# Granular cell tumor of cecum: a common tumor in a rare site with diagnostic challenge

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## Abstract

Granular cell tumor (GCT) also known as Abrikossoff's tumor is a benign neoplasm that is usually seen in the fourth to sixth decades of life with slight female preponderance. It is most frequently seen in the oral cavity, skin, and subcutaneous tissue. Gastrointestinal tract involvement is uncommon, in which esophagus is the most commonly affected site. There are case reports of GCT in stomach, appendix, colon and rectum. In this article, we report a case of GCT involving cecum. The cell of origin in GCT is controversial. There are various pools of thoughts regarding its histogenesis, the details of which are reviewed in this article with emphasis on the diagnostic difficulties encountered in this tumor.

## Introduction

Granular cell tumor (GCT) was first described in 1926 by a Russian pathologist, Alexei Ivanovich Abrikossoff, as a myogenic tumor.[1] Over a century, the true nature of this lesion remained enigmatic and a wide variety of cell types have been proposed as the cell of origin.[2-4] Most recent studies have favored Schwann cell origin based on immunohistochemical and ultrastructural studies.[5-8] GCT affects persons of varying ages with a peak incidence in the fourth through sixth decades of life. A slight female predominance exists with female to male ratio of 2:1. The head and neck region is involved in about 45 to 65% of the patients, while gastrointestinal involvement is seen in 8% of the cases.[5,9] Cecal involvement is rare and till now only 16 cases have been reported worldwide including one case in Indian literature.[9]

GCT is usually seen as a small, solitary, nodular growth in oral cavity, skin and subcutaneous tissue. In gastrointestinal tract, they are often found incidentally as submucosal polyp during endoscopic examination performed for other reasons as they are frequently asymptomatic.[10-13] Granularity of tumor cells is due to the accumulation of secondary lysosomes in the cytoplasm which shows positive reaction for CD68.[7] This change is rather nonspecific and can be observed in many non-neural tumors, including those arising from smooth muscle, connective tissue, neuroglia, endothelial and epithelial cells.[14] Even if the biological behavior of granular cell tumors is usually benign, accurate histological examination is mandatory to differentiate it from its mimics and to evaluate its malignant potential.

## Case Report

A 32-year-old female came with complaints of abdominal pain for 1 year. There was no history of altered bowel habits or blood in stool. On evaluation, ultrasonographic findings were within normal limits. Colonoscopy showed a submucosal polyp in cecum near the appendicular orifice involving <1/3rd of circumference. Biopsy from the polyp showed mucosa and a part of submucosa which were histologically unremarkable (Figure 1A). There was no evidence of tumor in colonoscopic biopsy. Meanwhile, contrast enhanced computed tomography (CECT) revealed a 2.8×2×1.8 cm well defined, smoothly marginated, homogenously enhancing cecal mass which was predominantly involving the wall with no wall thickening in surrounding area (Figure 2). CECT features were favoring a benign neoplasm. Laparoscopic resection anastomosis was performed.

Grossly a bulge was seen in the lateral wall of caecum. On cut section a well circumscribed, solid, yellowish tumor measuring 2.8×2×1.8cm was seen in the wall. Overlying mucosa was unremarkable. There was no evidence of hemorrhage or necrosis. Microscopy revealed a well circumscribed tumor in muscularis propria composed of sheets of polygonal to spindle cells. Tumor cells showed extensive coarse granular eosinophilic cytoplasm with uniform bland nuclear chromatin. The granules were positive for periodic acid Schiff (PAS) and luxol fast blue stains. Mitotic figures were infrequent (<1/10 hpf). There was no evidence of atypia or necrosis. There was a thin layer of stretched out muscularis propria on all sides of the tumor indicating it's pure intra muscular location. Morphological features favored the diagnosis of granular cell tumor. However, immunohistochemistry (IHC) was performed to rule out common lesions in caecum which can have similar morphology like leiomyoma, gastrointestinal stromal tumor and ganglioneuroma. IHC showed strong diffuse cytoplasmic and nuclear positivity for S-100 and weak diffuse cytoplasmic positivity for neuron specific enolase (NSE) in tumor cells. Desmin, CD-117, CD-34, CD-68, synaptophysin and chromogranin were negative confirming the diagnosis of GCT. Morphological and immunohistochemical features are shown in Figures 1-4.

