Original Article

Granular Cell Tumor of Thyroid: Challenging Pitfalls and Mimickers in Diagnosis

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Abstract

Mesenchymal tumors of the thyroid are extremely rare. Only few isolated cases of primary thyroid granular cell tumor (GrCT) have been reported. The anatomic location of this lesion plays an important role in the differential diagnosis. It is well-known that GrCT commonly involves the head-and-neck region, lower extremity, nuchal region, chest wall, and internal viscera such as the gastrointestinal tract. However, primary GrCT of the thyroid are unexpected and might lead to misdiagnosis, especially with pathological diagnosis limitations such as frozen section and fine-needle aspiration. We believe that it is important to establish a good differential diagnosis because of its ability to simulate the appearance of invasive carcinoma, especially in cases lacking tissue block examination. In this paper, we try to focus on clinical, radiological potential characteristics, and the differential diagnosis of the tumor.

Keywords: Granular cell tumor, head and neck, thyroid

Introduction

Granular cell tumors (GrCTs) are rare benign lesions of Schwannian origin composed of cells with abundant granular cytoplasm. GrCT was initially descried as myoblastoma in 1926 and thought to be originated from smooth muscle origin.[1] Later, with the aid of immunohistochemical and ultrastructural studies, this has been changed into the neuronal origin. Although, head and neck considered roughly the most common location of GrCT, particularly the tongue, it has been reported in other anatomic locations such as the skin, subcutaneous tissue, deep soft tissue, larynx, orbit, tracheobronchial tree, parotid gland, breast, gastrointestinal tract, esophagus, urinary bladder, and male and female reproductive systems.[2] The incidence of primary GrCT in the thyroid is uncommon. Extensive literature review revealed only 20 reported cases [Table 1].[3-22] Primary GrCT of the thyroid considered a challenging diagnosis; due to anatomic location rarity, clinical and radiological findings mimicking malignancy. Therefore, good differential diagnosis, careful pathologic, and immunohistochemistry studies are needed for an accurate diagnosis. We believe that further studies for this tumor are needed. This can add a significant value to more understanding of the correct diagnosis and surgical treatment. The aim of this study is to identify the clinical and radiological potential characteristics of the tumor and to discuss the differential diagnosis and its morphological pitfalls and mimickers in both fine-needle aspiration (FNA) and surgical resection specimens as well as the treatment methods available based on the currently available clinical evidence. A summary of the clinical, radiological, and histopathology findings of these 20 cases is provided.

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Clinical Features

Age and gender

There were two cases that lacked patient age information due to language barrier.[7,20] The mean age of presentation among male patients was 37 years, with a range between 21 and 53 years. Females' mean age of presentation was

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Table 1: Summary of reported cases of primary thyroid granular cell tumors (*n*=20)

