Review

Granular Cell Tumors of the Gastrointestinal Tract: Questions and Answers

Franco Radaelli, MD
Giorgio Minoli, MD
Gastroenterology Unit, Valduce Hospital, Como, Italy

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%).[1] 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.[2] Nevertheless, GCTs of the esophagus are rare; their incidence has been estimated to be approximately 0.033%, representing approximately 1% of benign esophageal tumors.[3] Involvement in other gastrointestinal localizations such as the duodenum, anus, stomach, biliary tree, and colon[4] are much more uncommon. According to Patti and associates,[2] 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,[5] 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.[5] 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[6] 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.[7-9] 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").[10] In a colon with diverticula, a polypoid "molar-like" lesion covered by normal-appearing mucosa should be distinguished from an introflexed 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.[11] 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).[12] 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.[6] Furthermore, in the case of esophageal GCTs, superficial biopsies can reveal hyperplastic changes (so-called pseudoepitheliomatous

Address correspondence to:
Dr. Giorgio Minoli, Via Molino 20, 22030 Montorfano (Co) Italy;
Tel: ++39031200474; E-mail: giorgio.minoli@gmail.com

hyperplasia) that can be confused with squamous-cell papilloma or carcinoma, potentially leading to misdiagnosis and hazardous clinical decisions.[8] 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.[13] 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.[14]

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.[3]

In 1998, Fanburg-Smith and coworkers[15] 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.[16] 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.[17] 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.[18,19]

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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