## Discussion

GCT is an intriguing neoplasm with much speculation and controversy regarding its histogenesis and behavior. Initially Abrikosoff suggested that GCT originates from skeletal muscle cells and so referred them as myoblastoma.[1] Later, many cell types like histiocytes, fibroblasts, myoblasts, neural sheath cells, neuroendocrine cells and undifferentiated mesenchymal cells were suspected as cell of origin.[15,16] Vered *et al*.[17] have proposed the possibility of GCT being a reactive lesion reflecting a local metabolic or reactive change rather than a true neoplasm. This view is further supported by granular cell tumor undergoing hyalinization and calcification.[18] However recent immunohistochemical and electronmicroscopic studies suggest derivation from Schwann cells of the peripheral nerve. Granular cells in GCT show positive staining for S-100, myelin

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basic protein, Leu-7 and protein gene product 9.5 suggesting Schwann cell origin[7] Rejas *et al.*[6] have further supported this view by demonstrating positive staining for S-100, p75, NSE and CD-68, and no immunoreactivity for SMA, EMA, HHF-35, Ki-67, Synaptophysin, Chromogranin, Progesterone, Androgen and Estrogen.GCT is frequently seen in oral cavity. GIT involvement is uncommon with most of the cases occurring in esophagus.[19] Our extensive search in literature revealed only 16 cases worldwide having cecal involvement.[9] Most of them presented as asymptomatic, solitary, submucosal nodule however Saleh *et al.*[20] have documented multiple GCT involving ascending colon, cecum, rectum and appendix. Schrader *et al.*[21] have reported multiple granular cell tumors associated with LEOPARD syndrome caused by mutation in PTPN11.

In our case, the tumor was well circumscribed and completely surrounded by muscularis propria on all sides. The tumor being purely in intra muscular location, it was not represented in initial colonoscopic biopsy. Although light microscopic features of tumor proper was strongly favoring granular cell tumor certain uncommon features like site, pure intra mural location and focal spindling of tumor cells made us to consider the possibility of leiomyoma, gastrointestinal stromal tumor and ganglioneuroma in the differential diagnosis. Immunostain for S-100 and NSE were positive in tumor cells supporting neural differentiation. Desmin highlighted the surrounding normal stretched out muscularis propria however tumor cells were negative which ruled out the possibility of leiomyoma. CD-117, CD-34, synaptophysin and chromogranin were negative in tumor cells which were against gastrointestinal stromal tumor and ganglioneuroma.

Most of GCT follow benign course. Nonetheless, malignant GCTs have been described but are extremely uncommon, representing 1% to 2% of all GCT. The malignancy rate is estimated to be less than 2% of all reported GCT. [22] The malignant GCT seems to be correlated with the size of the tumor since most malignant forms are larger than 4 cm.[23] Fanburg-Smith *et al.*[24] studied 73 cases of GCT to clarify the crite-

