

# Multiple Granular Cell Tumors of the Ascending Colon

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Granular cell tumor (GCT), also known as a granular cell schwannoma or Abrikossoff tumor, is rare in the colon.<sup>1</sup> GCT is commonly seen in the subcutaneous tissue and other soft tissue in the body,<sup>2</sup> most frequently in the oral cavity and esophagus, followed by the duodenum, anus, and stomach.<sup>3-5</sup> GCT is usually a benign tumor, though a malignant counterpart has been reported.<sup>6,7</sup> This tumor often presents as a single submucosal nodule or polypoid flat mass-like sessile polyp. An aggregate of multiple GCTs in the ascending colon has rarely been reported in the literature.<sup>8</sup> Most of the reported tumors measure less than 1.5 cm in diameter and are found incidentally during colorectal examinations for other reasons (eg, screening colonoscopy).<sup>2,7</sup> We present a patient with an aggregate of multiple GCTs (the largest of which measured more than 1.5 cm) found in the ascending colon during screening colonoscopy.

## Case Report

A 39-year-old man was referred to a gastroenterologist for a colonoscopy for colorectal cancer screening and intermittent rectal bleeding. The patient had multiple medical disorders, including hypertension, obesity, type II diabetes, hyperlipidemia, asthma, attention-deficit hyperactivity disorder, depression, and erectile dysfunction. He had recently begun to notice a small amount of painless bright red blood on the surface of the stool and on the toilet paper several times per month. He reported having regular bowel movements with soft stool and denied having any other gastrointestinal symptoms. The patient did not drink alcohol or use nonsteroidal anti-

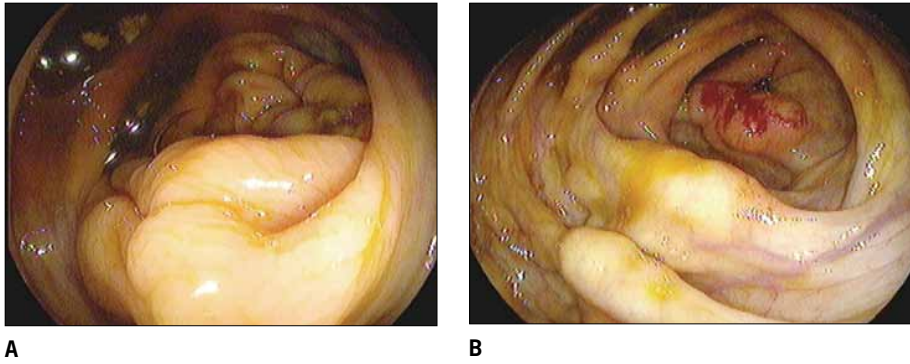
inflammatory drugs. He had lost 9 pounds in the last 3 months with an intensive diet and exercise program. A colon polyp had been recently found in his sister, and his father had been diagnosed with colorectal cancer in his early fifties. Concerned about his risk of colorectal cancer, the patient was referred for a screening colonoscopy. Physical examination revealed an obese man weighing 187 pounds with essential normal vital signs and no anemia or jaundice. A grade 2 internal hemorrhoid was detected in the patient, but no subcutaneous nodules or submucosal masses were detected in the oral cavity. Other physical examinations were unremarkable. Laboratory tests showed an alanine aminotransferase level of 45 U/L, fasting glucose level of 146 mg/dL, low-density lipoprotein level of 129 mg/dL, triglyceride level of 284 mg/dL, and hemoglobin A1C level of 7.8%.

At the time of the colonoscopy, a 6-mm polyp was noted in the cecum and removed via electrocautery snare. A polypoid flat mass was also found along one of the folds, just above the ileocecal valve, measuring approximately 1.5 cm × 2 cm. The overlying mucosa appeared normal, and biopsies were obtained. As the colonoscope was withdrawn further up the colon, several other similar polypoid flat lesions, of smaller sizes, were noted along the folds. As the lesions had normal-appearing overlying mucosa, the endoscopist elected to obtain biopsies and send them to a pathologist before making a definitive decision as to appropriate treatment. Another 5–6-mm polyp was noted in the sigmoid colon and removed by snare polypectomy. The colonic mucosa was otherwise unremarkable, with no evidence of inflammation, ulceration, or other mass lesions (Figure 1). The patient was observed for 30 minutes and then discharged. There were no immediate or delayed complications.

