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Case Report

Pathology Section

Case of Malignancy Arising from Giant Cell Tumour of Soft-tissue Involving Thyroid Mimicking Thyroid Carcinoma: A Potential Pitfall

LEKSHMI VIJAYAKUMARAN NAIR LILLY[1], DEEPTHI BEENA[2], RACHEL ABRAHAM[3]

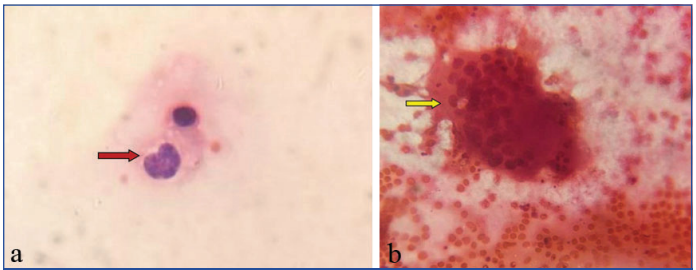
ABSTRACT

Giant Cell Tumour of soft-tissue (GCT-ST) is a rare neoplasm which is morphologically similar and genetically unrelated to GCT bone and included under intermediate rarely metastasising category. They are reported predominantly in superficial soft-tissue of the upper and lower extremities and less frequently in head and neck. The authors present a case of malignancy arising from GCT-ST involving thyroid gland mimicking primary thyroid malignancy. An 80-year-old female presented in the Outpatient Department (OPD) with a neck swelling of six months duration and sudden increase in size and hoarseness of voice for two weeks. An upfront surgery was planned with a clinical suspicion of primary thyroid neoplasm. Intraoperatively, the thyroid gland was replaced by multiple nodules, which were seen infiltrating adjacent structures. Due to the invasive nature, only a subtotal thyroid resection was done. The histopathology showed predominantly neoplasm composed of mononuclear cells and sheets of osteoclast like giant cells with foci showing features of malignancy. Histomorphology along with Immunohistochemistry (IHC) confirmed a diagnosis of GCT-ST involving the thyroid gland. Due to the rapidly progressive nature of the disease, the patient succumbed within two months.

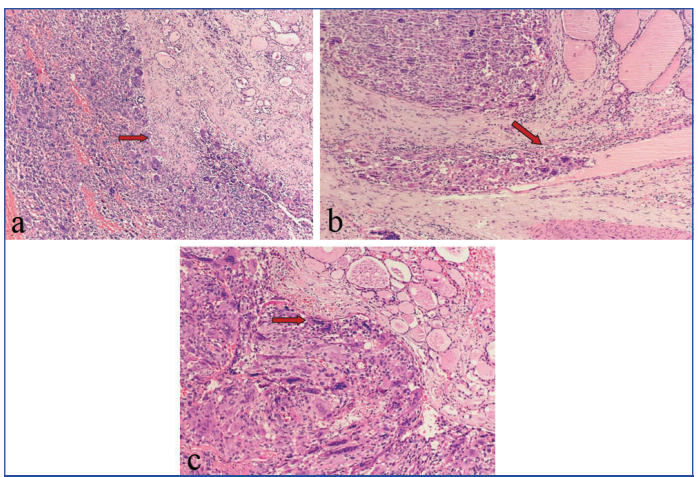
Keywords: Anaplastic thyroid carcinoma, Fine needle aspiration cytology, Immunohistochemistry, Metastasis, Spindle cells

