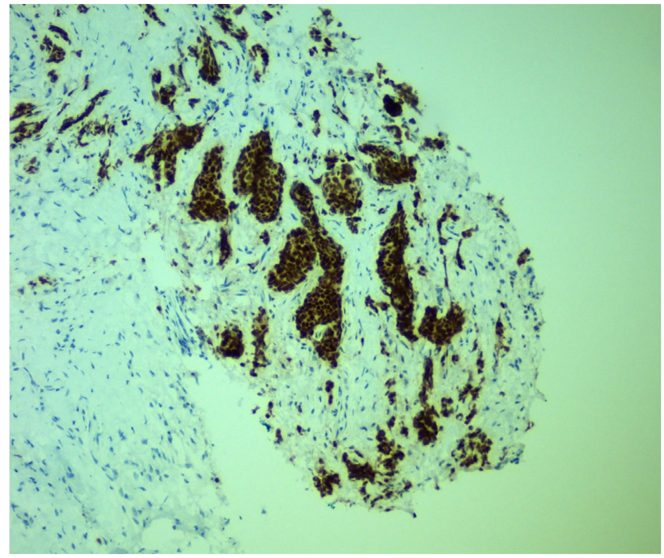

Figure 5 The neoplasm shows nuclear CDX2 positivity, indicating a possible gastrointestinal origin. CDX2 immunohistochemistry.

Several other tumours are reported to metastasise to the orbit, the commonest of which include breast carcinoma, renal cell carcinoma, lung carcinoma, and melanoma.[3] They most often presented with symptoms of visual disturbance and proptosis.

Low grade neuroendocrine tumours of the gastrointestinal tract are graded 1–3, based on mitotic activity, with a higher grade generally indicating a more aggressive behaviour. However, low histological grade is not a guarantee of benign behaviour.[4] Neuroendocrine carcinoma is diagnosed in the presence of poorly differentiated histology, of either small or large cell variety, and generally has a Ki67 proliferative index of over 20%. The well differentiated areas of this neoplasm would correspond to a grade 2 neuroendocrine tumour, according to the 2019 WHO grading system for low grade gastrointestinal neuroendocrine tumours (Ki67 proliferative index 5–20%).[5]

Paragangliomas have also been reported in the orbit.[6] These demonstrate an organoid (Zenballen) growth pattern associated with a surrounding S100 positive sustentacular cell network and are typically negative for cytokeratins. Depending on the location, other entities entering the differential diagnosis for neuroendocrine neoplasms involving the orbit would include olfactory neuroblastoma, sinonasal neuroendocrine carcinoma and other high grade carcinomas that can show a degree of neuroendocrine differentiation. ◆

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Practice points

- Neuroendocrine tumours can occur anywhere in the body – it is important to keep them in mind for any basaloid tumour, even in an unfamiliar location
- Salt-and-pepper chromatin is a helpful feature – don't forget to examine nuclei at high power
- Neuroendocrine tumours most commonly originate in the GI tract or lung – MDT discussion with clinical and radiological correlation is useful to ascertain the most likely primary source of origin
- Immunohistochemistry can be useful in the characterisation of these tumours:
  - Site-specific markers can help identify likely sources of origin e.g. CK7, CK20 and CDX2 (gastrointestinal tract), TTF-1 and napsin A (lung) etc
  - Cytokeratins and S100 can be used to differentiate neuroendocrine tumours from paragangliomas and olfactory neuroblastomas. These can show focal, rather than diffuse, cytokeratin expression and variable presence of sustentacular cells

Self assessment multiple choice questions

1. Which immunohistochemical marker is most useful to distinguish a neuroendocrine tumour from a paraganglioma?

a. Synaptophysin
b. Ki67
c. CD56
d. Chromogranin
e. Pancytokeratin

Correct answer: 1e

2. What are the two most common primary sites for metastatic neuroendocrine tumour?

a. GI
b. Skin
c. Lung
d. Adrenal
e. Liver

Correct answer: 2a/c

3. What is the best scanning modality to detect low grade GI neuroendocrine tumours?

a. CT
b. PET-CT
c. MRI
d. Somatostatin receptor scan (68-Gallium DOTATATE PET CT)
e. Ultrasound

Correct answer: 3d

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