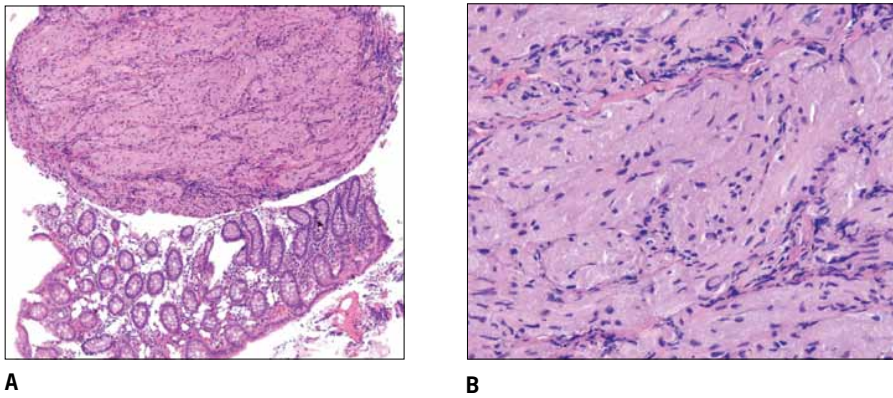
Histologic examination of the biopsy tissue revealed a nest of plump histiocyte-like tumor cells with abundant

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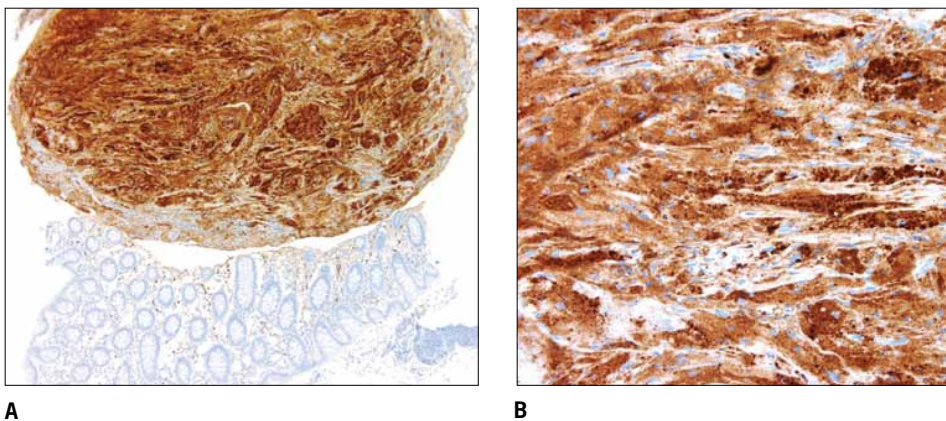
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**Figure 1.** Endoscopy revealed a large flat polypoid mass with normal-looking mucosa approximately 1.5 cm × 2.0 cm in diameter (A) and two other sessile polyps along other folds in the ascending colon (B). Two additional sessile polyps in more distal parts of the ascending colon are not shown.



**Figure 2.** Biopsy revealed a submucosal tumor consisting of nests of granular cells with eosinophilic granular cytoplasm (hematoxylin and eosin stain). Microscopic low-power view (A) and high-power view (B).



**Figure 3.** Diffuse and strong expression of S-100 protein in tumor (shown by immunohistochemical examination). Microscopic low-power view (A) and high-power view (B).

granular eosinophilic cytoplasm containing acidophilic periodic acid Schiff–positive, diastase-resistant granules (Figure 2). Immunohistochemical analysis showed that the tumor cells expressed S-100 protein (Figure 3). The flat lesions were diagnosed as GCTs occurring in the ascending colon, and 2 polyps that were removed showed hyperplastic architecture.

