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GRANULAR CELL TUMOR: A CHALLENGING AND UNDER REPORTED ENTITY; REPORT FROM A TERTIARY CANCER CENTER IN INDIA

Oncology

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ABSTRACT

Background: Granular cell tumor (GCT) is a very uncommon tumor which is originated from the Schwann cells and are found to express the neural markers like S-100 protein and SOX 10. Often, it is a benign lesion. Histopathologically, there are granular cell infiltrations without necrosis which are periodic acid Schiff (PAS) stain positive and reactive with CD68, SOX-10 and S-100. The aim of this study is the clinicopathological evaluation of GCT. **Material and Methods:** In this paper, we described the experience of 3 patients with a GCT in different locations (1 cases in the anterior abdominal wall and 1 case in the lung and 1 case in chest wall). **Result:** In one case, the presence of a lesion in the lung, which is extremely rare. The other two cases involved the dermis mimicking some adnexal tumors. Conclusion: Histologically, there were granular cell infiltrations without necrosis which are confirmed by immunohistochemistry.

KEYWORDS

INTRODUCTION:

Granular cell tumour (GCT), Abrikossoff's tumour or Myoblastoma is an uncommon benign neoplasm that was first described in 1926 by Abrikossoff. Initially it was termed as "myoblastic myomata", because this tumor was thought to be of skeletal muscle origin. However, on further research over the ensuing years, it was later noted that tumors were often located adjacent to peripheral nerves, implying a neural origin. Although their histogenesis is still uncertain, they are accepted to have been originated from the Schwann cells.[1,2]

GCT is a rare benign neoplasm, that occurs more commonly between the fourth and the sixth decades of life, being rare in children. It is more prevalent in women than in men.[6,7] Black patients are more prevalent than whites (3:1).[7] Most GCTs are found in the head and neck region, with tongue being the most common location (23–28%).[5,6] They have been reported in the skin, oesophagus, larynx, stomach, bile duct, and male and female reproductive tract also.[5,6,11] Herein, we discuss 3 case of granular cell tumor of uncommon sites with clinicopathological and immunohistochemical evaluation.

Case Reports:

Our first case was a 36-year-old female presented with complaints of fever and cough with expectoration for 3 months. She was on medication for Pneumonia, diagnosed in some outside hospital. CECT Thorax was done in-house, which revealed a well-defined rounded soft tissue density lesion in the right upper lobe of lung with minimal enhancement. The lesion was in close vicinity of mediastinum and the features were suggestive of benign neoplastic lesion. F-18-FDG PET/CT was done, which also showed a metabolically active nodule in the upper lobe of right lung, measuring 24x20mm, with SUV max 4.73. No suspicious nodules were noted in rest of the bilateral lung fields. Guided lung biopsy was done from the lesion. Histopathology revealed a benign neoplasm with sheets of large tumor cells having eosinophilic granular cytoplasm and uniform round nuclei. The adjacent lung parenchyma showed mild chronic inflammation, and was otherwise unremarkable. On immunohistochemistry the tumor cells were positive for S-100, SOX 10 and CD68, while negative for PAN-CK, hence a diagnosis of granular cell tumor of lung was given. A surgical management of wide excision was planned for the patient. However, the patient was lost to follow up.

The second case was a 45-year-old female presented with swelling over the anterior abdominal wall for 1 year, with history of hysterectomy 3 years back. On examination a lump was palpable in supraumbilical region, which was fixed, hard in consistency, and measured 3x3 cm in size. Contrast enhanced MRI of upper abdomen was done, which revealed a spiculated T1/T2 lesion measuring 2.3x3.4x3.7cm in anterior abdominal wall, within the supraumbilical region, closely abutting rectus abdominis muscle and linea alba. No intra abdominal extension was noted. Radiological differentials suggested were abdominal wall endometriosis and neoplastic lesion, likely sarcoma. In outside hospital, FNAC was done from the lesion which revealed suspicious atypical cells. Further, In house abdominal wall lesion biopsy was done and histopathology revealed neoplasm composed of cells arranged in sheets. The cells were polygonal-shaped with mild to moderate nuclear atypia with dispersed chromatin, conspicuous nucleoli, and moderate to abundant eosinophilic cytoplasm with coarse granules. On immunohistochemistry, tumor cells were diffusely positive for S-100 and CD68, hence a diagnosis of granular cell tumor was given. Patient was planned for wide local excision of the mass. Post-operative follow up for 13 months is uneventful.

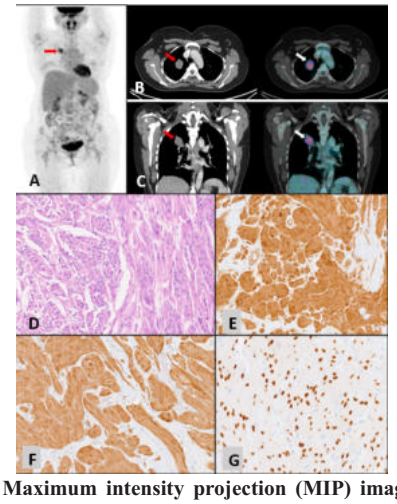

Figure 1: **Maximum intensity projection (MIP) image** showing focal increased glucose metabolism in the right upper mediastinal region (arrow) (A). Axial, Coronal CT and fused FDG PET/CT images showing a well defined rounded soft tissue lesion involving the upper lobe of right lung (arrows) (B,C). **Histopathology of the lung biopsy** shows nests of atypical cells having abundant granular cytoplasm, H&E 40X (D). **Immunohistochemistry** shows diffuse positivity of the tumor cells for CD68 (E), S-100 (F) and SOX-10 (G).

