PostScript

LETTERS TO THE EDITOR

Ganglioneuromatous hamartoma of the tongue

Ganglioneuroma is a rare tumour of autonomic ganglia arising in the sympathetic chain or the parasympathetic nervous system.¹ So far, no authentic solitary lesion has been recorded in the tongue.

A 30-year-old man presented with an asymptomatic submucosal mass in the right lateral border of the tongue, measuring 1.3 cm in diameter (fig 1A). The lesion was present since birth and had not changed in size recently. Neither the patient nor his family members had any relevant systemic disease. No recurrence has been noted 5 years after simple excision. Histologically, the tumour was composed of an encapsulated proliferation of myxoid neurofibromatous tissue. Mature ganglion cells varying in size, were randomly distributed, singly and in nests, throughout the loose fascicles of wavy neural cells. These cells were more prominent at the periphery (fig 1B). Occasionally, they contained vacuoles and Nissl substance, most of which were surrounded by satellite cells (fig 1C). Binucleate cells were present focally (fig 1D). No immature neuroblastic cells were observed. Ganglion cells showed diffuse immunostaining for neurone-specific enolase (fig 1E) and CD56, with variable reactivity for neurofilament protein (fig 1F) and chromogranin A (fig 1G). S-100 protein, glial fibrillar acidic protein and CD57 highlighted the schwannian element, but not ganglion cells (fig 1H).

A search through published accounts uncovered only a single convincing example of primary ganglioneuroma of the oral mucosa; this lesion arose in the upper lip of a 3-year-old boy.² It is well recognised that diffuse ganglioneuromatosis of the gastrointestinal tract, including the oral cavity, may occur in case of an inherited disease, multiple

endocrine neoplasia type IIb, neurofibromatosis type I and Cowden's disease.¹ None of these diseases were evident in this patient.

The difficulty in confirming the diagnosis results from the fact that autonomic ganglia are normal constituents in the tongue.^{4,5} As the lateral aspect is often subjected to trauma, a reactive origin as a traumatic neuroma, with the involvement of ganglion cells in the vicinity, namely pseudoganglioneuroma, has been postulated.³ Similarly, pre-existing ganglia entrapped by solitary neurofibroma must be excluded.¹ The key differentiating features rely on the definite capsule and the random distribution and multinucleation of ganglion cells in true ganglioneuroma, as seen in this tumour. Ganglioneuromatous maturation in neuroblastoma can readily be distinguished by the lack of immature elements.

The microscopic finding of an occasional tortuous neural structure, with many ganglion cells, has been reported in the tongue, and is designated as "subepithelial nerve plexus"⁴ or "subgemmal neurogenous plaques".⁵ This anatomical variation, when hypertrophic, may mimic neural tumours, but has received less attention. It is a small (<3.5 mm), non-encapsulated rectangular mass, exclusively juxtaposed with the epithelial undersurface of foliate papillae. Unlike in the lesion we describe, naturally existing ganglion cells in each structure are very few in number (<5) and are arranged singly. Given that the tumour was congenital and stable for 30 years, the primary lingual ganglioneuroma described probably represents a hamartomatous process of such aggregates.

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Figure 1 (A) Submucosal mass of the lateral tongue. (B) Well-encapsulated neurofibromatous tumour with numerous ganglion cells. (C) Cytoplasmic vacuole. (D) Binucleate cell. Ganglion cells are highlighted on immunostains for neurone specific enolase (E), neurofilament protein (F) and chromogranin A (G), but not for S-100 protein (H).

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Neither inadequacy of biopsy nor inaccuracy of reporting predict non-response to small-cell carcinoma chemotherapy

Lung cancer is the second most common cancer in the UK, accounting for one in seven new cancer diagnoses and 22% of cancer deaths (<http://info.cancerresearchuk.org/cancerstats>). Small-cell carcinoma (SCC) accounts for 20% of lung cancers, with most of these presenting at an advanced stage and being treated using chemotherapy and radiotherapy. About 25% of patients do not respond to chemotherapy. The reasons for this are uncertain and may be because of the heterogeneity of the disease or inaccurate pathological diagnosis, which may partly be related to adequacy of the specimen. A recent study of histological typing of lung tumours showed that a high level of agreement existed between observers for SCC, but that across all the specimens they reviewed, misclassification was higher for smaller specimens than resections.¹ We conducted a review of cases of SCC referred to the Edinburgh Cancer Centre, UK, to determine whether non-response to chemotherapy in our series was related to misclassification of the tumour on diagnostic biopsy.

