Fine-needle aspiration cytology of cutaneous granular cell tumor: Report of two cases with special emphasis on cytological differential diagnosis

ABSTRACT
Granular cell tumors (GCTs) are uncommon neoplasms with recently postulated origin from Schwann cell or neural crest. It can appear in different parts of the body and is most commonly found in the tongue. The cutaneous presentation is not that uncommon. Fine needle aspiration cytology (FNAC) has been suggested to be the diagnostic modality of choice. It will help to differentiate benign tumors from malignant ones and to differentiate GCT from frequent misdiagnoses such as granular histiocytic reaction, xanthogranuloma, rhabdomyoma, oncocytic rich lesions, alveolar soft part sarcoma (ASPS), epithelioid sarcoma, and carcinoma. We report two cases of GCT who presented with subcutaneous swellings in the right thigh and the left lumbar region for 24 months and 18 months, respectively. In the first case, a cytodiagnosis of chronic inflammation showing histiocytes was suggested while GCT was found in the second case. Subsequent histologic examination of the first case and immunocytochemistry in the second case gave the confirmatory diagnosis of GCT.

Key words: Alveolar soft part sarcoma (ASPS); fine-needle aspiration cytology (FNAC); granular cell tumor (GCT)

Introduction
Granular cell tumor (GCT) is an uncommon neoplasm. It can appear in different parts of the body and is most commonly found in the tongue.[1] The cutaneous presentation is not that uncommon.[2,3] The cutaneous tumor presents as solitary painless nodule in the subcutis or dermis and less frequently in the striated muscle. Breast is another common site.[4] Although aggressive and malignant variants do occur, most of the GCTs are benign. Fine needle aspiration cytology (FNAC) has been suggested to be the diagnostic modality of choice. This will help to differentiate benign tumors from malignant ones and to differentiate GCT from chronic inflammatory histiocytic reaction, xanthogranuloma, rhabdomyoma, oncocytic rich lesions, alveolar soft part sarcoma (ASPS), epithelioid sarcoma, and carcinoma.

Case 1
A 20-year-old female presented with a subcutaneous, firm-to-hard swelling on the right thigh since 2 years. The swelling had gradually increased in size and measured 4 cm × 3 cm at the time of presentation. The clinical diagnosis was lipoma. FNAC was performed using a 23-gauge needle mounted...
on a Cameco’s handle and scant material was aspirated. Wet fixed smears were stained with hematoxylin and eosin while dry fixed smears were stained with May-Grunwald-Giemsa. The cytologic diagnosis was a chronic inflammation showing granular histiocytes. Surgical removal and histologic examination of the lesion was done. A diagnosis of benign GCT was given.

**Cytologic findings**
The smears were mildly cellular showing tiny clusters, syncytia, and singly scattered cells [Figure 1]. The cells were large, polygonal shaped with slightly eccentric nucleus, fine nuclear chromatin, and abundant granular cytoplasm having indistinct cytoplasmic borders. Binucleation, stripped nuclei, nuclear smudging, and occasional intranuclear inclusions were also noted. Background showed some granules, few inflammatory cells, and fat. No atypia or necrosis was seen.

**Histopathologic findings**
Single gray white to gray yellow soft tissue piece measuring 4 cm × 2.5 cm × 1.6 cm was seen. Cut section showed encapsulated, circumscribed grey yellow nodule measuring 4 cm in diameter. Microscopic examination showed tumor cells arranged in clusters and anastomosing ribbons separated by dense fibrocollagenous tissue [Figure 2]. The tumor cells were large showing mild pleomorphism, low nucleocytoplasmic ratio, vesicular nuclei, and abundant eosinophilic granular cytoplasm. On periodic acid-Schiff (PAS) staining, tumor cells showed cytoplasmic granular positivity with some cells staining more intensely than others. On S-100 immunostain intense granular cytoplasmic positivity was seen. These cells were negative for cytokeratin.

**Case 2**
A 18-year-old female presented with a subcutaneous, firm-to-hard mobile swelling on left lumbar region since 1.5 years. The swelling had gradually increased in size and measured 3 cm × 3 cm at the time of presentation. Computed tomography (CT) findings were suggestive of a benign soft tissue tumor. FNAC was done and a cytologic diagnosis of benign GCT was given. Immunocytochemistry was also done on the unstained smears. Surgical removal and histologic examination of the lesion was advised. The patient refused to undergo surgical treatment.

**Cytologic findings**
The smears were moderately cellular comprising tiny clusters and singly scattered cells [Figure 3]. The cells were large with central to slightly eccentric nucleus showing fine nuclear chromatin, occasional small nucleoli, and abundant cytoplasm showing some granularity. Binucleation and multinucleation were seen. Background showed some stripped nuclei and blood. No atypia or necrosis was seen. PAS staining done on smears showed some cytoplasmic granular positivity [Figure 4a]. Immunocytochemistry for S-100 on unstained smear showed cytoplasmic granular positivity [Figure 4b] and that for pancytokeratin was negative.

