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Case Report

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Granular Cell Tumors of the Cecum: Report of Two Cases and Review of Literature

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A granular cell tumor (GCT) is a relatively rare benign tumor that has been seldom reported since Abrikossoff first described it as a granular cell myoblastoma in 1926. While GCTs can occur anywhere in the human body, they are very rarely observed in the gastrointestinal tract and are especially rare in the large intestine. Most GCTs are small and asymptomatic and are often found by endoscopy, upper gastrointestinal series, and autopsy. We report two cases in which a submucosal tumor in the cecum was accidentally discovered by colonoscopy and was subsequently removed by colon polypectomy and endoscopic mucosal resection. Immunohistochemical analysis of the samples confirmed both cases as GCT. The literature review and reports of other growths in the gastrointestinal tracts support the necessity for proper identification of GCTs within the body to differentiate them from more malignant tumors.

Keywords: Cecum, Endoscopic mucosal resection, Granular cell tumor, Polypectomy

Introduction

Granular cell tumor(GCT) is an uncommon submucosal tumor that is a mesenchymal lesion. GCT develops in the oral cavity, skin, and subcutaneous tissue, and about 5.6% of all GCT occurs in the gastrointestinal tract [1,2]. It develops in the esophagus, duodenum, and stomach of the gastrointestinal tract, and is rare in the colon and rectum [2]. In South Korea, since it was first reported in 1982, 14 cases have been reported in the rectum and large intestine (Table 1) [3]. In addition to these previous descriptions in the gastrointestinal tract, we report two cases in which we accidently discovered submucosal tumors in the cecum of both 66 and 56-year-old males. We removed the tumors by colonoscopy and confirmed both resections as a GCT using immunohistologic analysis.

Case Report

Case 1

A 66-year-old male came to our clinic with diarrhea that began a month ago. The patient's vital signs were normal, and physical examination showed no abnormal findings. In addition, he did not have previous medical history or any family history of cancer. Diagnostic tests revealed that there were no specific findings in blood tests and abdominal computed tomography (A-CT). The colonoscopy revealed a yellow lesion of 0.5 cm in size that was covered with a normal mucosa in the patient's cecum; the lesion felt firm and featured some mobility when manipulated with forceps (Fig. 1A). For histological diagnosis

Table 1. Colorectal granular cell tumors reported in South Korea

	Year	Author (ref no.)	Sex/age (yr)	Location	Size (cm)	Symptoms	Therapy
1	1982	Kim et al. [3]	F/44	Cecum	1.5×1.5	None	Surgery
2	1983	Lee et al. [12]	F/31	Cecum	1.0	None	Surgery
3	1991	Choi et al. [13]	F/39	A-colon	0.9×0.8	Loose stool	Polypectomy
4	2000	Kim et al. [14]	M/40	Appendix	0.7	None, Anal fistula	Polypectomy
5	2003	Lee et al. [15]	F/36	A-colon	1.5×0.6	Constipation	Polypectomy
6	2003	Kim et al. [16]	M/49	Rectum	0.7	None	Polypectomy
7	2003	Ryu et al. [17]	F/40	A-colon	1.5×1.5	Abdominal pain	Polypectomy
8	2004	Sohn et al. [18]	M/48	T-colon	0.4	None	Polypectomy
9	2006	Park et al. [19]	M/41	Cecum	1.5×1.2	Abdominal pain	Polypectomy
10	2007	Lee et al. [7]	F/40	T-colon	0.6	Abdominal pain	EMR
11	2009	Cha et al. [20]	M/41	D-colon	1.3×1.2	None	EMR
12	2009	Hong et al. [21]	M/56	Cecum	1.5×1.0	Abdominal pain, Diarrhea	Polypectomy
13	2010	Cho et al. [22]	M/44	Cecum	1.5	None	EMR
14	2017	Yang et al. [23]	M/51	Rectum	2	None	Surgery
15	Present case		M/66	Cecum	0.5	Diarrhea	EMR
16	Present case		M/56	Cecum	0.9	None	Polypectomy

A-colon, ascending colon; T-colon, transverse colon; D-colon, descending colon; EMR, endoscopic mucosal resection.

