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Granular cell tumour of the larynx

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Abstract
Granular cell tumour (GCT) of the larynx is an uncommon laryngeal tumour. It is always benign and commonly located in the posterior part of the larynx. Care must be taken to differentiate this lesion from others due to the presence of pseudo-epitheliomatous hyperplasia which overlies the GCT and may occasionally mimic squamous cell carcinoma. Therefore, histological differentiation is important because these tumours are normally managed conservatively. The origin of this tumour is a matter of debate, but most authors believe it to be neural in origin. The rarity of this tumour in the male population prompted reporting this case in the literature.

Key words: Laryngeal neoplasms, Granular cell tumour

Introduction

Granular cell tumour (GCT) is an uncommon benign lesion affecting the mucous membrane of the upper aero-digestive tract. No anatomical sites in the body are immune to the development of this tumour. About one third of all granular cell tumours occur in the head and neck (Kershisnik *et al.*, 1994). It presents as a submucosal swelling and commonly affects the head and neck region. The most common site is the anterior part of the tongue. In laryngeal cases the posterior part of the vocal fold is the usual site. Its cell of origin is not yet known and there is controversy over the popular belief of neural origin. It may occur in any age group but mainly occurs in adults. The pseudo-epitheliomatous hyperplasia which frequently overlies GCT may sometimes lead to confusion, and inappropriate treatment may result due to misinterpretation as squamous cell carcinoma. Co-existing carcinoma with GCT has also been reported (Goldstein *et al.*, 1971; Coitus *et al.*, 1976). It is not a pre-malignant lesion, neither does it undergo malignant transformation. In this paper another case of GCT of the larynx is added to the existing list. Also, highlighted are the recent advances in the diagnosis and management of this neoplasm.

Case report

A 32-year-old male Saudi presented to the Gastroenterology clinic with a history of heart burn and dyspepsia. After routine work-up he had an upper GI endoscopy which showed reflux oesophagitis. The endoscopist incidentally identified a mass in the larynx. The patient did not have any kind of laryngeal symptoms. However, the patient was referred to the Otolaryngology department. A microlaryngoscopy was performed which revealed a 1.5 cm (approximately) submucosal mass (Figure 1) in the right pyriform sinus. This was excised endoscopically. The rest of the larynx and upper airway was found to be normal. The histopathological examination report came back as granular cell tumour with free margins and pseudo-epitheliomatous changes on the surface (Figure 2). The patient was followed-up for approximately one year without evidence of any recurrence in the larynx but still has gastrointestinal symptoms and is on medical therapy.

Discussion

Granular cell tumours may occur anywhere in the body but 50 per cent of them occur in the head and neck (Thawley *et al.*, 1974) and the most common site is the tongue. This is a unique benign lesion of the larynx in which the patient may not have any symptoms related to it. It is usually a silent submucosal lesion discovered accidentally and is not normally suspected pre-operatively. Thus, the histology reports take the clinician by surprise. The aetiology of this tumour is not known, so its origin is debatable. This tumour is believed to originate from more than one cell because of the wide distribution of the

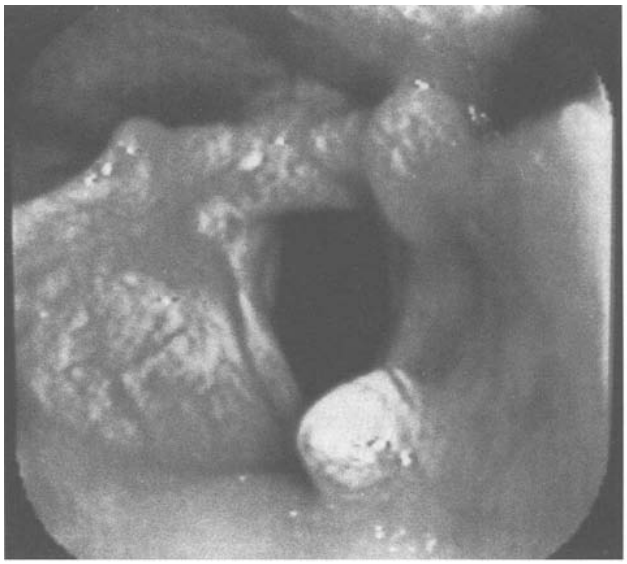

FIG. 1
Granular cell tumour situated in larynx. Endoscopic view.

