# Giant cell tumor of soft tissue originating from the thyroid: a case report and literature review

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**Case report**

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## Abstract

Background: Giant cell tumor of soft tissues (GCT-ST) is a low malignant uncommon neoplasm, with is histological and immunophenotype similar to that of GCT of bone. Primary giant cell tumor of soft tissue arising in the thyroid is exceedingly rare. Case presentation: We reported a new case of GCT-ST originating from the thyroid occurring in 69-year-old woman. Histologically, the tumor was composed of two morphological components, mononuclear cells admixed with multinucleated osteoclast-like giant cells. Tumor is devoid of atypia, pleomorphism, and atypical mitosis. Immunohistochemically, the tumor cells showed strongly positivity with antibodies to CD68, but were negative for AE1/AE3, EMA and additional muscle markers. Conclusions: Due to its rare occurrence, we analyzed the clinical features of patients with primary thyroid GCT-ST to summarize some of our experiences and conduct a literature. The interest of this case lies in the rarity of this entity, the difficulty in preoperative diagnosis, and the confusion with other malignancies.

## Background

Giant cell tumor of soft tissues (GCT-ST) is a very rare, hyperplastic neoplasm, with histological features similar to those occurring in the bone[1]. GCT-ST was first described in 1972, and characterized by the presence of a mixture of mononuclear cells and multinucleated osteoclast-like giant cells[2]. The cytological characteristics of monocytes are round to oval vesicular nuclei, and the osteoclast like giant cells are evenly distributed throughout the tumors, and their nuclei are similar to those of monocytes[3].

Most cases of GCT-ST have a benign clinical course, but can be locally aggressive, and only rarely metastasize[4]. Pulmonary metastasis is rare, but is usually clinically indolent[5]. However, in some reports, GCT-ST has exhibited a series of behaviors ranging from benign tumors to highly malignant tumors[6, 7]. The primary GCT-ST arising in the thyroid is indistinguishable histologically from its bone or soft tissue counterparts[8]. Benign giant cell tumors of the thyroid are extremely rare and under-recognized. In this article we reported a case of thyroid giant cell tumor and reviewed several reported cases to better described the clinicopathological features and differential diagnosis of this rare soft tissue tumor.

# Case Presentation

A 69-year-old woman presented with a recently self-detected mass in the left side of her neck. The patient had no other obvious symptoms and no history of thyroid disease. Physical examination revealed a palpable, firm, non-tender and well-defined mass in the neck, with a grade II enlargement of the left thyroid. No palpable axillary, supraclavicular, or infraclavicular lymphadenopathy were found to be palpable. Neck ultrasonography showed a 19 mm X 12 mm X 5 mm nodule with heterogeneous echo and clear boundary located within an enlarged left thyroid lobe (Fig. 1). The TSH level was normal at 2.66 mIU/liter, with T4 and T3 levels at 1.73 and 104.8 nmol/L, respectively. The results of laboratory tests including a complete blood count, serum amylase, glucose, liver and kidney function were normal.

Further computed tomography scan and general x-rays showed no additional soft tissue, bone, or lung masses. Given the suspicion for thyroid carcinoma, the patient underwent left unilateral thyroidectomy. Intraoperatively, the tumor was observed on the dorsal side of the middle pole in the left thyroid gland, about 4*3 cm in size, with obvious adhesion to trachea and cricothyroid muscle.

Insert Figure 1 here

## Methods

The excised specimens were fixed with 10% buffered formalin, tissue sections were routinely treated with hematoxylin and eosin. Immunohistochemical analysis was performed using the avidin-biotin complex immunoperoxidase technique and a set of commercially available primary antibodies. Immunohistochemical staining of formalin-fixed, paraffin-embedded sections were performed by heat-induced epitope retrieval, avidin-biotin synthesis and an automated immunestainer.

Specifications for the various antigens (Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd, Beijing, China) that we used were listed in Table 1. Corresponding positive and negative controls were performed on all test markers simultaneously.