**Discussion**

Since the first description by Abrikossoff in 1926,<sup>9</sup> fewer than 100 cases of GCTs have been reported in the litera-

ture.<sup>8,10</sup> An aggregate of multiple GCTs has been reported in only 15 patients in the literature.<sup>8</sup> Most GCTs are of small to average size (5–6 mm), with the largest reported GCT in the colon being 1.5 cm.<sup>10,11</sup> It is to our best knowledge that this is the first case report of an aggregate of multiple GCTs with the largest tumor measuring more than 1.5 cm in the ascending colon. The tumors in our patient appeared to be submucosal with intact overlying mucosa and were asymptomatic in their clinical presentation and found incidentally during colonoscopy for colonic cancer screening. There is no consensus for the optimal management of this tumor. A conservative

approach with endoscopic removal under endoscopic ultrasound is appropriate, as most GCTs are benign. Malignant GCTs are extremely rare; only 30 cases have been reported in the literature.<sup>8,12</sup> In a study of 622 patients under the age of 50 who had hematochezia and were undergoing screening colonoscopy for colonic polyps, only 1 case of GCT was found.<sup>6</sup> Malignant behavior correlates with tumor size; it has been found that more than 60% of metastatic GCTs are larger than 4 cm in diameter.<sup>5,7,12</sup>

GCT is assumed to derive from Schwann cells. There is a strong correlation between GCT and peripheral nerves.<sup>8</sup> The immunohistochemistry study with S-100 protein and myelin proteins or myelin-associated glycoproteins also supports the neural origin of GCTs. These tumors can be found anywhere in the body with a nerve supply, though predominantly in subcutaneous tissue.<sup>1</sup> Most colonic GCTs are found in the ascending colon or anorectal area, with flat polypoid submucosal nodules covered by normal mucosa resembling sessile polyps.<sup>8</sup> GCTs have also been reported in the muscle layer of the gastrointestinal tract as well as subserosal areas.<sup>3,5</sup>

It is almost impossible to diagnose GCTs based upon macroscopic and endoscopic examination, due to unremarkable appearance. In our case, GCT seemed unlikely, as the endoscopic features of the tumor resembled those of sessile polyps. Endoscopic ultrasound has been extensively used for determining the depth of tumor invasion in the gastrointestinal wall. The endoscopic ultrasound evaluation of GCTs will be helpful in the selection of tumor resection strategies, as endoscopic removal of large submucosal tumors carries a high risk of perforation and bleeding in the ascending colon.<sup>10,13,14</sup> An endoscopic ultrasound-guided endoscopic mucosal resection in an experienced center, or a partial colectomy with a thorough pathologic examination, can be a good option in our case with proper endoscopic follow-up. Esophagogastroduodenoscopy should be pursued to exclude GCTs in the upper gastrointestinal tract, as GCTs are more prevalent in the esophagus and stomach.<sup>3,15</sup>

In summary, we report the first case of an aggregate of multiple GCTs with the largest tumor measuring more

than 1.5 cm in the ascending colon. GCTs of the colon are often found incidentally during colonoscopy, and the possibility of GCT should be included in the differential diagnosis of sessile polyps of the colon. An endoscopic ultrasound-guided endoscopic mucosal resection in an experienced center, or surgical removal with a thorough pathologic examination, is recommended in our case with proper endoscopic follow-up.

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# Review

## Granular Cell Tumors of the Gastrointestinal Tract: Questions and Answers

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Granular cell tumors (GCTs) are rare, usually benign tumors, that can be located anywhere in the body. They are usually found in the oral cavity (40%), skin and subcutaneous tissue (30%), breast (15%), or respiratory tract (15%).<sup>1</sup> Approximately 8% of GCTs develop in the gastrointestinal tract, the most common site being the esophagus, which is involved in up to 65% of cases.<sup>2</sup> Nevertheless, GCTs of the esophagus are rare; their incidence has been estimated to be approximately 0.033%, representing approximately 1% of benign esophageal tumors.<sup>3</sup> Involvement in other gastrointestinal localizations such as the duodenum, anus, stomach, biliary tree, and colon<sup>4</sup> are much more uncommon. According to Patti and associates,<sup>2</sup> up until 2006, only 29 cases had been reported in the stomach, and all of them were surgically treated; in 1 case, described by David and colleagues,<sup>5</sup> the stomach and esophagus were involved simultaneously.