Biopsy specimens from 76 patients who had received chemotherapy were reviewed by three or, in some cases, four pathologists (TND, HM, DMS and WAW). All the specimens were assessed for adequacy of biopsy and confirmation of diagnosis of SCC. Disagreement between reviewers was settled by conference. In 70 cases, we believed that the biopsy was adequate and we could confirm the diagnosis of SCC. We identified six cases in which we were unable to confirm the diagnosis of SCC. Two cases of biopsy were judged to be inadequate, one a bone marrow trephine and one a liver fine-needle aspiration. Adequacy of biopsy was not related to size because a relatively large biopsy contained few assessable cells, reflecting errors in targeting. In two cases we were unable to confirm the diagnosis and in two we were unable to reach a consensus opinion. The survival data from these six patients in whom we did not confirm the diagnosis did not differ considerably from those in whom we could confirm the diagnosis. (Median survival interquartile range for the six unconfirmed cases was 278 (130-344) days as against 371 (210-519) days for the 70 confirmed cases.)

Of the 76 cases, 7 cases were classified as non-responders to chemotherapy. In all seven cases, we confirmed the diagnosis of SCC on biopsy review.

In this small series, non-response to chemotherapy did not seem to be related to misclassification of SCC on biopsy.

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Small-cell neuroendocrine carcinoma of the breast

We read the recent report of three cases of small-cell neuroendocrine carcinoma (SCNC) of the breast with interest.¹ We do agree with the authors that the vexing question of whether this is a primary breast neoplasm or a secondary deposit from other sites, most commonly from the bronchus, has to be considered. We would like to share our experience with two cases that we dealt with in the Department of Histopathology, East Lancashire Hospitals NHS Trust, Burnley, UK, and, in particular, the application of two more immunological markers, neuronal adhesion molecule (CD56) and thyroid transcription factor 1 (TTF1) to those already used by the authors. One of the patients was an elderly woman with a large mass in the breast. Histologically, the mass was a SCNC, with positive immunohistochemistry for CD56 and TTF1. No in situ component was observed. Clinical and imaging studies showed that this was a metastasis from a primary lung tumour. The second patient was a middle aged woman who presented with a breast mass of 5 cm. A core biopsy specimen showed SCNC, again positive for CD56 and TTF1. Clinical and imaging studies showed

Figure 1 In situ carcinoma showing positive staining for thyroid transcription factor 1.

that this was an isolated lesion in the breast, and it was therefore diagnosed as a primary breast tumour. After neoadjuvant chemotherapy, a mastectomy was performed. It showed a 3 cm tumour composed predominantly of SCNC, but with a central focus of invasive grade III carcinoma of no specific test, which was negative for CD56 and TTF1. Interestingly, the in situ component was of SCNC type, showing positive staining for CD56 and TTF1 (fig 1). We re-emphasise that TTF1 cannot be used to discriminate between a primary breast SCNC and a secondary deposit from a primary in the bronchus, as extrapulmonary SCNC can often be positive for TTF1.^{2,3}

In summary, we recommend the addition of CD56 to the other immunological markers for SCNC and advise caution in interpreting TTF1 immunoreactivity in extrapulmonary SCNC.

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The benefits of elastica – no stretch of the imagination

Venous invasion is a well-established prognostic factor in colorectal cancer and is an independent prognostic indicator of visceral metastases and decreased survival time.¹⁻⁴ Unfortunately, the use of only conventional haematoxylin and eosin staining to determine the incidence of venous invasion has yielded a wide range of results (10-90%).¹⁻⁶ In the July 2004 publication of the *Journal of Clinical Pathology*, Vass *et al*⁷ showed that using an elastica stain considerably increased the sensitivity of identifying venous invasion in colorectal cancer. Their study was carried out in a university teaching hospital by a specialist in colorectal pathology, as opposed to the original reports, which were made by a large team of non-specialists. The aim of our study was to determine whether using this technique had a similar benefit in the district general hospital setting with non-specialist reporting.

Methods

From our local database of colorectal audit forms, we identified 100 colorectal tumour resections, during the period 12 October 2003 to 31 December 2004, reported as having no evidence of extramural vascular invasion. A single section was cut from tumour blocks (three per case), stained with elastica and counterstained with haematoxylin and eosin. A trainee pathologist (GS) and a consultant pathologist (AR) assessed the presence of

Figure 1 Incidence of vascular invasion shown by staining with elastica haematoxylin and eosin.

Figure 2 Extramural venous invasion. An artery (top left) is shown, with the adjacent vein (bottom right) containing tumour. Elastica staining highlights the elastic fibres of both the artery and the vein.

Figure 3 Intramural venous invasion. Elastica stain highlights a vein (10 o'clock of centre) containing tumour. As this vein is embedded in the tumour, it is difficult to identify by conventional haematoxylin and eosin staining. This phenomenon is also seen in extramural venous invasion.

both extramural and intramural venous invasion. Controversial cases were examined through a double-headed microscope.

Results

Figure 1 details the results for the 100 tumour specimens examined using an elastica haematoxylin and eosin stain.

Of the 100 specimens (all of which had previously been reported as negative for extramural venous invasion by conventional haematoxylin and eosin staining), 17% were found to have extramural venous invasion by