Authors	Age (year)/ gender	Tumor site	Tumor size (cm)	Duration of presenting symptoms	Clinical presentation	Procedure done for diagnosis	Postsurgery outcome
Xu *et al*.[3]	16/female	Left lobe	3	Half a month	Painless swelling of front neck	FNA followed by left thyroid lobectomy	Disease free after 3 years
DU *et al*.[4]	14/female	Right lobe	2.5	3 months	Neck lump	Thyroidectomy	Disease free after 14 months
Park *et al*.[5]	46/female	Lower pole of the left lobe	2.4	Incidental	Incidental	FNA followed by left thyroid lobectomy	NA
Chen *et al*.[6]	14/female	Right lobe	3.3	3 months	Neck mass	FNA followed total by thyroidectomy	Disease free after 1 year
Cho *et al*., (Article in Korea)[7]	NA	NA	NA	NA	NA	NA	NA
Harp and Caraway *et al*. (2013)[8]	27/female	Right lower lobe	4.2	6 years	Palpable nodule	FNA diagnosis, confirmed by core needle biopsy	Disease Free
Min *et al*.[9]	24/female	Right mid-zone	1.8	3 years	Painless neck mass	FNA followed total by thyroidectomy	Disease free after 5 months
Singh *et al*.[10]	11/female	Right lobe	3.5	2 years	Nontender, firm swelling	FNA+biopsy tissue	NA
Bowry *et al*.[11]	36/female	Right lobe	0.8	3 months	Mobile lump	FNA followed by hemi-thyroidectomy	NA
Jang *et al*.[12]	44/female	Right lobe adjacent to isthmus	0.9	6 months	Neck mass	FNA followed by right thyroid lobectomy	NA
Cimino-Mathews *et al*.[13]	28/female	Left lobe	1	NA	Fullness in her neck	FNA was performed, followed by left thyroid lobectomy	Lost to follow-up
Espinosa-de-los-Monteros-Franco *et al*.[14]	21/male	Left lobe near the isthmus	1.8	NA	Painless thyroid nodule	Total thyroidectomy	NA
Chang *et al*.[15]	12/female	Isthmus	1.4	NA	Painless, hard neck mass	FNA followed by isthmusectomy	Disease free after 15 months
Chang *et al*.[16]	12/female	Isthmus	1.4	1 year	Painless neck mass	FNA followed by isthmusectomy	Disease free after 10 months
Baloch *et al*.[17]	47/female	Left lobe	2.5	NA	Palpable left thyroid mass	Thyroidectomy without FNA	NA
Milias *et al*.[18]	43/female	Left lobe	2.5	2 years	Weakness, anxiety, and palpitations due to mild hypothyroidism	Total thyroidectomy	NA
Paproski and Owen[19]	23/female	To the right of the isthmus	1.5	18 months	Painless, progressive midline enlargement of the thyroid gland	FNA followed by isthmusectomy	Disease free after 4 months then lost follow-up
Kang *et al*. (Article in Korea)[20]	NA	NA	NA	NA	NA	NA	NA
Mahoney *et al*.[21]	11/female	Middle of the right lobe	1.5	6 months	Distinct, firm nodule	Lobectomy	Disease free
Malignant thyroid GrCT							
Igarashi *et al*.[22]	53/male	Left lobe	2.8	Incidentally identified	Incidentally identified	FNA followed by total thyroidectomy, ablation of involved tracheal wall	Disease free after 1 year

*NA: Not available, *FNA: Fine-needle aspiration, GrCT: Granular cell tumor

25.5 years with an average between the age group of 11 and 47 years [Figure 1]. Most of the reported cases were females. Only two cases are reported in male patients, with a male-to-female ratio being 1: 8 (2:16).

Location

The primary location of the lesion in the thyroid gland involved both lobes almost equally. The number of cases reported in the right lobe 40% (8/20) and left lobe 35% (7/20). Only three cases were reported in the isthmus 15% (3/20), in which the patient underwent isthmusectomy. All of the reported cases revealed a local disease, limited to the thyroid tissue. Except one reported case of malignant GrCT[22] invades into adjacent tracheal wall over two cartilage rings.

Clinical Presentation

Patients diagnosed with primary thyroid GrCT varies widely in their clinical presentation symptoms. Most of them present with nonspecific signs and symptoms. It ranges as an indolent

slow-growing neck mass, mobile lump, and hard neck mass. Some patients were incidentally discovered while routine checkup for other medical reasons 10% (2/20). Majority of lesions presented as palpable nodule 45% (9/20), whereas others presented with painless neck swelling 30% (6/20). None of these reported cases presented with pressure and compression symptoms. Only one case presented with weakness, anxiety, and palpitation due to her know medical condition of hypothyroidism.

Radiographic Features

The maximum lesion size was variable from 0.8–4.2 cm. (Male mean tumor size, 2.3 cm; females mean tumor size, 2 cm) [Figure 1]. In the thyroid, half of the previous reported cases of GrCT are characterized radiologically as a small hypoechoic nodular lesion 50% (10/20). None presented with hyperechoic density. Thirty percent (6/20) of cases were well-defined lesions. Where only 10% (2/20) were ill-defined nodular lesions. Neither of the reported cases were cystic lesions nor large complex mass. The radiographic presentations of thyroid GrCT are summarized in Table 2.