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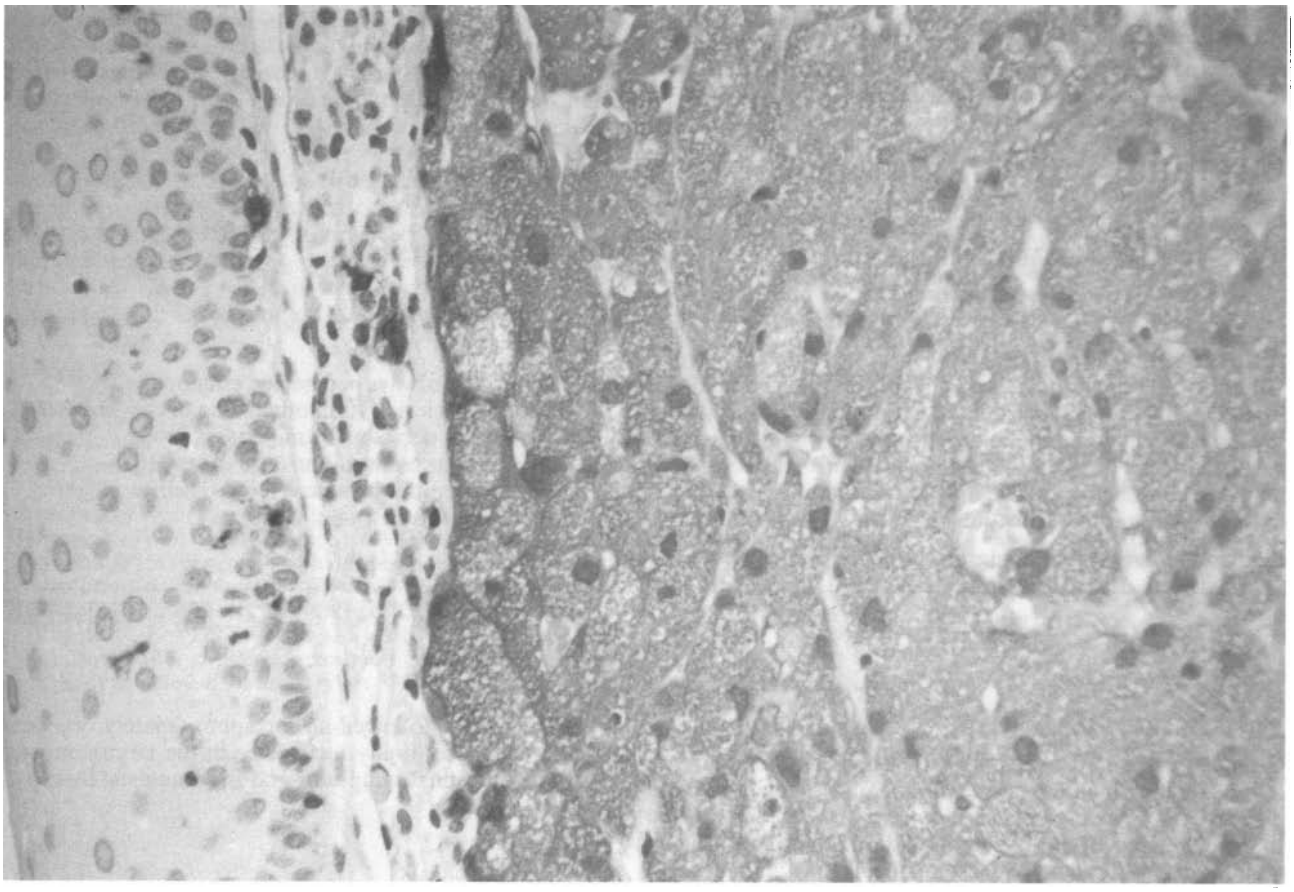

FIG. 2
Showing pseudoepith-eliomatous changes and granular cells in the tumour mass. (H & E stain with S100 protein).

tumour, its unpredictable biological behaviour and whether it is reactive hyperplasia or neoplasia. Various cell types have been postulated as the cells of origin e.g., smooth muscle cells, striated muscle cells, fibroblasts, histiocytes, Schwann cells or nerve-related mesenchymal cells. However, histochemical findings of immunoactivity for S100 protein furnished strong evidence for this tumour being of neural origin (Enzinger and Weiss, 1988).

Abrikossoff (1926) first identified the tumour as a separate clinical entity. He used the term granular cell myoblastoma because the typical cells found in this tumour were derived from striated cells of embryonic muscle, the myoblasts. The term granular cell myoblastoma is probably not correct because the tumour is not clearly derived from muscle cells. The biological nature and the histogenesis of the granular cell lesions is still debated. Although most authors consider it to be a neoplasm, the preferred term for this lesion is the noncommittal term granular cell tumour. Ravich *et al.* first reported malignant granular cell tumour in 1945. Busanny-Caspiri and Hammar described malignant granular cell tumour of the larynx in 1958 and used the same terminology. Since then these have been reviewed by many authors. An ultrastructural study by Thompson in 1984 found granular cell tumours in direct continuity with striated muscle (within the same sarcolemmal sheath). In tumours in other areas of the body striated muscle is not found. Furthermore, the absence of immunoperoxidase staining for myoglobin is more evidence against the muscle origin of this tumour.

