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Granular Cell Tumour of the Thyroid Gland: A Case Report and Review of the Literature

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Abstract Granular cell tumours of the thyroid gland are rare, with only six previously reported cases in the English literature. Current histological, immunohistochemical and electron microscopic evidence favours a neural/Schwannian relationship. A case of a granular cell tumour of the thyroid gland in a healthy 36-year-old woman is described. The tumour was found incidentally following a right thyroid lobectomy for symptoms from an asymmetric multinodular goitre. Macroscopically, the lesion resembled a papillary microcarcinoma. Microscopically, the tumour was composed of nests of epithelioid cells with abundant granular, eosinophilic cytoplasm. The nests were divided by fibrous septa and peripherally interdigitated with surrounding thyroid follicles. Immunohistochemistry helped to distinguish the lesion from other neoplasms such as Hurthle cell tumour, medullary carcinoma or metastasis, and also from a histiocytic reaction to previous fine needle aspiration. On the basis of this diagnosis, no further intervention was required, and the patient was discharged following post-operative review.

Keywords Thyroid gland · Granular cell tumour

Introduction

Granular cell tumours, originally described as granular cell myoblastomas [1], are benign, soft tissue lesions which occur most commonly in the skin of the trunk and the tongue [2]. Approximately 50% of cases are reported to arise in the head and neck region. Less common sites include the parotid gland and the pancreas [3, 4]. Granular cell tumours are twice as common in women as in men and usually occur in the fourth to sixth decades of life. The recurrence rate is low (<5%) and usually reflects incomplete excision [2]. Immunohistochemistry, which is pivotal in establishing the diagnosis, has played a crucial role in supporting a neural/Schwannian relationship rather than a myogenic origin. Granular cell tumours are benign neural lesions and are sufficiently distinctive to be separated from neurofibromas and schwannomas [5]. The balance of opinion regarding the origin of these tumours favours a neoplastic rather than a metabolic or degenerative process; however, there is no evidence to date in the English language literature demonstrating either clonality or consistent karyotypic abnormalities.

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Case Report

A 36-year-old woman of African origin was referred to the Head and Neck Unit at Guy's Hospital via her general practitioner, with a 3-month history of a smooth, gradually enlarging right sided neck lump. Clinical examination revealed a 3-cm lump within the right lobe of the thyroid gland which was mobile on deglutination. An ultrasound scan revealed multinodularity and a large dominant cyst in this area. Fine needle aspiration cytology on two occasions yielded scanty thyroid follicular epithelial cells and foamy macrophages, consistent with cyst contents. The cyst regressed completely following each fine needle aspiration biopsy but subsequently recurred. An uneventful right hemithyroidectomy was performed.

Pathological Findings

The tissue was studied with informed patient consent. The surgical specimen was an encapsulated, lobulated right thyroid lobe weighing 16 g and measuring 54 mm in maximum dimension. The surface of the specimen was inked, and serial slicing revealed two large colloid cysts on a background of multinodularity. One mid-thyroid slice revealed an ill-defined, 8-mm, whitish sub-capsular nodule. The tissue was fixed in 10% buffered formalin and was processed routinely for paraffin embedding. Sections were cut at 5 μm and stained with haematoxylin and eosin (H&E). The 8-mm lesion was subjected to immunohistochemical evaluation using the panel listed in Table 1.

Microscopic examination confirmed the macroscopic features of a multinodular goitre with a dominant colloid cyst. The macroscopically suspicious, sub-capsular nodule revealed a poorly demarcated lesion composed of nests and trabeculae of polygonal cells within a lightly hyalinised stroma. The cells were characterised by small, hyperchromatic nuclei and abundant pale, granular eosinophilic cytoplasm. The lesional cells interdigitated with adjacent thyroid follicles (Fig. 1a) and focally showed a perineural distribution (Fig. 1b). There was no nuclear pleomorphism, necrosis or mitotic activity. The results of the immunohistochemistry panel that was used (Table 1) showed that the lesional cells labelled with S-100, CD68, inhibin-A, calretinin and NSE (Fig. 1b, d–f). The tumour was uniformly negative with the pancytokeratins AE1/3 and MNF116, thyroglobulin, TTF1, synaptophysin, chromogranin A and calcitonin.