Fine-needle aspiration findings

FNA is a very common and useful diagnostic tool to establish the primary diagnosis of most thyroid neoplasms. Around 65% (13/20) of reported cases have done FNA for their problematic lesions. GrCT of the thyroid could be easily misdiagnosed or confused with similar lesions. Making a diagnosis of thyroid GrCT by cytological examination only is very challenging. Therefore, pathologists should keep primary GrCT in the differential diagnosis of granular cell lesions of the thyroid. Tumor cells can appear as large, polygonal cells, syncytial (pseudofollicular patterns), and indistinct cell borders, with fragile cytoplasm that contain prominent eosinophilic granules. Nuclei of cell can be polymorphic, bland oval, round, or even spindle shape. The nucleolus is usually and rarely found and inconspicuous. This morphology can be misdiagnosed easily with common thyroid neoplasms such as Hürthle cell lesions (adenoma and carcinoma), macrophages and benign cystic changes of thyroid, oncocytic metaplasia of adenomatous hyperplasia, medullary thyroid carcinoma, and neuroendocrine tumors. Hürthle cell neoplasms usually show large cells with round nuclei that contain abundant pale cytoplasmic granules greenish-to-orange in color, with well-defined cell borders. They can show cherry-red nucleoli. Granular debris is not typically seen in the background. In cases with Hürthle cell metaplasia, mixture of lymphocytic background can be seen as well. The distinction between Hürthle cell adenoma and carcinoma cannot be established on FNA examination and should be examined under prober tissue resection. Macrophages present commonly in benign cystic changes of thyroid; they often show more vesicular nucleus, foamy cytoplasm that usually contains tawny hemosiderin-laden granules. A background containing degenerative red blood cells also can be helpful in cystic content changes. Medullary thyroid carcinoma of thyroid can show wide spectrum of cytological morphology, including spindle, oncocytic cells, granular cytoplasm, stippled chromatin, large nuclei with prominent nucleoli or intranuclear inclusions can be seen. Cellblock with positive immunostaining studies for synaptophysin, chromogranin, carcinoembryonic antigen (CEA), and calcitonin are useful in confirming the diagnosis. Neuroendocrine tumors are uncommon, which can be mimicker of medullary thyroid carcinoma. The smear shows numerous isolated cells of dyshesive cellular aggregates with minimal nuclear pleomorphism, few mitoses, fine evenly dispersed nuclear chromatin with occasional inconspicuous nucleoli. The scant amount of amphophilic cytoplasm is seen. Clustering of tumor cells can aggregate around segments of capillaries or rosette formation. Positive immunostaining studies for synaptophysin, chromogranin, whereas negative for CEA, and calcitonin are helpful.[6,8] It is always recommended to do cell block and immune staining to confirm the diagnosis.

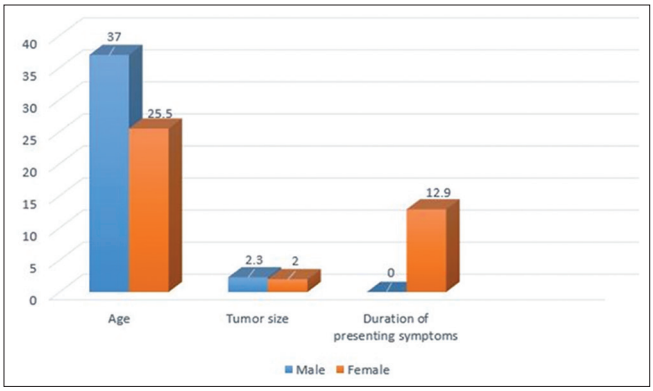

Figure 1: Mean age (years) of the diagnosis, mean tumor size (cm), and mean duration of presenting symptoms (years) among male and female population