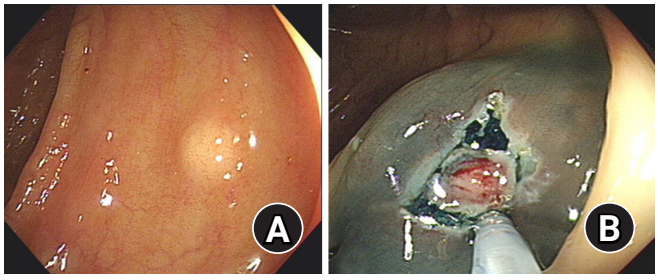

Fig. 1. (A) Colonoscopic findings. A yellowish, submucosal lesion that measured 0.5 cm in size is observed in the cecum of a 66-year-old male. (B) Endoscopic mucosal resection findings. Overlying colon mucosa was resected with a dual knife, and the tumor was removed by an endoscopic snare.

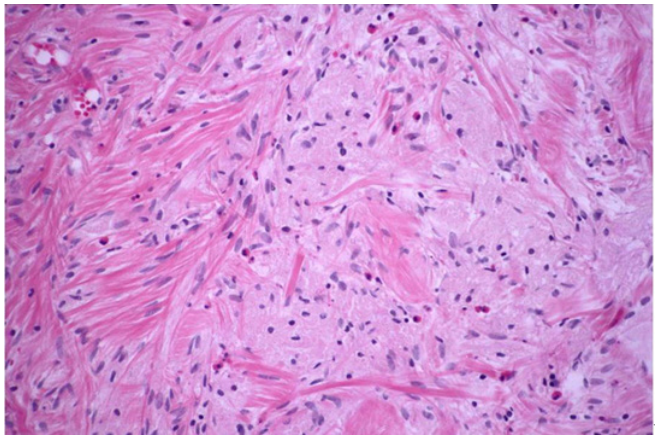

Fig. 2. Histopathologic evaluation of the specimen from the cecum shows a well-defined tumor border and polygonal cells with granular eosinophilic cytoplasm (H&E stain, ×200).

and treatment, 10% glycerin-epinephrine-indo carmine mixture was sufficiently administered around the lesion, and the mass was successfully removed using a snare after circumferential cutting with a dual knife. The patient was discharged without any complications after the endoscopic mucosal resection (EMR) (Fig. 1B). Histological findings included a well-defined tumor border and polygonal cells with granular eosinophilic cytoplasm (Fig. 2). Additionally, the tumor cells were strongly positive for S-100 protein in the Immunohistochemical (IHC) analysis and was diagnosed as GCT (Fig. 3).

Case 2

During a colonoscopy performed as part of routine health checkup for a 56-year-old male, a submucosal tumor of about 0.9 cm in size was observed in the cecum. The patient did not have previous medical history or any family history of tumors, and there were no specific findings in blood tests. The colonoscopy revealed a hemispherical lesion in the cecum with a smooth surface and was covered with a normal mucosa, its rigidity and slight mobility was confirmed using forceps (Fig. 4A). After the 10% glycerin-epinephrine-indo carmine mixture was injected around the tumor, it was completely removed with a snare upon confirming a well-defined border between the lesion and the normal mucosa. The patient was discharged with no complications after colon polypectomy

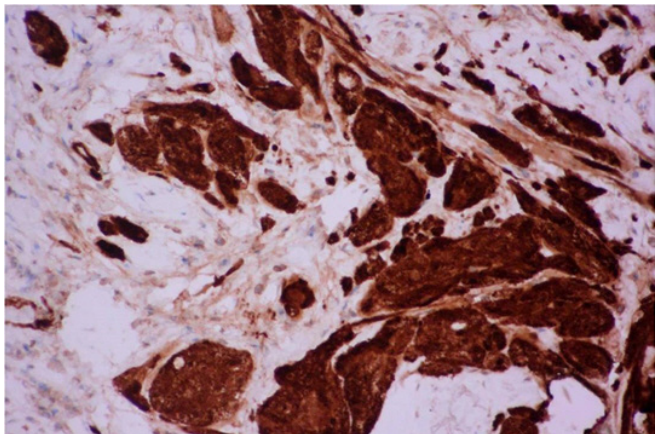

Fig. 3. Immunohistochemical staining shows the positive reaction for S-100 protein (immunohistochemical stain, ×200).