On the basis of morphology and immunophenotype, this lesion was diagnosed as a granular cell tumour (GCT).

Discussion

GCTs of the thyroid gland are rare with only six previously reported cases in the English language literature [6–11]. Furthermore, Park et al. [12] reported a case of multiple granular cell lesions in a 29-week-old male foetus involving sites such as the kidneys, gingivae and testes, as well as the thyroid gland. However, the results of the immunohistochemistry panel for this case and in particular the negativity of the lesional cells for S-100 (Table 1) are consistent with those that would be expected for a congenital GCT which is a separate, well-known entity. A review of the literature confirms the female preponderance of GCTs in the thyroid gland as at other sites. The current case is the smallest reported lesion and may reflect the fact that this is a specialist/referral unit.

GCTs are a recognised mimic for malignancy, particularly on frozen section, and can present challenges during histological interpretation. Submucosal and subdermal GCTs can be accompanied by overlying pseudo-epithelial hyperplasia [12] which is a feature that may lend itself to histological resemblance of a squamous cell carcinoma. This case posed no such difficulties as it lacked any of the well-documented features which suggest actual malignancy within a GCT and include necrosis, spindling of tumour cells, mitotic activity, nuclear pleomorphism, increased nuclear-to-cytoplasmic ratio and vesicular nuclei with prominent nucleoli [7]. The morphology of GCTs with ill-defined margins and extension into adjacent thyroid tissue does not indicate infiltrative or aggressive behaviour. Accurate recognition of this benign entity obviates the need to proceed to total thyroidectomy and allows the clinician to adequately reassure and discharge the patient.

Table 1 Granular cell tumours of thyroid reported to date

Reference	Age/gender	Macroscopic dimensions	Immunohistochemistry
Espinosa-de-los-Monteros-Franco [10]	21/M	18 mm	+ S-100, Calretinin—AE1-3, Thyroglobulin, TTF1, Inhibin-A
Baloch et al. [9]	47/F	25 mm	+ S-100—TTF1, Thyroglobulin, Calcitonin, Chromogranin
Milias et al. [8]	43/F	25 mm	+ S-100, CD68, Vimentin, Laminin, NSE—AE1&AE3, CAM5.2, EMA, CEA, Calcitonin, SMA
Paproski et al. [7]	23/F	15 mm	+ S-100—Thyroglobulin Electron microscopy
Mahoney et al. [6]	11.5/F	15 mm	+ S-100—Thyroglobulin, calcitonin, chromogranin, EMA, vimentin, ER, PR
Park et al. [12]	29 week old foetus/M	Multiple lesions	− S-100, lysozyme, α_1-anti-trypsin, Cytokeratin, vimentin
Chang et al. [11]	12/F	14 mm	+ S-100, vimentin—Thyroglobulin, TTF-1, Chromogranin A, Synaptophysin, Calcitonin, Cytokeratin
Current report	36/F	8 mm	+ S-100, CD68, Calretinin, Inhibin A, NSE—AE1/3, CK7, TTF1, Thyroglobulin, Synaptophysin, Chromogranin A, Calcitonin