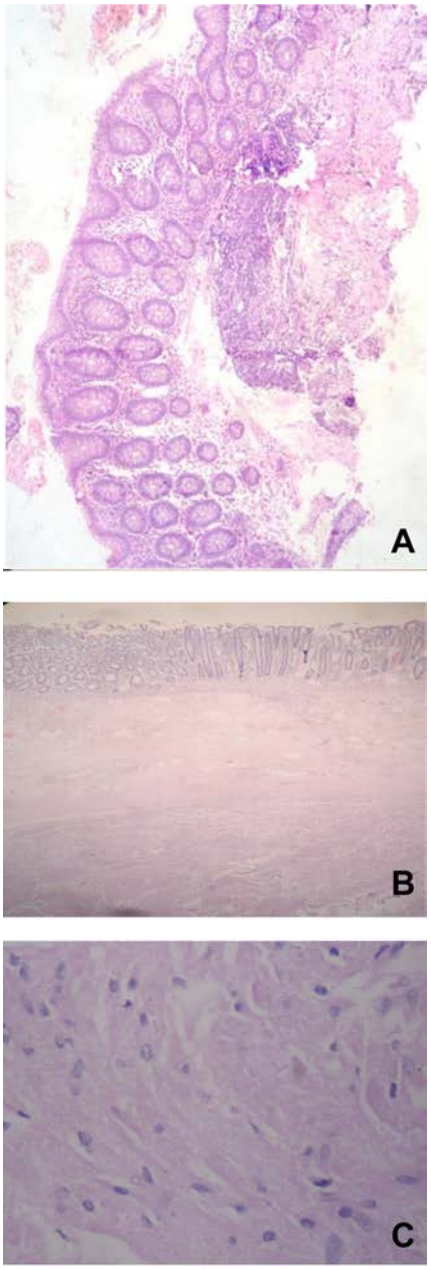


**Figure 1. A) Non diagnostic intestinal mucosal biopsy. B) Well circumscribed tumor in muscularis propria. Overlying mucosa and submucosa are free of tumor. C) Tumor cells showing abundant coarse granular eosinophilic cytoplasm. Hematoxylin & Eosin; respectively 20×, 40×, 400× magnification.**