Table 1
List of Antibodies for Immunohistochemical Studies

| Antiserum | Clone | Dilution | Source | Tumor cell reactivity mononuclear/giant cells | |
|---|---|---|---|---|---|
| AE1/AE3 | AE1/AE3 | 1:500 | Zsbio | negative | negative |
| CK19 | UMAB2 | 1:50 | Zsbio | negative | negative |
| TTF-1 | 8G7G3/1 | 1:100 | Zsbio | negative | negative |
| TG | OTI8F2 | 1:20 | Zsbio | negative | negative |
| Synaptophysin | UMAB112 | 1:200 | Zsbio | positive | negative |
| CD68 | KP1 | 1:500 | Zsbio | positive | positive |
| EMA | UMAB57 | 1:500 | Zsbio | negative | negative |
| Pax8 | OTI6H8 | 1:20 | Zsbio | negative | negative |
| Vimentin | V9 | 1:500 | Zsbio | positive | Positive |
| Desmin | D33 | 1:200 | Zsbio | negative | negative |
| HMB45 | HMB45 | 1:200 | Zsbio | negative | negative |
| S-100 | 15E2E2 + 4C4.9 | 1:50 | Zsbio | negative | negative |
| P63 | 4A4 + UMAB4 | 1:200 | Zsbio | negative | negative |
| SMA | UMAB237 | 1:500 | Zsbio | negative | negative |
| Ki67 | MIB1 | 1;100 | Zsbio | 10% | 30% |

## Results

# Gross and microscopic findings

Macroscopically, the excised specimen showed a well-defined nodular mass of 3.5*2.0*1.8 cm in size located in the thyroid lobe. The cut surface of the tumor was grayish brown and was a heterogeneous solid area. Areas of necrosis or hemorrhage were not grossly apparent. Low-magnification microscopic examination revealed a multinodular and well circumscribed mass that in areas interlaced with the surrounding thyroid gland. The lesion was segmented by fibrous connective tissue of varying thickness into nodules of varying sizes. Invasion of adjacent benign thyroid parenchyma with no epithelial hyperplasia or atypia.

The tumor was composed of mononuclear cells and osteoclast multinucleated giant cells. The nuclei of mononuclear cells are very similar to those of osteoclast multinucleated giant cells in nuclear morphology, and osteoclast giant cells were evenly distributed in nodules (Fig. 2). Monocytes in the tumor showed minimal pleomorphism and mitosis was rarely seen in our case (1–2/10 HPF). The cytoplasm of a monocytes is eosinophilic, and the nucleus is central, similar to that of giant cells. There was no osteoid formation, necrosis or invasion of lymph vessels.

Osteoclastic cells were mainly found in oval to round monocytes, but not in spindle monocytes. In addition, these cells tended to cluster at sites with extravasated erythrocytes. The number of nuclei in the giant cells ranged from 3 to more than 50. The tumor had no cellular atypia or pleomorphism. The nuclei of mesenchymal cells and giant cells was similar in morphology, with round to oval appearance, vesicular chromatin, eosinophilic prominent nucleoli, and surrounding radiating sulcus.

Insert Figure 2 here

# Immunohistochemistry

The mononuclear cells were positive for CD68, but negative for CK(pan), TG and TTF-1. Immunohistochemistry for CD68 was diffusely positive in the tumor, but the staining of multicellular cells was more intense than that of monocytes. The MIB-1 labeling index was high, ranging from 10–30% (Fig. 3). No epithelial structures of pan- cytokeratin, EMA, and TPO immunostaining were found in the tumor. The mononuclear tumor cells were negative for additional smooth muscle actin, desmin, and calcitonin. The tumor was diffusely positive for vimentin and negative for HMB45 as well as for S-100 protein (Table 1).

Insert Figure 3 here

# Clinical Course

Since there is no evidence of skeletal disease, these histopathological and immunophenotypic features were consistent with primary thyroid GCT-ST. He was admitted to another hospital with recurrence of left thyroid tumor, and total thyroidectomy was planned 3 month later. The diagnosis of GCT-ST was confirmed by pathologists of the Fudan University Shanghai Cancer Center. In the postoperative setting, the patient was totally asymptomatic, without hypocalcemia or recurrent nerve. No adjuvant chemotherapy was required. The patient remained well without signs of recurrence or metastatic spread after 8 months following up.