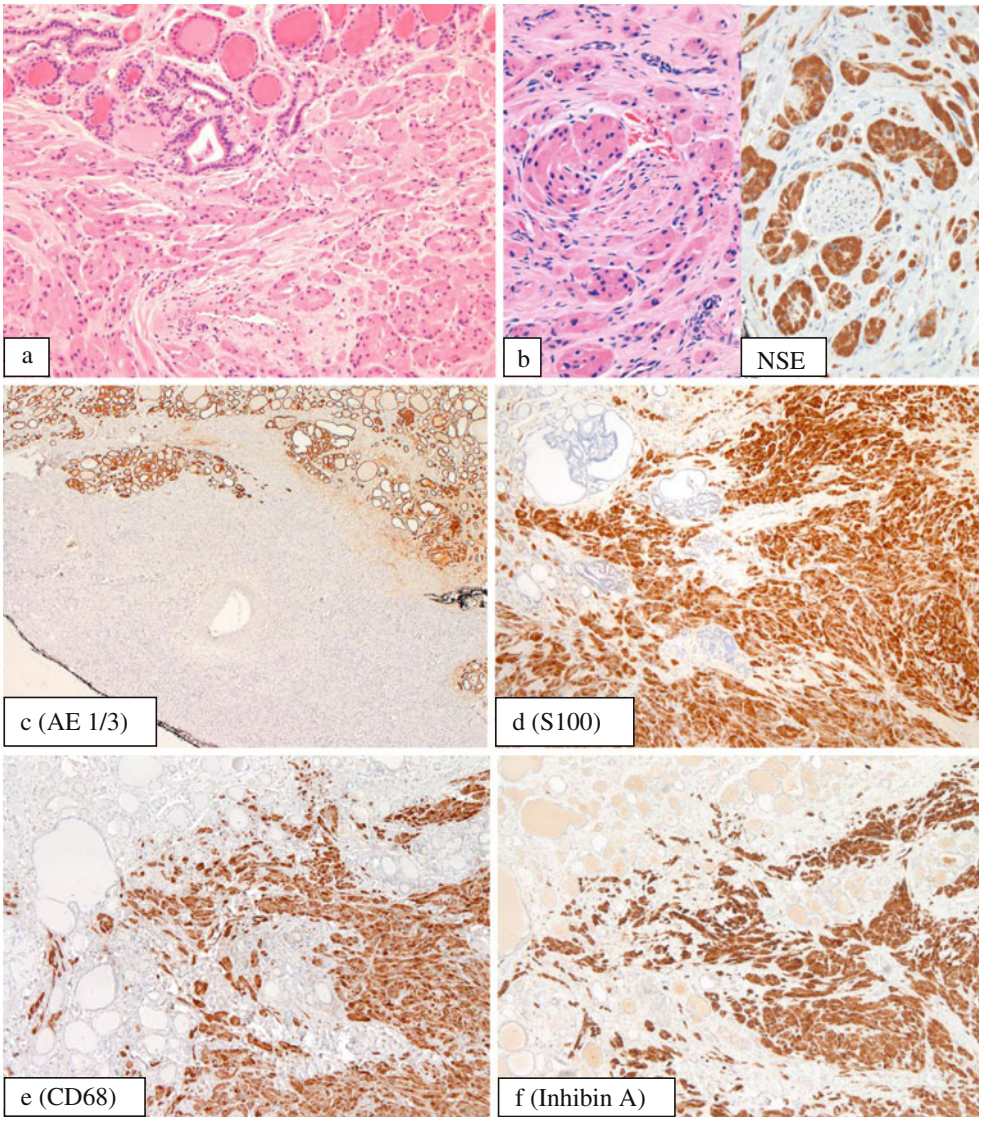

Fig. 1 **a** H&E-stained section of the GCT showing large polygonal cells with abundant eosinophilic cytoplasm extending between adjacent thyroid follicles. **b** Perineural distribution of granular cells on H&E and NSE (immunostain). **c** AE 1/3 labels surrounding thyroid follicles but not the granular cells. **d**–**f** Uniform labelling of granular cells with S-100, CD68 and inhibin-A