Although usually a solitary tumor, GCT can be found in an aggregate in approximately 10% of cases, either only in the esophagus or in other sites.<sup>5</sup> Most GCTs are asymptomatic (dysphagia is the most common symptom of presentation when the esophagus is involved); hence, they are usually incidental findings on endoscopy. These lesions are rarely associated with complications such as bleeding or lumen obstruction. Most information on this pathology is obtained from case reports or small series due to the low prevalence of these tumors.

Ye and colleagues<sup>6</sup> present a case of multiple GCTs in the ascending colon in a patient undergoing screening colonoscopy. This interesting and unique report gives us the opportunity to address some common questions that inevitably arise whenever we are faced with unusual findings on endoscopy, particularly any submucosal lesions in the colon. These questions include: what is being

observed? How should the diagnosis be determined? How should the tumor be treated?

Endoscopy alone is not reliable for detecting the nature and origin of a subepithelial mass, and GCTs are not an exception to this rule. On endoscopy, GCTs are typically sessile, small in size (usually less than 20 mm), yellowish-white in color, and covered by normal-appearing mucosa. They can range from a plaque-like thickening of the mucosa to a nodular or polypoid mass, the shape of which resembles a molar on the gingiva.<sup>7-9</sup> Although all these features are advocated as quite typical, it is not possible to make a differential diagnosis from other submucosal lesions such as lipomas, carcinoid or stromal tumors, hamartomas, or metastatic tumors by endoscopy. In particular, larger lesions may mimic atypical lipomas, though GCT lesions feel firm or rubbery when prodded with a biopsy forceps, without the typical indentation ("pillow-sign").<sup>10</sup> In a colon with diverticula, a polypoid "molar-like" lesion covered by normal-appearing mucosa should be distinguished from an intoflexed diverticulum. Advanced techniques for chromoscopy and image enhancing such as narrow-band imaging or FICE have no role in the diagnosis, except for ruling out the adenomatous nature of the lesion whenever a typical pit pattern cannot be identified. Conversely, endoscopic ultrasonography has provided a major breakthrough for characterizing subepithelial lesions. Endoscopic ultrasonography represents the most accurate imaging test for detecting the component of the gastrointestinal wall from which the mass arises, information that, when combined with the echogenicity of the mass, helps narrow the differential diagnosis and evaluate the likelihood of endoscopic resection.<sup>11</sup> Although limited information is available regarding endosonographic features, GCTs usually appear as hypoechoic, homogeneous lesions with smooth margins arising from the mucosa and/or submucosa (second or third layer of the gastrointestinal tract).<sup>12</sup> The reports of GCTs located in the muscular layer of the gastrointestinal tract or in the subserosal area are anecdotal. The echogenicity pattern allows differentiation between GCTs and lipomas (the latter of which usually appear as homogeneous, hyperechoic masses arising from the third layer). In spite of this, it is well known that hypoechoic lesions in the third layer are most prone to misclassification; therefore, conclusive diagnosis can usually be achieved only by histology.

In the case of GCTs, unlike other submucosal tumors, standard cold biopsy forceps usually provide adequate tissue to reach a diagnosis. However, tunneled biopsies are often needed because superficial biopsies may be normal or may miss the diagnosis, showing only fragments of normal mucosa.<sup>6</sup> Furthermore, in the case of esophageal GCTs, superficial biopsies can reveal hyperplastic changes (so-called pseudoepitheliomatous

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hyperplasia) that can be confused with squamous-cell papilloma or carcinoma, potentially leading to misdiagnosis and hazardous clinical decisions.<sup>8</sup> Snare polypectomy may sometimes be needed to obtain adequate diagnostic material from large lesions.