Our third case is a 31-year-old female presented with right axillary mass since 2 years with associated back pain. Patient had last child birth, 1 year back and breastfed the child for more than 6-month duration. On examination, a lump was noted behind posterior right axillary line in 5th Intercostal space, measuring 3x 3 cm lump. No right axillary lymph node was palpable. MRI thorax was performed and a well-defined lobulated lesion was identified with skin and

subcutaneous plane altered signal intensity, involving the right chest wall, measuring approximately 4 x 2.6 x 2.8 cm in size. The underlying muscles and bones were uninvolved. Reactive right axillary adenopathy were noted. Biopsy was done from the lesion, histopathology done revealed fibro collagenous tissue infiltrated by a tumor arranged in sheets and nests. The individual cells were round to polygonal, with abundant granular cytoplasm, small hyperchromatic nuclei showing mild nuclear atypia. On immunohistochemistry, the tumor cells were positive for CD68, SOX10 and S100, while negative for PanCK and Inhibin A. Hence a diagnosis of granular cell tumor was made. A wide local excision was done for the patient and specimen was sent for histopathology. On meticulous examination of the specimen and slides, a diagnosis of Malignant granular cell tumor was made. All the margins of resected specimen were free of tumor. The patient is doing well, with no recurrence in 17 month follow up.

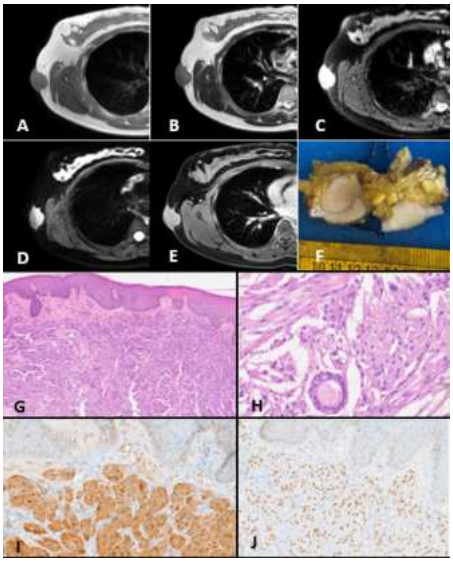

Figure 2: Axial MRI images showing a well-defined lobulated altered signal intensity lesion involving the skin and subcutaneous plane of right chest wall region (arrow). It appears isointense on T1 weighted image (A), iso to slightly hyperintense on T2 weighted image (B), hyperintense on T2 weighted FAT SAT image (C), shows diffusion restriction (D) and heterogeneous post-contrast enhancement (E). Gross image of the specimen shows solid, grey-white tumor in the dermis (F). Histologically the tumor is composed of nests and lobules of large polygonal cells infiltrating the dermis, H&E 10X (G). The cells have abundant granular cytoplasm and uniform round nuclei, H&E 40X (H). Immunohistochemically tumor cells are positive for S-100 (I) and SOX-10 (J)

DISCUSSION:

Granular cell tumors were first described by Abrikossoff in 1926 and named as myoblastomas, as they were considered to derive from smooth muscle. In 1935, Feyrter, postulated that these tumors were neural in origin and termed them granular cell neuromas. In 1948, Fust and Custer proposed a new term– granular cell neurofibroma. In 1962, Fisher and Wechsler conducted ultrastructural and immunohistochemistry studies to find that Schwann's cells were the most likely origin of these tumors, and thus termed them as granular cell schwannomas (Garin et al., 1992). However, granular cell tumor (GCT) is the current nomenclature adopted by the World Health Organization (WHO) (Garin et al., 1992).[7]

Granular cell tumour (GCT), is an uncommon, neuro derived tumor, originating from Schwann cells. In spite of the arguments around the origin of GCTs, the apparent connection with Schwann's cells is based on concrete findings such as ultrastructural similarity between Schwann's and granular cells; similarity between the granules in granular cells and altered myelin; concentric arrangement of granular cells around nerve ends; presence of lipoproteins and sphingomyelin in granular cells indicating that the granules in granular cells are made of myelin or the product of its degradation; and positivity for protein S-100, enolase, and myelinic proteins PO and P2 by immunoperoxidase techniques.[7]

Majority of GCTs present as solitary, non-tender, slow-growing, non-ulcerative lesions. 5% of GCTs can be multicentric. The abdominal wall is not a common site for both benign and malignant GCTs. Rehan et. Al. reported 30 previous cases of abdominal wall GCTs so far. Out of these 30 cases, 11 were malignant, 1 atypical, and 18 were benign. These were distributed between 6 to 70 years of age, 20 were females and 10 males. The average size for MGCT was 7.25 cm (4.5–11 cm) and benign GCTs were smaller with an average size of 4.0 cm (0.5–10 cm). 6 patients with MGCT developed recurrence and or metastatic deposits at sites including lungs, liver, breast, bone and lymph nodes.[1] And herein we report a case of abdominal wall GCT in a 45-year-old female.