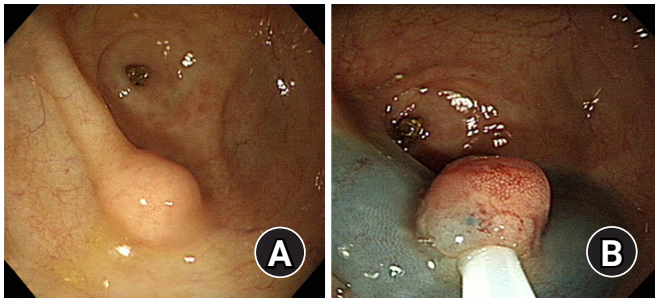

Fig. 4. (A) A hemispheric submucosal lesion in the cecum of a 56-year-old male that is 9 mm in size, with a smooth surface and covered with a normal mucosa revealed by colonoscopy. (B) The tumor was removed by colon polypectomy with snare successfully.

(Fig. 4B). Histologic examination revealed abundant eosinophilic cytoplasm with coarse granules of various sizes in the tumor cells. The result of the IHC study was positive for S-100 protein, and it was diagnosed as GCT.

Discussion

Although GCTs can occur in any site of the human body, they are mainly found in the tongue and mouth (40%), skin and subcutaneous tissues (30%), breast (15%), and respiratory system (10%). GCTs rarely occur in the digestive system, such as, the gastrointestinal tract (5.6%) or the bile duct (3%) [2]. When a GCT is found in the gastrointestinal tract, it develops mainly in the esophagus and rarely develop in the large intestine and/or stomach [4]. In the large intestine, GCTs usually occur in the anus of the rectum and in the ascending colon [2,5,6].

Abrikossoff first suggested that GCTs originated from denatured skeletal muscle cells, and therefore referred to them as myoblastoma [7,8]. Since then, many cells, such as histiocytes, fibroblasts, myoblasts, neural sheath cells, and neuroendocrine cells, have been suspected as the cells of origin for GCTs [3,8]. Vered et al. [9] suggested that GCTs could result from reactive lesions that are caused by local metabolic or reactive changes. Pareja et al. [10] identified that ATP6AP1 and ATP6AP2 loss-of-function mutations are the likely drivers of GCTs. Despite differing opinions of the tumor's origins, GCT is still considered to be caused by Schwann cells since it shows positive staining for S-100, myelin basic protein, Leu-7 and protein gene product 9.5 in recent IHC and electron microscopy studies [8].

To date, more than 130 cases of colonic GCT have been reported in the English literature [11]. In South Korea, 16 cases [3,7,12-23] of GCT in the large intestine have been reported since 1982 (Table 1). In the reported literature of over 100 cases of GCT in the large intestine, the rectum and cecum have been the most common sites [20]. In South Korea, it has been mainly found in cecum; however, other sites include the ascending colon, transverse colon, rectum, descending colon, and appendix, and are listed in the order of their respective incidence rates (Table 1). The age and gender distribution of GCT in the large intestine has been controversial in the literature. Singhi et al. [11] reported an equal sex distribution, with ages ranging between 31 and 60 years, while An et al. [24] observed a male predominance, with a wider age distribution between 21 and 75 years. However, in general, GCTs have been more frequently observed in females than in males, and patients are aged between 40 and 70 [8]. In South Korea, a sample of patients of various ages from 30 to 70 revealed that patients in their 40s accounted for 56% of all cases and a male predominance has been observed at a ratio of 1:1.6 (Table 1).

In the gastrointestinal tract, GCTs are mostly located under the mucous membrane. Most of them are asymptomatic and are accidentally found during the colonoscopy for a routine health checkup [11,25]. About 10 to 15% of patients with a GCT in the large intestine have experienced symptoms that include hematochezia, abdominal pain, and changes in bowel habits [11]. The cases in this study include a patient who presented to our clinic for diarrhea and an asymptomatic patient undergoing a routine health checkup. Most other cases in South Korea have been asymptomatic, followed by cases with abdominal pain, and symptoms including diarrhea, constipation, and loose stool (Table 1).