CASE REPORT

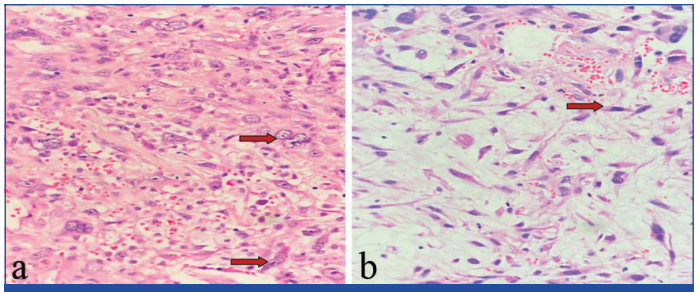
An eighty-year-old female patient presented in the Outpatient Department (OPD) with complaints of painless right-side neck swelling for six months with sudden increase in size and hoarseness of voice for past two weeks. On clinical examination, the right lobe was enlarged with restricted mobility and deviated carotid pulsation. Thyroid function tests were within normal limits. Ultrasound scan done outside showed Thyroid Imaging Reporting and Data Systems (TIRADS)-4 large heteroechoic nodule with multiple cystic areas, punctate calcification and internal septations measuring 4.1×2.5 cm, which almost completely replaced the right lobe of thyroid. Fine Needle Aspiration Cytology (FNAC) done from the swelling showed paucicellular smears with a few mononuclear cells with anisonucleosis and multinucleated giant cells with osteoclast like morphology [Table/Fig-1a,b]. With differential diagnosis of Anaplastic Thyroid Carcinoma (ATC) and soft-tissue neoplasm infiltrating thyroid gland, an FNAC diagnosis of Bethesda System of Reporting Thyroid Cytology (Category V)- suspicious of malignancy was given. An upfront surgery was planned. Intraoperatively, the thyroid gland was replaced by multiple nodules which were infiltrating strap muscles, tracheal surface and right Internal Jugular Vein (IJV). A complete resection of thyroid gland was not possible due to the highly invasive nature of the lesion and hence subtotal resection of thyroid was done. Gross examination showed an ill circumscribed grey white firm lesion involving thyroid with areas of haemorrhage. Microscopy showed portions of a neoplasm composed predominantly of mononuclear cells and multinucleated osteoclast like giant cells infiltrating the thyroid gland, with large areas of haemorrhage, fibrosis and focal metaplastic bone formation. Mitotic activity, necrosis and vascular invasion were seen [Table/Fig-2a-c]. Foci showing atypical spindle cells arranged in sheets with bizarre nuclei, were suggestive of malignancy [Table/Fig-3a,b]. With this, a provisional diagnosis of malignancy of thyroid with osteoclast like giant cells was rendered. The main differential diagnosis considered at this point was: 1) Osteoclastic variant of ATC; and 2) Malignancy in Giant Cell Tumour of soft-tissue (GCT-ST) involving thyroid. In order to differentiate between these two, an Immunohistochemistry (IHC) panel of Cytokeratin (CK), Paired-box gene 8 (PAX8) and Cluster



[Table/Fig-1]: a) FNAC smear (PAP stain, 400x) showing mononuclear cells with anisonucleosis. b) FNAC smear (PAP stain, 400x) showing multinucleated giant cell with osteoclast-like morphology.

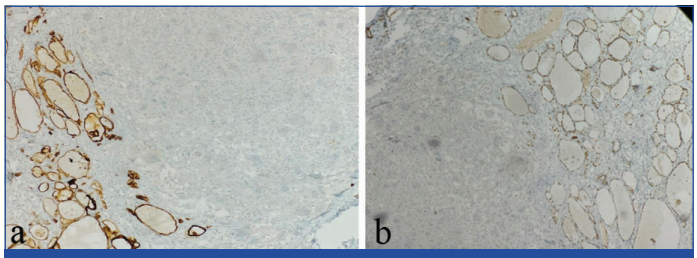


[Table/Fig-2]: a) Low power (H&E stain, 200x) view of neoplasm composed of mononuclear cells and multinucleated osteoclast-like giant cells infiltrating thyroid. b) Low power (H&E stain, 200x) view of neoplasm with thyroid showing lymphovascular invasion. c) High power (H&E stain, 400x) view of neoplasm composed of mononuclear cells and multinucleated osteoclast-like giant cells infiltrating thyroid.

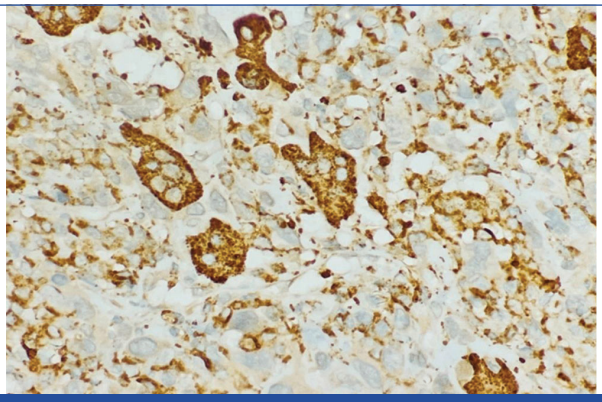


[Table/Fig-3]: a) High power (H&E stain, 400x) view showing atypical spindle cells and bizarre cells in sheets. b) High power (H&E stain, 400x) view showing atypical spindle cells in loose stroma.