Histologically, GCTs are composed of large polygonal cells containing numerous eosinophilic granules.<sup>13</sup> They resemble Schwann cells under electron microscopy and usually stain positive for S-100 protein and neuron-specific enolase, suggesting that they originate from cells of neural origin. The expression of nestin, an intermediate filament protein normally found in neuroectodermal stem cells, in these tumors further suggests that they may arise from a common multipotential stem cell in the gastrointestinal tract that has the capability to differentiate between both interstitial cells of Cajal and peripheral nerve pathways.<sup>14</sup>

Although GCTs are usually benign, a malignant potential has been described, particularly for larger lesions. In a review of 183 cases, 8 lesions (4%) were malignant and all of these 8 lesions were greater than 4 cm.<sup>3</sup>

In 1998, Fanburg-Smith and coworkers<sup>15</sup> studied 73 cases of GCTs to clarify the criteria for malignancy and prognostic factors. Six histologic criteria were assessed: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 high-power 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. The patients with benign multicentric and atypical GCTs had no metastases, and there were no tumor deaths. In contrast, 11 of 28 patients (39%) with malignant GCT died from the disease at a median interval of 3 years, 8 of the 28 patients (29%) had local recurrence, and 14 of the 28 patients (50%) had metastases. Only 9 of the 28 patients (32%) were disease-free at the 7-year follow-up. Upon multivariate analysis, malignancy (based upon histology) emerged as a significant adverse prognostic factor with regard to survival, along with other clinical variables such as larger tumor size, local recurrence, and the presence of metastases. Multifocality does not appear to carry an increased risk of malignant behavior. This study indicates that GCTs, when associated with peculiar histologic features, should be considered a high-grade sarcoma with a negative prognosis.

Once the histologic diagnosis of GCT is obtained, the course of action for treatment mainly depends upon the number of lesions and their size and location in the gastrointestinal tract, in addition to other clinical features such as the patient's age and comorbidities.

Some physicians suggest resection of all lesions, by either endoscopy or surgery, because of the malignant potential. Other physicians advocate a less aggressive strategy with surveillance endoscopy for asymptomatic small lesions whenever resection-related risks outweigh the potential benefits. No data exist to determine the most cost-effective approach in the management of these tumors.

The surveillance strategy sounds reasonable for asymptomatic esophageal GCTs, which can be easily monitored by endoscopy, and possibly by endoscopic ultrasonography, for an increase in size every 1–2 years; on the other hand, this strategy appears to be troublesome for colonic lesions. Colonoscopy is an invasive and unpleasant procedure, and submucosal lesions may not be easy to detect on follow-up endoscopy. Furthermore, in spite of recent improvements in the flexible endosonography techniques and the more widespread use of high-frequency miniprobe technology, endoscopic ultrasonography of the colon is far from the standard of practice and its application is still limited to a few referral centers. Hence, resection is usually preferred to the surveillance strategy for the management of colonic GCTs located outside of the anorectal area.

Smaller GCTs (<1 cm) are usually limited to the mucosa and can be successfully removed with a biopsy forceps or standard snare polypectomy. Thermal ablation of GCTs by laser has been reported in small case series.<sup>16</sup> Argon plasma coagulation can likely be considered a valid alternative, though no case has been reported in the literature. However, before using these techniques, it is crucial to achieve a reliable histologic diagnosis.

Larger GCTs require either endoscopic mucosal resection, which has been demonstrated to be a safe and useful therapeutic procedure for gastrointestinal submucosal tumors, or endoscopic submucosal dissection. In this instance, a pretreatment endoscopic ultrasonography evaluation is strongly recommended to confirm that the tumor is confined to the submucosa and to reduce the risk of perforation. For colonic lesions that are not accessible for endoscopic ultrasonography study, submucosal injection of saline solution is important to assess the tumor lifting and the possibility of resection.

In esophageal GCTs, endoscopic therapeutic techniques have overtaken surgery in most cases due to their efficiency, safety, and fewer complications.<sup>17</sup> Recurrence after resection has not been described. For large colonic lesions, surgery is still a valid therapeutic option, though the views concerning treatment have been changing over the years and the number of reports documenting colonic GCTs successfully treated by endoscopic mucosal resection or endoscopic submucosal dissection are now increasing.<sup>18,19</sup>

However, despite the growing enthusiasm regarding advanced endoscopic techniques, a wise endoscopist should always keep in mind that laparoscopic surgery or minimally invasive interventions (ie, laparoscopy-assisted resection with or without colonoscopic guidance or transanal resection for rectal lesions) represent appropriate and effective alternatives to endoscopic resection for selected cases. The choice between an endoscopic or surgical approach should be established based upon the features of each case on an individual basis and local experience.

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