According to an analysis conducted by Endo et al. on the endoscopic findings in 33 cases of GCT in the large intestine,

mostly, yellow or yellowish white lesions of less than 2 cm in size were found, and they felt slightly firm in the form of submucosal tumor and were well- distinguished from the surrounding tissue [26]. Therefore, with the naked eye, GCT appears similar to other submucosal tumors, such as, ectopic pancreas, fibromas, lipomas, cysts, and carcinoids, which makes it difficult to diagnose GCT solely based on endoscopic findings [7,19]. GCT is only 50% diagnosed by tissue biopsy, and can be accurately diagnosed by using jumbo biopsy forceps or using the tissue obtained by colon polypectomy and EMR [22]. In fact, 13 out of 16 patients in South Korea were diagnosed by colon polypectomy and EMR (Table 1). In the cases of this study, yellow and yellowish white lesions of 0.5 cm and 0.9 cm in size and covered with normal mucosa were observed in colonoscopy, and diagnosed as GCT through histopathologic analysis after colon polypectomy and EMR.

In endoscopic ultrasound (EUS), GCT appears as a tumor originating from the submucosal layer with uniform internal echoes and hypoechogenicity. Tumors originating from the submucosal layer include lipomas, cysts, metastatic lesions, neurofibromas, and carcinoids. While lipomas are easily distinguishable as homogeneous hyperechogenic lesions, cysts as non-echogenic lesions, and metastatic lesions as lesions with heterogeneous internal echogenicity, it is difficult to differentiate carcinoids from GCTs [22]. Therefore, the role of EUS for submucosal tumors in the gastrointestinal tract is limited to the degree of determining the depth of tumor infiltration and helping with the diagnosis of submucosal tumors by measuring echogenicity of ultrasound [20].

Diagnosis is confirmed by pathological findings as it is difficult to distinguish based only on endoscopic findings. GCTs are composed of spindle-shaped or polygonal cells with varying sizes and unclear cell boundaries. In each tumor cell, eosinophilic granules are uniformly distributed in the cytoplasm, with an oval-shaped nucleus located in the center of the cytoplasm. These eosinophilic granules respond to periodic acid-Schiff staining and show strong positivity to IHC staining for S-100 protein and neuron-specific enolase [7,13,15,19]. In the cases of this study, strongly positive S-100 protein staining was observed (Fig. 3).

Most GCTs in the large intestine are tumors that are less than 2 cm in size and are well-separated from the muscularis propria layer. Therefore, these tumors tend to be diagnosed and treated by endoscopic removal, and followed up periodically for relapse by colonoscopy [13,19]. In the past, GCTs of more than 2 cm in size were surgically resected [27], however, Znati et al. [28] performed polypectomy or EMR for GCT of less than 4 cm and suggested surgical resection for tumors over 4 cm in size. In addition, Chen et al. [27] completely removed lesions of 3 to 5 cm in size, limited to submucosa, by endoscopic submucosal excavation. As the first malignant GCT was reported by Ravich et al. [29] in 1945, GCT is mostly benign, but rarely malignant (1 to 2%), in which case the prognosis is very poor with high metastasis and recurrence rates. Fanburg-Smith et al. [30] came up with the six histological diagnostic criteria: tumor necrosis, tumor cell spindling, pleomorphism, high nuclear to cytoplasmic ratio, large nucleoli, and increased mitotic activity, and suggested that malignant GCT could be diagnosed upon meeting three or more of such criteria. Also, local recurrence, metastasis, larger tumor size, older patient age, histologic classification as malignant, presence of necrosis, increased mitotic activity, spindling of tumor cells, vesicular nuclei with large nucleoli, and Ki-67 values less than 10% were suggested as prognostic factors [23,30]. Therefore, for cases with advanced patient age, tumor size >5 cm, rapid recent growth, and an infiltrative growth pattern, it was suggested to perform A-CT and EUS to determine the possibility of endoscopic treatment [27]. If the GCT is over 5 cm in size, or if there is an infiltrative growth pattern invading the muscular layer, lympho-vascular invasion or further metastasis, a surgical resection is required. Although there have been some reports that chemotherapy of malignant GCT is effective, the effect of chemotherapy and radiotherapy remains unclear [23,27].

But since GCTs smaller than 2 cm have very low malignant potential, if they are accurately diagnosed as GCT based on EUS and biopsy and there is no malignant potential per the histological criteria presented by Fanburg-Smith et al. [30], follow-up observation may be considered without endoscopic removal.

In conclusion, we report two cases of endoscopic removal of GCT accidentally found in the cecum, without complication. Upon detecting a submucosal tumor in the large intestine, colonoscopists shall consider that, although rare, there is chance of it being GCT. We hope that this analysis of 16 cases reported so far in South Korea will help in treatment and diagnosis.

Conflict of interest

All authors declare no conflicts-of-interest related to this article.

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