Table 2: Radiological features of reported cases of primary thyroid granular cell tumors ($n=20$)

	Number of cases
Hypoechoic mass	10
Hyperechoic mass	0
Well-defined	6
Ill-defined	2
Total	18

Role of frozen sections (intraoperative consultation)

Histology of frozen sections is generally not useful for accurate diagnosis interpretation. It can be easily interpreted as hürthle cell neoplasms, medullary thyroid carcinoma, and follicular thyroid neoplasms. In our review, frozen sections examination of the surgical specimen was carried out in five cases. Only one case was suspicious for the correct diagnosis, and they send for electron microscopy conformation.[19] Four cases (80%) failed to facilitate the correct diagnosis. One case was mistaken for medullary thyroid carcinoma [Table 3]. Although GrCT interpretation during frozen section is difficult and challenging

due to freezing artifacts, it might help by encouragement for surgical resection intervention as done in all reported cases in the literature review.

Pathogenesis

Normally, neural tissue present within the thyroid gland. This includes two types: vasomotor fibers and adrenergic fibers. Vasomotor fibers or the nonmyelinated fibers are the postganglionic origin, arising from the cervical sympathetic ganglion. It serves the secretory activity of the thyroid through blood vessels. Adrenergic fibers, on the other hand, supply membranous receptors located adjacent to the thyroid follicular basement membrane. C-cells of the thyroid are supplied by cholinergic fibers, which have been found in animals. However, it is not been found in human. All of the above-mentioned nerves are surrounded by Schwann cells which explain the presence of GrCT of the thyroid.[19]

Management

Most of the reported cases of primary thyroid GrCTs are benign, slow-growing nodules. Some of them were incidentally discovered during routine checkup for other medical reasons.[5] Surgical resection used in all of the previously reported cases, except one case, which was confirmed by core needle biopsy, the patient declined surgery.[8] GrCT has an excellent prognosis after complete surgical resection.[6] Malignant GrCTs, can be treated with wide local excision with regional lymph nodes dissection if needed. Radiotherapy and chemotherapy could hardly improve clinical outcomes. Follow-up is needed, especially for cases with high risk of recurrence and metastasis.[23]

Discussion

A lot of theories were mentioned regarding the origin of GrCTs. It was first described in the literature as myoblastoma, in 1926 and thought to be from smooth muscle origin.[24] In 1935; Feyrter suggests that the tumor is neuronal in origin and named "granular cell neuromas." The name was changed to "granular cell neurofibroma" by Fust and Custer in 1948. Finally, in 1962; Fisher and Wechsler studied the ultrastructural organization of the tumor cells and concluded that GrCTs are mostly originating from Schwann cell and thus named as "granular cell schwannomas."[24] Nowadays, the well-known nomenclature by the WHO is GrCT.[25] GrCT most commonly arises in the tongue, but it can be seen in the skin, extremities, soft tissue and internal visceral organs.[2] Ninety percent of GrCTs are solitary lesions. Approximately 10% can be multicentric in the different anatomic location which can appear synchronously or metachronously.[23] Multiple and solitary GrCTs have been reported in association with Noonan and LEOPARD syndrome.[26,27] Schrader *et al*. report a patient with a clinical and molecular diagnosis of LEOPARD syndrome associated with multiple GrCTs, bidirectional sequencing of exons 7, 12, and 13 of the PTPN11 gene revealed the T468M missense mutation in exon 12.[28] The peak age is averaged in the 40–60 years of age with female predilection.[24] Few cases are reported in pediatric age group.[1] It is more prevalent in African-American ethnic. The clinical presentation of GrCT is usually slow-growing, painless nodule, plaque, or mass. Grossly, GrCT is usually small 3 cm or less (mean: 1–2 cm) in diameter. Deep lesions are often larger (5–6 cm) and have a yellow cut surface.[24] Microscopically, GrCT is usually none capsulated, irregular borders, that may appear to infiltrate adjacent dermal collagen, adipose tissue or skeletal muscle [Figure 2a and b]. Tumor cells are often appear to entrap small nerves. Moreover, it can extend directly up to the surface epithelium. Low-power examination of the tumor cells can be seen arranged in sheets, nests, and cords of plump, polygonal cells with abundant granular eosinophilic cytoplasm due to

