Original Article
Granular cell tumor of the thyroid in a 16-year-old girl: a rare entity

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Received November 1, 2015; Accepted January 5, 2016; Epub February 1, 2016; Published February 15, 2016

Abstract: Granular cell tumor (GCT) is a rare soft tissue neoplasm that can virtually affect any site of the body. They commonly arise on lower extremity, nuchal region, chest wall, gastrointestinal tract, head and neck but very rarely in thyroid. Here, a case is described of granular cell tumor in a 16-year-old girl, which is a very rare occurrence, since these tumors typically manifest in subjects between the fourth and sixth decade. The patient had noticed a thyroid mass half a month back which was operated. And then, unilateral thyroidectomy and isthmectomy was done. Immunohistochemistry stain of excision specimen was diagnosed as GCT. Histopathological features, differential diagnosis and therapeutic implications of granular cell tumor were discussed, together with a brief review of the recent literature.

Keywords: Granular cell tumor, thyroid, therapy

Introduction
Granular cell tumor, first described by Abrikossoff in 1926 [1] and suggested to be of myoblastic origin, are uncommon soft-tissue tumors. The cell origin of these tumors is still debatable, although a Schwannian cell derivation is currently favored based on immunohistochemical and ultrastructural studies [2-5]. It can affect soft tissues virtually in anybody site, and typically manifests in adults between the fourth and the sixth decade, usually showing a benign behavior; women are affected twice as much as men [6]. By convention, granular cell tumors are considered malignant when a morphologically benign granular cell tumor metastasizes to regional lymph nodes or to distant sites or causes death. It has been demonstrated that GCT of the thyroid can occur both in paediatric and advanced age, but their incidence usually peaks between the fourth and the sixth decade [6], while their occurrence before the age of 20 years is very rare. GCT frequently appears as a solitary tumor. Despite the fact that most of these lesions arise in the cervico-facial region, few cases of thyroid had been reported in the English-language literature report.

Case report
A 16-year-old girl presented with painless swelling of front neck incidentally discovered for half a month. She did not complain of fever and no significant clinical data (diabetes, hypertension, allergies) were present in her clinical history; there was no history of cough. The patient had always been well and she referred to a healthy lifestyle; she was not on any anticoagulants or antiplatelet drugs. The general hematological and biochemical laboratory investigations were substantially normal, including thyroid function tests, carcinoembryonic antigen, calcitonin and serum calcium levels were in the normal range. Physical examination confirmed the presence of a primarily 3.0 cm × 2.0 cm spherical swelling on the front of the left neck and move with the swallow in the thyroid. The skin over the swelling was normal. There was no local rise of temperature but the swelling was mildly tender, firm, and no pulsatile on palpation. The neck and shoulder movement were normal and no peripheral neurological deficit was present. The patient had no history of family thyroid disease or external irradiation. Ultrasonogram showed a left thyroid nodule measuring 3.0 cm × 2.0 cm. The patient received treatment of fine needle
Aspiration cytology examination revealed thyroid adenoma. Under general anesthesia left thyroid lobectomy and isthmusectomy was surgical resection and the specimen general for histopathological examination. Surgical margins were negative. The postoperative period was uneventful, without any complications or sequelae.

The surgical specimen measured 5.5 cm × 3.5 cm × 2.5 cm, and the thyroid lesion appeared grayish yellow and smooth with capsular and diameter about 3.0 cm. On histological examination, the epithelium showed marked pseudopapillomatosus hyperplasia, while with a neoplastic proliferation was observed. Neoplastic cells were mainly round, with small hyperchromatic nuclei and abundant granular eosinophilic cytoplasm, strictly intermingled with bundles of striated muscle and fibrous tissue (Figure 1). At immunohistochemistry showed positive on neuron-specific enolase (NSE), in tumor cells (Figure 2), while negative on smooth muscle actin (SMA) (Figure 3). All neoplastic cells were S-100-positive (Figure 4) and vimentin-positive; while negative on Syn (-), CgA (-), CK (-), TTF1 (-), Tg (-), CT (-), Des (-). The proliferation index, semiquantitatively evaluated with Ki67 labeling index, was very low, less than 1%.

In conclusion, all histomorphological and immunohistochemical findings were consistent with GCT of thyroid. The patient was first examined one week later and then, respectively, 1, 3, 6 and 12 months after the surgical excision; no sign of recurrence has been noted three years after surgery in the follow-up. Even so, further close follow-up has been planned to assess the effectiveness of the eradication and to prevent any possible relapse of the disease.

**Discussion**

Granular cell tumor is a rare soft tissue neoplasm that can virtually affect any site of the
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body and represent 0.5% of all soft tissue tumors [7]. Its histological origin is controversial, since several studies have shown that different cells are involved. GCT was initially described as myoblastoma, but, at present, a neural origin is supported by most Authors, due to the immunohistochemical pattern. Even if the biological behavior of GCT is usually benign, accurate histological examination is mandatory, because in a small number of cases they can be malignant. While both benign and malignant GCTs present in a similar age range of 30-50 years [6]. GCT was unusual in the first and second decade, therefore, in children and adolescents, many other benign lesions should be considered in the differential diagnosis: amongst which, minor salivary gland tumors, dermoid cysts, vascular lesions, lipomas, benign mesenchymal neoplasm, neurofibroma and traumatic fibroma [8]. In the study, a case is described of GCT in a 16-year-old girl, which is a very rare occurrence, since these tumors typically manifest in subjects between the fourth and sixth decade.