**Discussion**
GCT was originally described by Abrikossoff in 1926. Earlier, it was thought to be myogenic in origin and was known as “granular cell myoblastoma” but immunohistochemistry (IHC) and electron microscopic findings pointed an origin from precursor of the Schwann cell or neural crest cell. GCTs primarily affect adults with a female predilection as was also seen in these two cases. This tumor can appear in different parts of the body;
nevertheless more than half of the cases are presented in the head and neck area with tongue being the most common site.\textsuperscript{[1-4]} Other sites of predilection are breast, upper respiratory tract, subcutaneous tissue in extremities, and trunk.

The FNAC findings of the above two cases of GCT were similar to those described in literature.\textsuperscript{[2,4]} GCT has been variably misdiagnosed as xanthogranuloma of subcutaneous region, carcinoma breast, Hurthle cell neoplasm of trachea, and inflammatory lesion.\textsuperscript{[2,4,4]} The main reason for misdiagnosis is the rarity of this entity. In the subcutaneous region, the main differential diagnoses are chronic inflammation showing granular histiocytes, rhabdomyoma, hibernoma, ASPS, and xanthogranuloma.\textsuperscript{[7-9]} The cytologic features and the ancillary studies that help to differentiate GCT from these close mimickers have been described in Table 1.

ASPS warrants special emphasis as it is the closest malignant differential diagnosis of GCT. This tumor occurs commonly in young age with a female preponderance on the extremities as a large soft tissue mass.\textsuperscript{[9,10]} High nucleocytoplasmic ratio, single prominent nucleolus, and intra cytoplasmic rhomboid crystals help to differentiate it from GCT. PAS positive diastase resistant granules are seen in both the lesions. On IHC, ASPS will show nuclear transcription Factor Binding To IGHM Enhancer 3 (TFE3) positivity that may be expressed by some GCTs, a potential pitfall. In most instances, strong S100 protein expression in GCT helps it to be differentiated from ASPS as was seen in both the cases described here.

Sometimes metastatic carcinoma, melanoma, and epithelioid sarcoma may also come under the differential diagnosis of...
GCT.[2] GCT cells are negative for antibodies to cytokeratins AE1, AE3, desmin, MyoD1, myogenin, HMB-45, melan-A, and MART-1, which helps to exclude metastatic carcinoma, epithelioid sarcoma, and melanoma. Cytokeratin was negative in both the cases thus ruling out epithelioid sarcoma and metastatic carcinoma. Rarely benign adnexal tumors may also come under the clinical differential diagnosis but the cytology of GCT is very characteristic and different from these.[11] Also, the adnexal neoplasms are cytokeratin positive.

In most of the cases, GCT has a benign behavior and a wide local resection has been considered to be the treatment of choice.[1-4] Malignant GCT accounts for 1-2% of all the cases. They are usually >5 cm in diameter and show nuclear pleomorphism, high mitotic activity, and necrosis. None of these features were seen in our two cases and thus both the cases were diagnosed as benign GCTs. However, a careful follow-up is mandatory even if a complete resection is achieved in all GCTs.

Conclusion

GCTs are rare and occur in a wide variety of sites with a wide spectrum of differential diagnoses. A cytopathologist has to be aware of the cytomorphologic features of GCT and its mimickers. Ancillary studies can help to arrive at the final diagnosis in most cases.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Eguia A, Uribarri A, Gay Escoda C, Crovetto MA, Martinez-Conde R, Aguirre JM. Granular cell tumor: Report of 8 intraoral cases. Med Oral Patol Oral Cir Bucal 2006;11:E425-8.
2. Toi PC, Siddaraju N, Basu D. Fine-needle aspiration cytology of granular cell tumor: A report of two cases. J Cytol 2013;30:195-7.
3. Singh A, Sawhney M, Das S. Granular cell tumor of skin diagnosed on fine needle aspiration cytology. Indian J Dermatol 2012;57:330-1.
4. McCluggage WG, Sloan S, Kenny BD, Alderdice JM, Kirk SJ, Anderson NH. Fine needle aspiration cytology (FNAC) of mammary granular cell tumor: A report of three cases. Cytopathology 1999;10:383-9.
5. Kintanar EB, Giordano TJ, Thompson NW, Michael CW. Granular-cell tumor of trachea masquerading as Hurthle cell neoplasm on fine needle aspirate: A case report. Diagn Cytopathol 2000;22:379-82.
6. Naresh KN, Soman CS. Granular cell tumor of the mammary skin. Acta Cytol 1996;40:610-2.
7. Limbach AL, Goyal A. Adult rhabdomyoma: A challenging diagnosis on cytology. Cytotechnology 2012;9:20.
8. Lemos MM, Kindblom LG, Meis-Kindblom JM, Remotti F, Ryd W, Gunterberg B, et al. Fine-needle aspiration characteristics of hibernoma. Cancer 2001;93:206-10.
9. Shabb N, Sneige N, Fanning CV, Dekmezian R. Fine-needle aspiration cytology of alveolar soft-part sarcoma. Diagn Cytopathol 1991;7:293-8.
10. Folpe AL, Deyrup AT. Alveolar soft part sarcoma: A review and update. J Clin Pathol 2006;59:1127-32.
11. Nasit JG, Chauhan S, Dhruva G. Granular cell tumor of hand presenting as subcutaneous nodule mimicking dermal adnexal tumor: A diagnosis by cytology. Indian Dermatol Online J 2013;4:33-6.