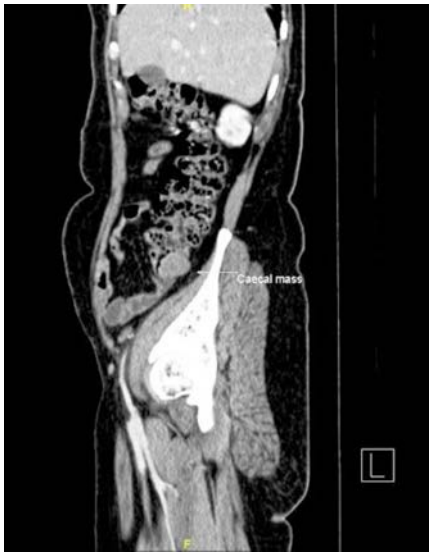


**Figure 2. Contrast enhanced computed tomography scan abdomen highlighted the small circumscribed mass in the caecum.**

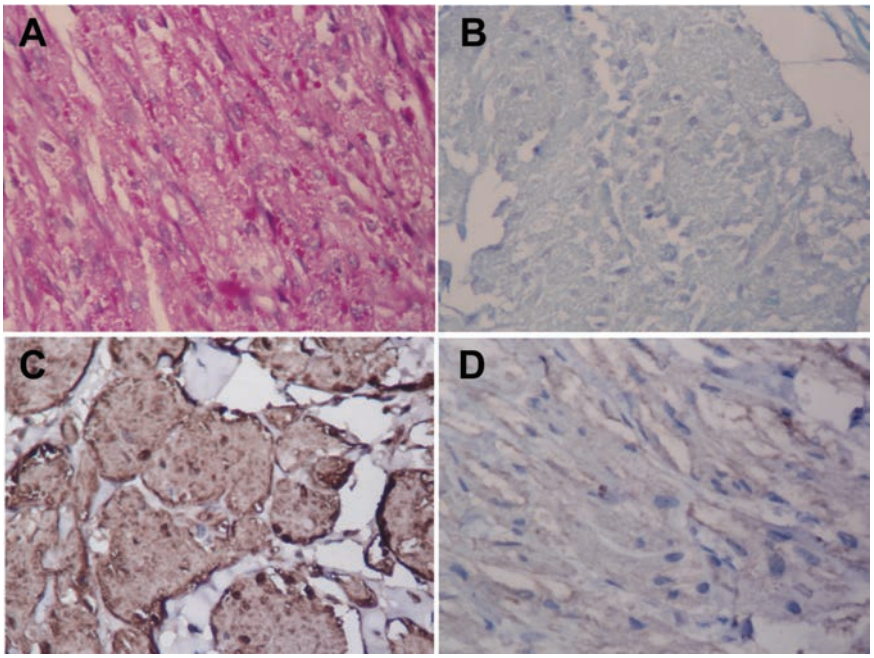


**Figure 3. A) PAS positive granules in the cytoplasm of tumor cells; B) Luxol fast blue stain showing positive reaction in the granules of the tumor cells; C) S-100 showing strong nuclear and cytoplasmic positivity in the tumor cells; D) NSE showing weak diffuse positivity in the tumor cells (all images are 400× magnification).**

ria for malignancy and prognostic factors. Six histologic criteria were assessed: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 highpower fields at 200× magnification), high nuclear to cytoplasmic ratio, and pleomorphism. Neoplasms that met 3 or more of these criteria were classified as histologically malignant; those that met 1 or 2 criteria were classified as atypical; and those that displayed only focal pleomorphism but fulfilled none of the other criteria were classified as benign. It is important to arrive at a conclusive diagnosis of GCT, since there are a wide spectrum of tumors, having granular cells showing varying behavior, which alters the treatment planning and the prognosis of the patient. The definitive diagnosis can be established by IHC techniques. Surgical excision of the GCT with wide margins has been suggested as the treatment of choice. Radiation and chemotherapy are not recommended because of the resistance of the tumor and potential carcinogenic effect.[25] A low rate of recurrence of the lesion has been reported. A strict follow up colonoscopic examination is required when the tumors are multiple or a risk of malignancy exists. Our patient does not have any complication after the surgery and on follow up (1 year) is doing fine. The recurrence depends on the resectability of the tumor, in our case the tumor was well contained within the muscle layer on all aspects and 4 cm of intestine was resected on either side of the tumor. Follow up abdominal ultrasound and CT scan does not show any evidence of recurrence.

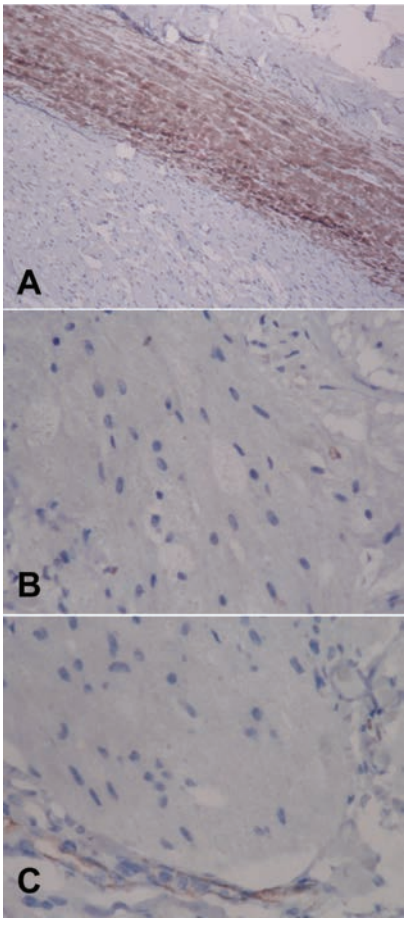


**Figure 4. A) Desmin staining the normal muscularis layer however tumor cells below are negative (100×); B) Immunostain for CD-117 is negative in the tumor area (400×); C) CD-34 highlights scattered endothelial cells however tumor cells are negative (400×).**

## Conclusions

GCT is a benign tumor with neural differentiation particularly Schwann cell type is currently in favor. When a submucosal yellowish nodule is encountered on colonoscopy with negative finding in small biopsy one has to consider the possibility of GCT. However it is very difficult to diagnose a case of granular cell tumor on colonoscopy because this tumor in colonic area is located in the submucosa and muscularis with variable local infiltration. There is no definite described radiological detail of granular cell tumor at that location.[26] This case is reported because of its rare site and to discuss the diagnostic difficulties encountered in this location.

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