# Discussion

Giant cell tumor of soft tissue (GCT-ST) is a rare tumor, which often occurs in the superficial and deep soft tissue of the extremities. The etiology and histology of GCT-ST are controversial and largely unexplained[9]. In 1972, Salm and Sissons described 10 soft-tissue tumors with the same histological structures as giant cell tumors of bone[2]. Although the patients had local recurrence, the clinical manifestation was benign without metastasis[2]. Folpe et al. later proposed the term “low-malignant potential giant cell tumor” for patients with frequent clinical recurrence and unknown metastatic potential[9]. Currently, the World Health Organization classifies these tumors as GCT-ST with low malignant potential (GCT-LMP) and malignant GCT-ST[5, 10].

Primary giant cell tumor of soft tissue in visceral organs is uncommon, and GCT-ST arising in thyroid is extremely rare. To our knowledge, the case that we reported is the third case of a primary giant cell tumor originating in the thyroid in the English-language literature (Table 2)[8, 11]. Due to its rare occurrence, we analyzed the clinical features of patients with primary thyroid giant cell tumor, summarized some of our experience and reported in the literature.

Table 2
Clinico-pathological features of primary giant cell tumor of the thyroid

| Cases | Age/gender | Symptoms | Ultrasonography | Size (cm) | Gross features | Treatment | Follow-up | Outcome |
|---|---|---|---|---|---|---|---|---|
| Xiaorong Zhang et (2018) [11] | 40/M | An increasing enlarged mass with pain and hoarseness | With heterogeneous echo and clear boundary | 5.8 | NA | Removed the tumor by surgery | NA | NA |
| O. Derbel et (2012) [8] | 38/M | A swelling on the neck | Appeared as a hypoechogenic and heterogeneous mass with central vascularization | 3.5 | NA | Treated with denosumab and total thyroidectomy | NA | NA |
| Dai et al (current case) | 69/F | Self-detected mass on the neck | A mixed echo mass with clear boundary and insufficient bold supply | 3.5 | the tumor was gray-brown with heterogeneous firm area | Total thyroidectomy | 8 months | Without recurrence or metastatic |

| Cases | Characteristic features on microscopic examination | MIB-1 labeling | Positive immunostains | Negative immunostains | Lymph node metastasis | Distant metastasis |
|---|---|---|---|---|---|---|
| O. Derbel et (2012) [8] | Histopathological findings corresponded to proliferation of round to oval or elongated mononuclear cells mixed with numerous osteoclast-like giant cells | Less than 10% only on mononuclear cells | CD68, mononuclear cells were weakly stained with p63 and RANK; giant cells were weakly RANK ligand stained | TTF-1, AE1/AE3, TG | Absent | Absent |
| Xiaorong Zhang et (2018) [11] | The section of cell block showed mononuclear cell proliferation with scattered giant cell component | Ranged from 5–10% | The mononuclear cells were positive for P63, the giant cells were positive for CD68 | PCK, TG, TTF-1 and CT | NA | NA |
| Dai et al (current case) | The tumor was composed of two morphological components, mononuclear cells admixed with multinucleated osteoclast-like giant cells. | Ranged from 15–40% | The tumor cells showed strongly positivity with CD68 and vimentin | AE1/AE3, EMA, HMB45, S-100 and additional muscle markers | Absent | Absent |
| Abbreviations: NA, not available; NED, no evidence of disease | | | | | | |

The clinical manifestation of this disease is not specific, the first patient had no symptoms of pain, and the second patient had accompanied with pain and hoarseness. In our case, the patient was suffering from a painless growing mass in the neck. All lesions have been solitary, well-defined and ranged in size from 3.5 to 5.8 cm. Although the number of reported cases of thyroid GCT-ST is small, these tumors appear to occur in elderly patients. The patients were initially misdiagnosed as thyroid carcinoma because of the variable patterns of the tumor.