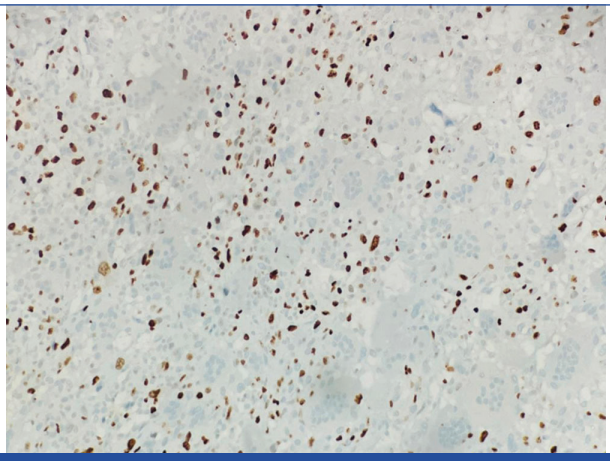
of Differentiation 68 (CD68) were done. Kiel67 (Ki67) was done to know the proliferation index. Immunoprofile showed CK and PAX8 positivity in the thyroid follicles and negative in the mononuclear cells, multinucleate giant cells and atypical spindle cells [Table/Fig-4a,b]. Mononuclear cells, multinucleate osteoclast like giant cells and atypical spindle cells were strongly and diffusely positive for the histiocytic marker CD68 [Table/Fig-5]. Ki67 showed a proliferation index of 35-45% in atypical spindled areas [Table/Fig-6]. A final diagnosis of malignancy arising in GCT-ST involving thyroid gland was rendered. Postoperatively, the symptoms worsened and the patient succumbed within two months.



[Table/Fig-4]: a) Cytokeratin (CK) positivity in thyroid follicles and negative in mononuclear/multinucleate giant cells (IHC,200x). b) PAX8 nuclear positivity in thyroid follicles and negative in mononuclear/multinucleate giant cells (IHC, 200x).



[Table/Fig-5]: Strong diffuse cytoplasmic positivity of CD68 in mononuclear/multinucleate giant cells (IHC, 400x).



[Table/Fig-6]: Ki67 showing proliferation index of 35-45% in atypical cells (IHC, 200x).

DISCUSSION

The GCT-ST is a rare neoplasm with an uncertain behaviour [1]. Salm R and Sissons HA first described GCT-ST in 1972 [2]. Superficial soft-tissue of upper and lower extremities are the most common sites of its occurrence, less frequently involve trunk and head and neck region [3]. It occurs predominantly in the 5th decade of life with no sex predilection [1]. GCT of bone and GCT-ST are morphologically similar but genetically unrelated [1]. GCT of bone harbour mutations of H3.3 Histone A (H3F3A) gene, while GCT-ST lacks this mutation [1]. GCT of bone is a locally aggressive and rarely metastasising neoplasm, which represents 4-5% of all primary bone tumours. Malignancy arising from GCT is less than 10%.

Clinically, GCT-ST usually manifests as an asymptomatic mass, but some may show an aggressive behaviour. The usual course of disease is benign with high chance of local recurrence and rare metastasis. Malignant GCT-ST is extremely rare, characterised by pleomorphism, nuclear atypia and increased mitosis [4].

Microscopically, GCT-ST displays a multinodular architecture with cellular nodules separated by fibrous septae. The nodules are composed of mixture of round to oval mononuclear cells and osteoclast-like multinucleated giant cells with similar nuclear features. Stroma is richly vascularised. Mitotic activity can be seen in some of the cases. Nuclear pleomorphism and bizarre giant cells are usually absent. Necrosis is rarely found. Metaplastic bone formation is seen in around 50% of cases. Aneurysmal bone cyst-like changes may be seen. Vascular invasion is identified in around 30% of tumours [1]. GCT-ST show similar immunohistochemical staining profile as GCT of bone; hence IHC is not helpful in differentiating both these entities [1]. CD68 shows immunoreactivity mainly in osteoclast-like giant cells and focally in mononuclear stromal cells [4]. Mononuclear cells may be weakly stained with an antibody against p63 [5].