The immunohistochemical profile (pancytokeratin, TTF1, thyroglobulin, calcitonin, chromogranin A and synaptophysin negative) distinguished this lesion from a Hurthle cell tumour or a metastatic carcinoma. An intra-thyroidal paraganglioma was also considered on a list of differential diagnoses, as although this tumour bore no morphological resemblance to the nested cellular pattern which is found within a paraganglioma, it was considered on the basis of two other histological features which presented in this case and were the granular cytoplasmic content of the cells and the lack of a clear boundary between the tumour and surrounding thyroid tissue [13]. However, a paraganglioma was again excluded on the basis of immunohistochemistry which was a valuable aid in the definitive diagnosis of the GCT. This was most reliably supported by the uniform, strong positive labelling of the entire cellular component of the tumour with S-100, whereas only the sustentacular cells of a paraganglioma would be expected to stain positively for this marker [13]. The results of the immunohistochemistry panel also helped to distinguish this tumour from a medullary carcinoma, largely due to the negativity of the tumour cells for calcitonin. This was backed up by certain histological features of the tumour such as the lack of abundant hyaline stroma [14]. This element also enabled the exclusion of hyalinising trabecular adenoma from the differential diagnoses—another rare thyroid tumour which was also considered due to its potential to present with a granular cellular appearance. In addition to this, several other well-documented features of a typical hyalinising trabecular adenoma were absent in this case, such as a trabecular growth pattern, a circumscribed or encapsulated tumour and nuclear grooves, inclusions, clearing and enlargement—which occasionally mirror the histological appearance of a papillary thyroid carcinoma [15, 16]. Hyalinising trabecular adenomas have also been documented to stain positively for TTF1, which was negative in this case.

Granular cell change is also recognised to occur in a variety of other neoplasms, including neuromas and smooth muscle and connective tissue neoplasms [2, 5]. These are distinguished from a GCT by the coexistence of the primary lesion showing the typical histological features.

Granular cell changes in soft tissue in response to trauma are a recognised mimic of granular cell tumours and usually occur at sites of surgical trauma. In these cases, in contrast to GCTs, collections of histiocytes usually surround nodules of granular and amorphous debris and are associated with inflammation and necrosis [5]. Furthermore, the homogeneous nature of the GCT in this reported case, and the lack of inflammation, scarring or haemosiderin pigment helped to distinguish it from a reaction to fine needle aspiration (FNA). The results of FNA biopsy for this case appeared to be consistent with the clinical and radiological appearances of a dominant thyroid cyst, which was present adjacent to the comparably considerably smaller GCT. The authors are aware that if sampled however, the granular cells may have shown a similar appearance to cells which were interpreted as foamy macrophages, and this highlights the importance of reviewing cytological, histological and immunohistochemical evidence together in order to achieve an accurate diagnosis. A GCT may not have been included in a list of differential diagnoses on the basis of FNA biopsy alone due to the unusual anatomical location of this tumour. However, FNA remained of value in the overall care for this patient who presented with a cystic multinodular goitre as her main problem.

Abrikossoff first described a lingual granular cell tumour in 1926 and postulated a myogenic origin [1] on the basis of the close relationship and morphological resemblance to striated muscle fibres. However, the close association between the cells of a GCT and nerves, the frequent incidence of a perineural distribution of the tumour cells and the immunophenotype of a GCT are factors which help to firmly establish it as a neural lesion [5]. Schwann cells in the thyroid gland are associated with vasomotor and adrenergic fibres which are thought to regulate thyroid secretion by direct neural and indirect vascular nerve signals [17]. In addition to neuron-specific enolase (NSE) and S-100, GCTs stain with calretinin and the alpha-subunit of inhibin. Calretinin is a calcium-binding protein belonging to the family of E-F hand proteins that include S-100 protein. It is expressed primarily in certain subtypes of neurons in the central and peripheral nervous system, and its expression in GCTs supports neural differentiation [18]. The alpha-subunit of inhibin is a useful marker for ovarian sex cord-stromal tumours and adrenocortical neoplasms and is reported to occur in 100% of GCTs [18]. Of the previously reported GCTs, one was reported to be inhibin-A negative [10]. The molecular specificity in GCTs is as yet undetermined. Although granular cell tumours label with CD68 (monocyte–macrophage-associated lysosomal antigen), this antibody is not a macrophage-specific marker as there is no reactivity with MAC 387 [19]. Ultrastructurally, the cells within a GCT contain numerous secondary lysosomes with prominent myelin figures [2].

In conclusion, the commonest incidental lesions detected pathologically in our practice are papillary microcarcinomas for which further surgery and follow-up may be required. The precise diagnosis of the current lesion as a granular cell tumour enabled our surgeon to reassure and discharge this patient. This rare lesion should be considered in the differential diagnosis of oncocytic/Hurthle cell lesions of the thyroid.

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