Histologically, Granular cell tumour is composed of sheets and nests of largely monotonous epithelioid to polygonal cells with abundant eosinophilic, granular cytoplasm. Cell borders may be indistinct, producing a syncytial appearance. Nuclei are usually centrally situated and range from uniformly small and mildly hyperchromatic to larger and vesicular with distinct nucleoli. Mitoses are variable in number but usually not prominent. The finely granular appearance of the cytoplasm is due to massive accumulation of lysosomes including larger intracytoplasmic granules highlighted by clear haloes. [3,9] On immunohistochemistry, are positive for S100, SOX10, nestin, inhibin, and calretinin while are negative for EMA, desmin, AE1/AE3 and SMA.[3,9]

Table 1: Clinicopathological details of the cases.

Case no	Age	Sex	Site	Size	Histopathology	IHC markers positive	IHC markers negative	Type	Treatment
1	36	F	Right upper lobe Lung lesion	2.4x 2cm.	Nests of neoplastic cells. These cells are polygonal having small, oval to spindle shaped nuclei, fine chromatin, indistinct nucleoli and abundant, eosinophilic, coarsely granular cytoplasm.	S100, SOX10 and CD68	PanCK	Benign	Right upper Lobectomy
2	45	F	Anterior abdominal wall lesion	3x3 cm	Cells arranged in sheets. The cells are polygonal-shaped with mild to moderate nuclear atypia with dispersed chromatin, conspicuous nucleoli, and moderate to abundant eosinophilic cytoplasm with coarse granules.	S100, SOX10 and CD68	Pan CK and Inhibin	Benign	Wide local excision
3	31	F	Right chest wall lesion	4 x 2.6 x 2.8 cm	Tumor arranged in sheets and nests. The individual cells are round to polygonal and have abundant granular cytoplasm with small hyperchromatic nuclei showing mild nuclear atypia. Mitoses :(~3-4/10 HPF)	S100, SOX10 and CD68	Pan CK and Inhibin	Malignant	Wide local excision

Malignant granular cell tumours are rare, comprises 2% of all granular cell tumors. Mostly they are located in skin and subcutis. They are associated with sudden increase in size, ulceration and distant metastasis. Although metastasis remains the most important criteria for defining malignancy, not all malignant GCTs truly metastasize.[2,6,7]

Features vary from overtly sarcomatous to morphologically bland on rare occasions. Histological features associated with malignancy include increased cellularity, prominent spindling, high N:C ratio, vesicular nuclei with prominent nucleoli, marked pleomorphism, increased mitotic activity (> 2 mitoses per 2 mm^2), and geographical necrosis.[9]

Fanburg smith and colleagues proposed the following six criteria to determine whether a tumor is malignant or not: (1) the presence of necrosis, (2) the emergence of spindle cells, (3) a vacuolar nucleus with an enlarged nuclear body, (4) increase in nuclear division (2 mitoses/10HPF), (5) increase in the nucleocytoplasmic ratio, and (6) polymorphism. If none of these diagnostic criteria are met, the tumor is considered to be benign. If one or two criteria are met, the tumor is considered to be atypical, and if three or more criteria are met, the tumor is considered to be malignant.[6,10]

One of our case (CASE 3) showed a tumor disposed in sheets, nests and vague fascicles. The individual cells were round, polygonal to elongated with mild to moderate pleomorphism, vesicular nuclei, prominent nucleoli and abundant granular cytoplasm. Tumor cell spindling, vesicular nuclei with large nucleoli were noted. Mitotic count was ~3-4/10 HPF. High nuclear to cytoplasmic ratio, pleomorphism and necrosis were not seen. Thus, it was considered malignant based on Fanburg smith criteria.

Reportedly, surgical resection with adequate margin is the primary option for treatment of granular cell tumor. Wide excision with adequate margins is necessary because the tumor is not capsulated and has invasive front. Insufficient tumor resection often results in local recurrence, and has a tendency to spread both hematogenously. Chemotherapy and radiotherapy treatments are not expected to be effective. [6] Hence, granular cell tumor is best treated by conservative local excision. In all our three cases, wide local excision with adequate margins was performed.

CONCLUSION

Although GCTs are uncommon and mostly benign, they have a tendency for local recurrence. Wide local excision is the treatment of choice. Hence it is important that clinicians, radiologists and pathologists are aware of the clinical presentation and histopathology of this condition for appropriate management, counselling and follow-up. In our cases, we had a complete radiological, morphological and immunohistochemical characterization of the lesion for definitive diagnosis. All the cases were treated by wide local excision.

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