Recent studies agree with the neurogenic theory which is based on the close association of these lesions with the nerves and ultrastructural findings of neurofilament and neurotubules in the granular tumour cells (Manara *et al.*, 1981). This theory was further supported by positive immunohistochemical staining for S100 protein and neuron specific enolase. The S100 protein is found in the neurons and also in Schwann cells of both myelinated and unmyelinated nerves as well as ganglion cells. This protein is expressed late in cell development, so its presence indicates considerable Schwann cell differentiation. Schwanoma, neurofibroma and melanomas also stain positively for S100 protein. Increased support is now available in the literature to attribute granular cell tumour with a fair degree of certainty as a Schwann cell tumour (Kaiserling *et al.*, 1995). The Schwann cell theory is generally accepted by most authors. Ultrastructural findings of a flattened layer of cells with a continuous basal lamina resembling perineurium around tumour cells supported this theory. Schwann cells are also capable of phagocytosis which accounts for the finding of autophagocytic vacuoles. These cells strongly stain for S100 protein (Fliss *et al.*, 1989).

The histiocytic theory of the origin of the granular cell tumour was proposed by Whitten (1968). The finding of autophagocytic vacuoles and positive immunohistochemical staining in some tumours for α-1-antichymotrypsin and α-1-antitrypsin suggest a histiocytic cell origin (Ulrich *et al.*, 1987). It is believed by some authors that granular cells are histiocytes and store altered myelin.

A unifying theory (Ulrich *et al.*, 1987) has recently been proposed which suggests that cells of granular cell tumours are actually of a heterogeneous population derived from more primitive precursors or at least from a heterogeneous group of cells expressing different epitopes. The ultrastructural findings, the carcino-embryonic-related antigen (Mathews and Mason, 1983) expression of GCT and the immunohistochemical (Kanitakis *et al.*, 1985) test results

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for neural precursor cell support this theory. However, this unifying theory is not accepted by all investigators and needs further experimental confirmation.

Granular cell tumours are diagnosed histologically. The hallmark of the fine structure of a granular cell tumour (benign or malignant) is the presence of large numbers of irregular, dense cytoplasmic lysosomes in various stages of fragmentation. These confer on tumour cells the granularity that is apparent by light microscopy (Kershisnik *et al.*, 1994). The tumours are composed of large polyhedral cells with small central nuclei, and have abundant granular eosinophilic cytoplasm. Electron microscopy produces a characteristic picture of the lesion. Cells are often surrounded by a basal lamina-like material (Franzen and Stenkvist, 1968). Occasionally noted are cytoplasmic angulated membrane-bound structures containing parallel arrays of microtubules, called angulate bodies. Because cytoplasmic borders are indistinct, there is a resulting syncytium of cells which is not a capsule. The cells do not have malignant features but the closely adjacent squamous cells may undergo hyperplasia which may lead to an incorrect diagnosis of carcinoma: this is called pseudo-epitheliomatous hyperplasia.

A nine to 33 per cent incidence of this finding is reported in the literature (Alessi and Zimmerman, 1988). A marked pseudo-epitheliomatous hyperplasia sufficient to be misdiagnosed as a squamous cell carcinoma, is found in about 10 per cent of granular cell tumours (Kershisnik *et al.*, 1994). Malignant granular cell tumours are often misdiagnosed because of lack of histological definition. The distinction between the benign and malignant tumour is usually made at the time of definitive surgery because of infiltration of the adjacent structures by the tumour or on the basis of metastasis. Usually the malignant potential is suggested by cellular and nuclear pleomorphism, prominent nucleoli and mitotic activity but not in cases of malignant granular cell tumours. Even DNA ploidy analysis may not be useful in predicting the clinical behaviour of this tumour, although Parayno and Carey (1995) reported a case of malignant granular cell tumour which showed DNA diploidy. Batsaki and Manning (1986) described two types of malignant tumour, one is biologically malignant without histological correlates and the other is both histologically and biologically malignant. Malignancy arising in a multifocal granular cell tumour is extremely rare. The prognosis of patients with malignant granular cell tumour is not good. Metastases to the regional lymph nodes and distant metastases are common. Usually these tumours kill their host within five years (Kershisnik *et al.*, 1994) and two years (Busanny-Caspiri and Hammar, 1958) after the diagnosis.

The treatment of choice for this tumour is wide local excision by the endoscopic, transoral or laryngofissure method. Tumour-free surgical margins are essential because recurrence is common in cases with positive margins. The recurrence rate after adequate local excision is eight per cent (Lack *et al.*, 1980) and the recurrence rate after positive margin excision is 21–50 per cent and 16 per cent develop multiple tumours (Alessi and Zimmerman, 1988). Excision of recurrence is usually curative. Its association with squamous cell carcinoma is also reported (Coitus *et al.*, 1976). Radiotherapy is not a treatment, and long-term follow-up is strongly recommended.

Conclusion

Another case of laryngeal granular cell tumour is reported. World literature is reviewed and important points highlighted. This tumour should be called granular cell tumour and not myoblastoma. In the larynx granular cell tumour diagnosis often surprises the clinicians. This lesion is diagnosed histologically. If histological findings are inconclusive then ultrastructural and immunohistochemical studies may prove helpful. Malignant granular cell tumour needs rigorous histological confirmation. The treatment of choice is wide surgical excision. Radiotherapy may be used as palliation to malignant tumours. GCT may present in multiple locations in the body. This could be as high as 16 per cent, and this should be excluded before planning the treatment. Long-term follow-up is advised because of its recurrence rate.

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