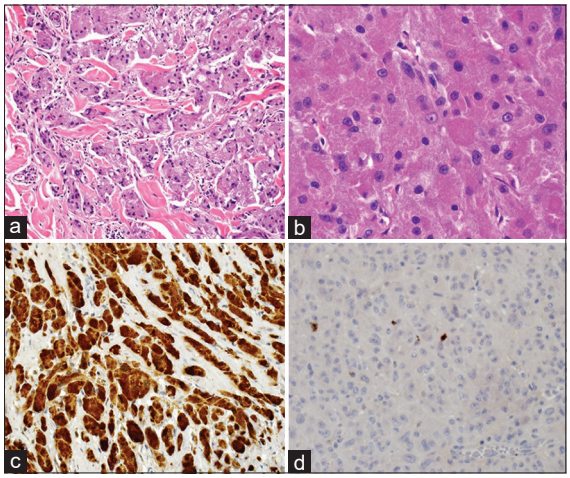

Figure 2: Histopathology examination of granular cell tumor by H and E. (a) Clusters and nests of tumor cells with abundant eosinophilic granular cytoplasm separating thick collagen bundles (H and E; 20x); (b) Large pink epithelioid type cells and bland nuclei containing granular eosinophilic cytoplasm, occasional intranuclear pseudoinclusion seen (H and E; 40x); (c) Immunohistochemistry showing strong diffuse positivity for S-100 (40x); (d) Benign GrCT show rare reactivity to Ki-67, <2% (40x)

Table 3: Frozen section (intra-operative consultation) result, prior to surgical resection

Authors	Age (year)/gender	Tumor site	Tumor size (cm)	Frozen section diagnosis
DU *et al*.[4]	14/female	Right lobe	2.5	Failed to facilitate a diagnosis
Park, *et al*.[5]	46/female	Lower pole of the left lobe	2.4	Couldn't confirm malignancy, deferred
Jang *et al*.[12]	44/female	Right lobe adjacent to the isthmus	0.9	Medullary thyroid carcinoma
Baloch *et al*.[17]	47/female	Left lobe	2.5	Deferred
Paproski and Owen[19]	23/female	To the right of the isthmus	1.5	Possible GrCT was rendered

GrCT: Granular cell tumor

the phagolysosomes which give raise to the dense enlarged granular appearance of the cells. The cell membrane is often indistinct; merge with one another giving the appearance of syncytial fashion of growth. Central small vesicular nuclei with subtle nucleoli may present. Mitosis and necrosis usually absent.[24] Fanburg-Smith *et al*. propose six histology criteria to define the malignant and atypical GrCT (not meeting criteria for malignancy).[1] These are include the following: necrosis, spindling of cells, high N:C ratio, pleomorphism, vesicular nuclei with prominent nucleoli, and mitosis more than 2 per 10 high-power field. Any lesion that contains 3 or more of the above-mentioned features is diagnosed as malignant GrCT, where any lesion contain only 1–2 features is considered as atypical GrCT.[1]

GrCTs are usually benign in nature, where atypical and malignant are extremely rare as previously mentioned. The latter, accounting for 1%–2% only.[24] The percentage of atypical GrCTs is still not known. Periodic acid–Schiff can be used as an ancillary study which shows diffuse, chunky staining pattern. Immunohistochemistry of GrCT are typically strong and diffuse expression for S-100 (correlated to neuronal origin) [Figure 2c], with low proliferate index [Figure 2d], CD68 (correlated to phagolysosomes). CD57 and Neuron-specific enolase (NSE) may also be expressed. Some authors suggest the role of Ki-67 proliferative index (more than 10%) and P53 expression (over 50% of tumor cell nuclei) to indicate the malignant behavior of the tumor.[24] Electron microscopy reveals continuous external lamina around cell nests, pleomorphic secondary lysosomes. The histologic differential diagnosis can be related to any tumor mincing the cytoplasmic nature of GrCT.