Head and neck region is a rare site for this tumour with a few case reports till date [6]. GCT-ST involving the thyroid region is extremely rare, which can be misdiagnosed. Differential diagnosis of thyroid giant cell lesions includes subacute thyroiditis, papillary carcinoma, anaplastic carcinoma and granulomatous lesions. The dual cell pattern and immunophenotype of GCT-ST contribute in diagnosis. The most important differential diagnosis is the osteoclastic variant of ATC [7]. ATC is a highly malignant tumour composed of undifferentiated cells with marked cytological pleomorphism and mitotic activity, which retain features of epithelial origin. Lack of expression of CK and thyroid lineage marker (PAX8) rules out ATC [4] and CD68 positivity confirms GCT [8]. Other differential is giant cell variant of Malignant Fibrous Histiocytoma (MFH)/pleomorphic sarcoma [9], which show highly pleomorphic and bizarre mononuclear cells in storiform pattern with atypical multinucleate giant cells. The present case showed predominantly a uniform distribution of bland mononuclear cells and osteoclastic giant cells with foci of cytological atypia in mononuclear cells, hence can rule out MFH. Another rare differential diagnosis is extraosseous osteosarcoma, which exhibits marked atypia and pleomorphism with osteoid formation. GCT-ST shows metaplastic bone formation and no osteoid [9]. In the present case, the tumour had no connection with underlying bone, both in radiology and intraoperatively; hence can rule out GCT-bone and giant cell rich osteosarcoma.

Derbel O et al., discussed a case of a 38-year-old male with GCT-ST involving thyroid cartilage, initially treated as thyroid cancer. The patient received denosumab, with a complete reduction in tumour size after treatment. Later, partial laryngectomy was done and showed complete pathological response [5].

Chen J et al., discussed another case of a 69-year-old woman with a mass in the neck, who underwent total thyroidectomy and diagnosed as primary thyroid GCT-ST. The patient remained well without signs of recurrence or metastatic spread after eight months of follow-up [9].

Chen JY et al., described a similar case of GCT-ST in a 70-year-old female patient with a painless swelling in the neck. Complete tumour resection was difficult in that case. The patient later presented with tumour relapse and showed malignant features. The patient was then treated with denosumab and showed tumour shrinkage [4].

Surgical complete excision is the treatment of choice, however, in cases of unresectable tumours a systemic therapy may be tried. Bisphosphonates such as zoledronic acid and pamindronic acid can induce apoptosis in GCT-ST, so is used in treatment [8]. Denosumab, a monoclonal antibody directed against Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) is a treatment option for unresectable GCT. RANKL is a member of Tumour Necrosis Factor (TNF) cytokine family, which is a key factor for osteoclast differentiation and activation. Denosumab was approved by the United States Food and Drug Administration (USFDA) in May 2019 for treatment in GCT of bone [4]. Other treatment options include interferon α and radiotherapy [10].

CONCLUSION(S)

GCT-ST in the head and neck region is very rare with only a few cases reported till date. The morphology along with the IHC of this rare entity should prompt pathologists to keep this in the differential diagnosis when dealing with lesions of the head and neck. Also, the treatment modalities differ when compared to primary thyroid malignancy.

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PARTICULARS OF CONTRIBUTORS:
1. Specialist, Department of Pathology, KIMSHEALTH Hospital, Thiruvananthapuram, Kerala, India.
2. Consultant, Department of Pathology, KIMSHEALTH Hospital, Thiruvananthapuram, Kerala, India.
3. Consultant and Head, Department of Pathology, KIMSHEALTH Hospital, Thiruvananthapuram, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Rachel Abraham,
'Muttattu', House No. 411, 4th Lane, Mar Ivanios Nagar, Kesavadasapuram,
Pattom PO, Thiruvananthapuram-695004, Kerala, India.
E-mail: dr.rachelabraham@gmail.com

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