Surgical excisional biopsy of the tumor represents the first choice, both for diagnosis and treatment. In the majority of cases, it is curative; albeit, removal of the lesion should be wide enough to grant oncological radicality, irrespective of the final histological diagnosis. Upon histological examination, GCT typically shows small nests and sheets of polygonal cells with small vesicular nuclei and granular eosinophilic cytoplasm (Figure 1). The latter is due to intracytoplasmic accumulation of lysosomes and appears to be the main morphological feature of GCT. Another peculiar finding is S100-reactivity that suggested a neural origin of the tumor; it should be remembered that granular cell populations have been described in some non-neural neoplasms of the skin, including benign fibrous histiocytoma, dermatomyofibroma and cutaneous leiomyosarcoma.

Another rare and recently described entity, sharing common histological features with GCT, is congenital granular cell lesion (CGCL), also known as congenital granular cell epulis or congenital granular cell tumor. Based on a recent review, moreover, differential diagnosis between GCT and CGCL can be made by immunohistochemical staining for S-100, which is negative in CGCL and positive in GCT [9].

The potential aggressiveness of this tumor should never be overlooked. Malignant granular cell tumors (MGCT) are extremely rare neoplasms, representing only 1-2% of all GCT [2]. The most accepted histological criteria for diagnosing MGCTs were established by Fanburg-Smith et al. [2] (FS criteria). These researchers proposed the following six histological criteria for the MGCTs in their study: necrosis, spindling of the tumor cells, vesicular nuclei with large nucleoli, an increased mitotic rate, a high nuclear-to-cytoplasmic ratio and pleomorphism. A GCT was classified as “malignant” if it had 3 or more of these features, “atypical” if it had only 1-2 features and “benign” if none of these features or a focal nuclear pleomorphism was present. In contrast, Curtis et al. [10] classified MGCT into 3 categories: (1) tumors with both malignant behavior and malignant histology, (2) tumors with atypical histology that are clinically aggressive but not metastatic and (3) tumors with aggressive clinical behavior that are histologically benign. Therefore, it is notably difficult to diagnose a GCT as malignant because, although unusual, metastases can occur in histologically benign or atypical GCT. Moreover, accurate histological examination should include the assessment of proliferation markers, with particular regard to the Ki67-labelling index; nuclear antigen Ki67 is expressed during every phase of the cell cycle except G0 and, therefore, it can represent an important predictive factor [11]. In malignant GCT, the Ki67-index is usually > 10% [2]. In our case, the presence of hyperchromatic, but typical nuclei, abundant cytoplasm, lack of mitotic figures, and very low Ki67-index (less than 1%) ruled out an aggressive behavior and the lesion was hence diagnosed as benign GCT. It should be emphasized that a definitive diagnosis of GCT can only be made following accurate histological examination and that the risk of recurrence is strongly influenced by the status of the surgical margins [12, 13], which, in our case, were tumor-free. After surgery, long-term follow-up should be started, because of the risk of local or distant recurrence even several years after surgery [14]. The recurrence rate is very variable, ranging from 2-50%, depending on surgical radicality and on the presence of infiltrative growth pattern [15]. Because of the rarity of case reports of thyroid GCT, we could not know the influence of the tumor to the function of thyroid. In the present study, triiodothyronine and
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tetraiodothyronine in blood were normal, which illustrated this tumor did not influence the function of thyroid.

Conclusion

Despite its low prevalence, GCT should be considered in the differential diagnosis of thyroid lesions. Differential diagnosis between GCT and several other benign and malignant neoplasms, eventually showing granular cell features, such as smooth muscle, vascular, fibro-histiocytic, true histiocytic, and melanocytic tumors, is extremely important with regard to treatment and prognosis [11]. In this setting, complete surgical removal of the tumor must be attempted, given the possibility of GCT to recur, and histological examination is the only way to assess the biological behavior. Histology and immunohistochemistry can confirm the diagnosis of GCT. Adverse immunohistochemical prognostic factors of GCT include Ki67-index. In the present case, we did not find any histological criterion of malignancy, and, not unlike the findings of Chrysomali et al. [11], the Ki67-index was very low, resulting positive only in occasional cases. Albeit, several cases of local and distant recurrence, even many years after excision of the primary tumor, have been reported in the literature, hence these lesions require long-term follow-up. In conclusion, we suggest that every oral lesion of unknown nature should undergo physical examination and/or appropriate imaging to reveal the clinical extension of the disease, and then, when feasible, surgically removed. The excision should be wide enough to ensure oncological radicality and accurate histological examination of the specimen; when granular cells are seen on histology, an appropriate immunohistochemical panel should be applied in order to assess the histological derivation and proliferative index of the tumor. Further clinical management can vary depending on the final histological diagnosis: when GCT is diagnosed, close follow-up should be planned in order to prevent any relapse. Anyway, morphological criteria and the Ki67-index can offer important prognostic information which allows the clinician to predict the biological behavior and the risk of recurrence and to avoid emotional discomfort to the patient, when no histological criteria of malignancy are observed and the proliferative index is low.

Disclosure of conflict of interest

None.

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