Differential diagnosis includes Hürthle cell neoplasms, schwannoma, paraganglioma, medullary thyroid carcinoma, melanoma, and metastatic carcinoma. Oncocytic (Hürthle cell) neoplasms are usually consist of thick encapsulated lesion, which contains at least 75% large size cells, well-defined cellular borders, abundant deeply eosinophilic and granular cytoplasm, with a complete loss of cell polarity. High power exanimation reveals centrally located large nuclei with prominent nucleoli. Tumor cells can grow in follicular around vascular network, solid, or trabecular pattern. Hürthle cell carcinoma tends to have thicker capsule, more solid growth than follicular, small size cells with increased mitosis, and capsular, lymphatic and/or vascular invasion. Electron microscopy of Hürthle cell neoplasms shows cytoplasm packed with numerous large mitochondria with myelin figures. It is usually positive for thyroglobulin, thyroid transcription factor-1 (TTF1), CK7 whereas negative for CK20 immunostaining.[29] Schwannoma is biphasic neural tumor with cellular component (Antoni A) which palisades (Verocay bodies) with hypocellular myxoid area (Antoni B). No granular cytoplasm seen in GrCT is observed in schwannoma. Adjacent blood vessels may show thickened hyalinized walls. It reveals diffuse strong immunoreactivity for S100. Electron microscopy reveals basal lamina with electron-dense material.[30] Thyroid paraganglioma is rarely diagnosed neuroendocrine tumors. Around 50 reports are found in English literature since the first description. Cells are arranged in organoid (zelbellen) pattern with positive staining for chromogranin, synaptophysin, and NSE while S100 positive in sustentacular cells.[31] Medullary thyroid carcinoma is a neuroendocrine-derived tumor. Originated from C-cells (parafollicular cells) of ultimobranchial body of neural crest, which secrete calcitonin. Often, it is arranged in a mixture of round, polygonal, spindle, or plasmacytoid cells arranged in nests, trabeculae, solid sheets, or follicles. It contains round nuclei with indistinct nucleoli, finely stippled to coarsely clumped chromatin, occasional nuclear pseudo inclusion seen. Stromal amyloid deposits are very characteristic. Calcitonin, CEA, TTF1, and Congo red stains are positive. While it is negative for thyroglobulin.[32] Melanoma composed of large cells with eosinophilic granular cytoplasm, nuclear atypia with marked pleomorphic nuclei, large eosinophilic nucleoli. Nuclear pseudoinclusions, grooves can be seen. Prominent deep mitosis can be easily detected. Melanin pigments are a very good clue to diagnose. Electron microscopy show melanosomes and premelanosomes. S-100, human melanoma black 45, melan-A (MART-1), and Fontana-Masson (to detects melanin granules) are useful positive staining.[33] Overall, the clue to GrCT is the diffuse granular changes of the cytoplasm rather than focal changes tend to occur in the above differential. However, diffuse cytoplasmic staining of S-100 and CD68 would be helpful to confirm the diagnosis of GrCT.

Conclusion

We present a rare tumor of the thyroid gland through a retrospective study. Clinical presentation with radiology correlation can be nonspecific. FNA thyroid can be misdiagnosed if not included in the differential diagnosis. Histopathology and immunohistochemistry examination play a crucial role in accurate diagnosis and to apply morphology criteria of Fanburg-Smith *et al*. to differentiate benign tumors from others. Wide surgical resection is the suitable treatment for benign GrCT with an excellent prognosis.

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Conflicts for interest

There are no conflicts for interest.

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