Histopathological examination revealed that the tumor consisted of mononuclear cells mixed with osteoclast-like cells, similar to the GCT of bone. The tumor, although well defined, showed superficial infiltration into the surrounding tissue. Both types of tumor have a diffuse distribution of osteoclast-like giant cells, but the histopathological diagnosis is based on the background component of mononuclear cells. The mononucleated and multinucleated cells showed mild atypia but no necrosis. Mononuclear differentiation of these two cell components had been proposed, and polynuclear cells are formed by fusion of the mononuclear component. The mononuclear cells lacked obvious atypia and are round to ovoid with nuclei similar to giant cells. Mitotic activity may be active, but there is no abnormal mitotic image in the case description of either tumor type.

Immunohistochemical examination showed staining for p63 and CD68, and no staining with a panel of cytokeratin antibodies in one case was found. In one case, the mononuclear cells were positive for RANK and giant cells were positive for RANKL[8], which would explain the osteolysis associated with these giant cell rich tumors[12, 13]. Immunohistochemical staining was positive for CD68 and vimentin, but was negative for a group of epithelial and additional smooth muscle markers, suggesting a mesenchymal lineage[14]. The exact nature of both osseous and extra-osseous osteoclast giant cell tumors is still controversial, although many protocells including undifferentiated mesenchymal, endothelial cells, reticular endothelial cells and epithelial cells have been identified as the source for extra-osseous GCT[12, 15–17]. In addition, p53 can be expressed not only in GCT of visceral organs, but also of bone, and the malignant form of GCT of bone has been presented as a new entity in the recent WHO classification[3, 10].

Differential diagnoses of thyroid giant cell lesions include subacute thyroiditis, papillary carcinoma, anaplastic carcinomas and true granulomatous, such as fungal infection, tuberculosis, or sarcoidosis[18]. The dual cell pattern and immunophenotype of GCT-ST contribute to identification. In contrast, these should be no significant nuclear atypia to distinguish from giant cell rich sarcomas or malignant GCT. In our case, carcinoma was ruled out because of the lack of staining for epithelial markers. The absence of significant nuclear pleomorphism excluded the possibilities of malignant fibrous histiocytomas and giant cell osteosarcoma.

In the differential diagnosis of GCT-ST, lesion rich in osteoclast giant cells should include the giant cell variant of malignant fibrous histiocytoma (MFH), plexiform fibrohistiocytoma (PFT), and extra-osseous osteosarcoma (ES-OGS)[7, 19, 20]. The giant cell variant

of MFH include pleomorphic sarcoma with abundant giant cells and interstitial spindle cells. If GCT-ST is not malignant, there is no atypia or anaplasia. If it is malignant, only mononuclear cells appear atypia and not pleomorphic sarcoma characteristics. The main differences between GCT-ST and PFT are non-plexus growth pattern, large nodular size and the osteoclastic aspect of the giant cells. Histologically, the nodules found in GCT-ST are larger and frequently exhibit the histological characteristics of a uniformly distributed multicellular osteoclast like giant cell, which is not found in PFT.

The ES-OGS, rich in giant cells, is a distinctly anamorphic tumor, with the cellular population that exhibits marked atypia and pleomorphism, as well as numerous bizarre, mitotic figures. Bone and osteoid formation in ES-OGS is produced by the sarcomatous, spindle cell stroma, different from the osteoblast-lined, metaplastic bone trabeculae seen at the cases of GCT-ST. Another important consideration is to exclude the possibility of soft tissue expansion or recurrence of primary giant cell tumor of bone, which can be achieved by careful radiologic exanimation and a concentrated clinical history of any patient with GCT-ST. Because of the similarities between the 2 entities, potential primary bone tumors should be excluded before rendering a diagnosis of GCT-ST. In our case, these was no clinical or radiological evidence of bone involvement.

Since most GCT-ST have a benign clinical course, the best treatment is to perform conservative surgical resection with free surgical margins whenever possible[3, 4, 21]. Radiotherapy should be considered in the case of incomplete resection of the surgical margin, as it is close to the critical structures.[20] Currently, GCT-ST treatment has no standard treatment; however, some clinical case studies and one retrospective case-control study have shown that denosumab, a RANKL inhibitor, may reduce local recurrences after surgical treatment in the lower extremities by inducing apoptosis of giant cells and stromal cells within the tumor[12]. The prognosis factors of GCT-ST are unclear, strict follow-up is recommended as local recurrence and metastasis cannot be predicted[22]. No metastasis was identified in either case and there was no evidence of recurrence after 8 months of follow-up in our case. Most cases of GCT-ST and GCT of bone have a benign clinical course, but can be locally aggressive. Pulmonary metastases occur rarely, but are usually clinically indolent[23]. The prognosis of pure de novo GCT in visceral organ is similar to the bone counterparts and aggressive behavior is very rare, thus total excision is an adequate treatment choice.

In summary, primary thyroid GCT-ST is a rare neoplasm composed of mononuclear and multinucleated cells. Familiarity with this rare entity and its salient histologic and immunochemical findings ensures accurate diagnosis and discrimination from other thyroid tumors. Given the rarity primary thyroid GCT-ST, the management and prognosis of these patients need to be individualized until larger studies are available.

## Conclusion

The prognosis of GCT-ST may vary widely, with some patients presenting a slow-growing disease and others presenting a rapidly progressive form, however, thyroid GCT-ST, compared to other tumor, is considered to be associated with excellent prognosis. Pathologists and clinicians need to be aware of the rare diagnosis of GCT-ST in thyroid and should carefully evaluate its clinical and ultrasonography findings.

## Declarations

### Ethics approval and consent to participate

The Ethics Review Committee of Zhuji People's Hospital of Zhejiang Province. A copy of the written consent is available for review by the author of this paper.

### Consent for publication

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

### Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon request.

### Authors' contributions

Jianrong Chen, Haiyong Zhang were responsible for the conception and design of the experiments. Xiufang Li and Mengjun Hu contributed to the acquisition, analysis and interpretation of the data. Jiangrong Chen and Huan Lei drafted the manuscript. Xiaomin Dai and Fang Peng revised the manuscript. All authors have read and approved the final manuscript.

### Competing interests

The authors declare that they have no competing interest.


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# Figures

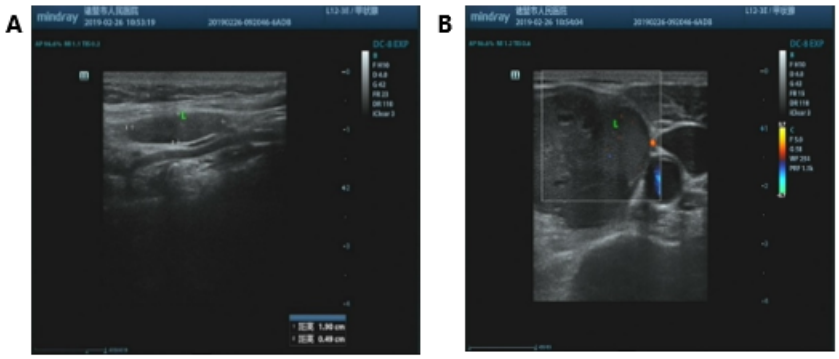



**Figure 1**

The neck ultrasonography showed an oval mass with soft tissue density and unclear boundary adhered to the left lobe of the thyroid.

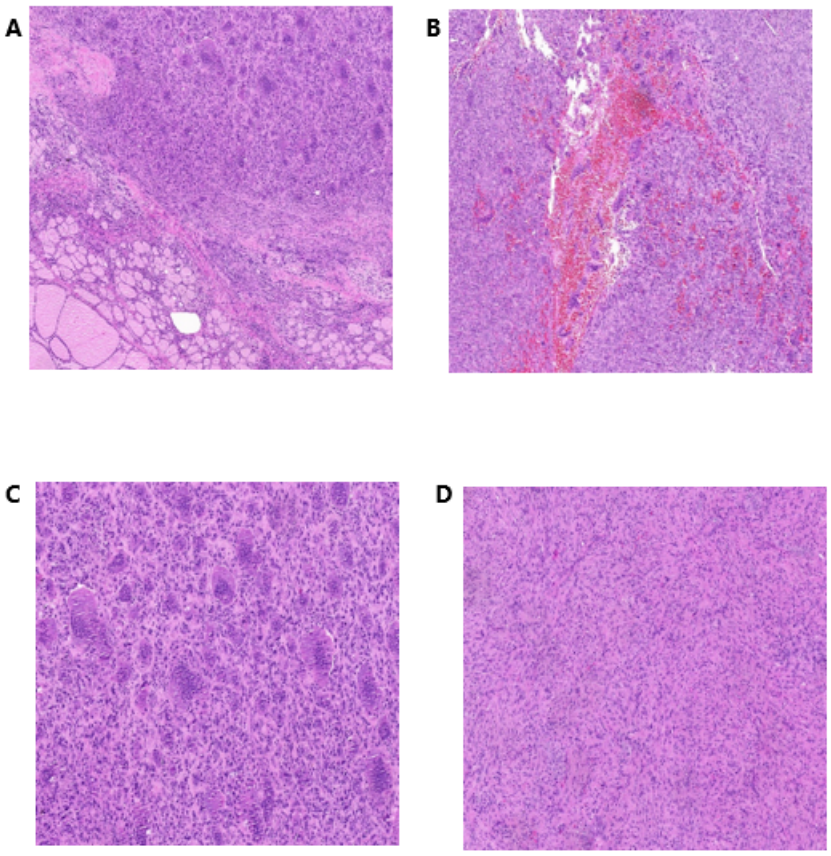
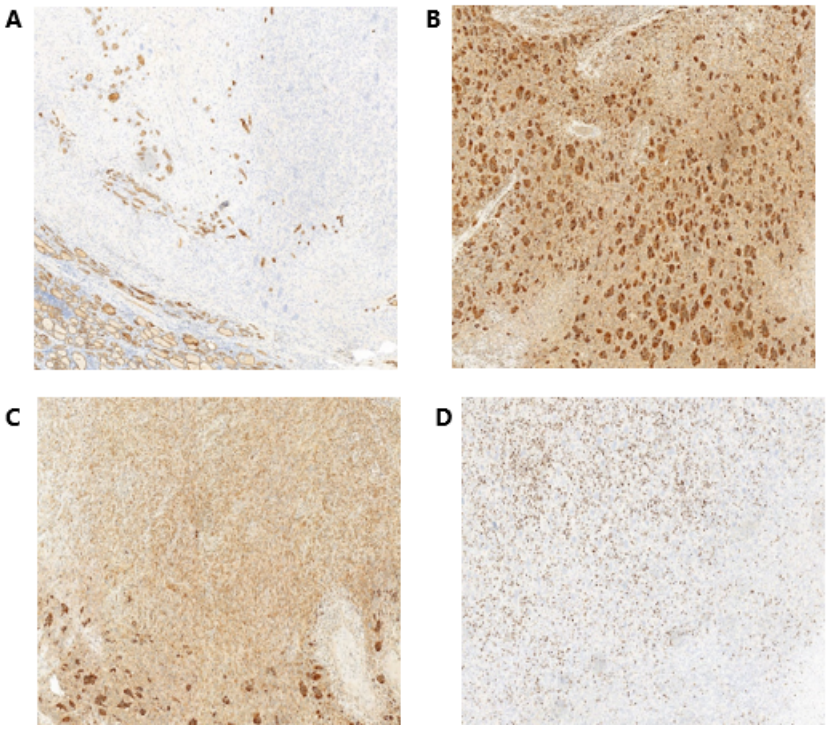



Figure 2

Histological features of thyroid GCT-ST. A. Mononuclear stromal cells and a large number of multinucleated cells mixed with foamy macrophages. B. Hemorrhagic cystic formation is seen in the nodules, with marked interstitial fibrosis. C. Osteoclast-like giant cells can be very large, with more than 40 nuclei. There are recognizable mitotic forms, but the cells exhibit minimal nuclear pleomorphism. D. Mononuclear cells are histological and locally spindle shaped, with mitotic appearance but no cell atypia (Hematoxylin and eosin, with original magnifications of 100x, 100x, 200x, and 200x, respectively).



## Figure 3

Immunohistochemical staining characteristics of thyroid GCT-ST. (A. The tumor cells are negative for CK(pan) by immunohistochemical staining. B. Immunostaining for CD68 is positive in mononuclear cells. C. Immunostaining for CD68more significant in multinucleated giant cells. D. Immunostaining of the proliferation marker Ki-67 mainly existed in the mononuclear cells (IHC staining, 100x).