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#### Case 11

A 22-year-old woman, with no significant past medical history, presented to her general practitioner complaining of dysphagia. She was treated symptomatically but maintained her complaints, and eventually consulted a gastroenterologist, who performed an upper endoscopy. The examination was unremarkable, and biopsies of the distal esophagus revealed a normal squamous epithelium. She was then sent to an ear, nose, and throat specialist, who did not notice evidence of nasopharyngeal regurgitation, hoarseness, or aspiration. Given the persistence of symptoms, she finally had a CT scan that revealed a poorly defined, circumferential thickening of the esophageal wall. A second set of biopsies was performed that again came back negative. She eventually underwent a partial esophagectomy.

Diagnosis: Infiltrative granular cell tumor of the esophagus

Granular cell tumors (GCTs) are uncommon tumors of neurogenic origin that rarely occur in the esophagus, where it was described for the first time in 1931.<sup>1</sup> Between 1% and 8% of all GCTs occur in the GI tract and among those, about one third occur in the esophagus, where about 200 cases have been reported.<sup>12, 14, 16</sup>

The great majority of esophageal GCTs are benign. Fewer examples of a particular infiltrating variant associated with a good outcome have been reported and only a few truly malignant esophageal GCTs have been diagnosed.

#### Clinical Features

Most esophageal GCTs are diagnosed incidentally on upper endoscopy done for other reasons. It has been reported that about 50% of patients with esophageal GCT were symptomatic but that almost half have complaints not related to the tumor. When symptomatic, dysphagia is commonly reported and is related to tumor size. Hoarseness and heartburn also have been noted.<sup>11</sup>

GCTs occur in patients of all ages, but are most common between the fourth and sixth decade of life. A noted female predilection is not unanimously reported.<sup>14</sup> However, there is a disproportionate number of esophageal GCTs diagnosed in the black population.<sup>11, 26</sup>

#### Gross and Endoscopic Features

Endoscopically, GCTs typically appear as an isolated submucosal nodule with a normal or slightly granular overlying mucosa. Most (65%) of the tumors are found in the distal esophagus, with only 20% and 15% in the middle and proximal esophagus, respectively.<sup>22</sup>

Endoscopic ultrasound can provide additional information, such as the layer of origin as well as the depth of tumor extension. In one series, 95% of GCTs arising in the esophageal inner layer display a hypoechoic solid pattern with smooth margins.<sup>23</sup>

Nearly all esophageal GCTs are solitary, but between 11% and 5 of 13 of patients have two or more tumors.<sup>22</sup> The tumors are usually synchronous, although metachronous esophageal GCTs have been reported.<sup>4</sup> Several cases of multifocal GCTs localized to the gastrointestinal tract have been reported.<sup>11, 13</sup> For example, in one case, multiple tumors ranging in diameter from 3 to 7 mm were found in the larynx and in the middle and distal esophagus.<sup>11</sup> Another patient presented with

a solitary esophageal tumor associated with extraesophageal GCTs, including cutaneous and gastric localization.<sup>11</sup>

### Microscopic Features

GCTs are composed of a proliferation of slightly ovoid cells with abundant eosinophilic granular cytoplasm. The cells are usually organized in distinct nests. The nuclei are small and pyknotic, and generally centrally located. When present, only a minimal variation in size and shape is seen. Nucleoli are inconspicuous, and mitotic figures and tumor cell necrosis are usually not seen. The cytoplasm shows PAS-positive, diastase-resistant granules that represent the numerous lysosomes characteristic of these cells.

An important pitfall is the pseudoepitheliomatous hyperplasia of the epithelium overlying the tumor, which should not be incorrectly interpreted as a well-differentiated squamous carcinoma.

### Natural History

Most GCTs are histologically and clinically benign, and malignant tumors are extremely rare, estimated to be 1-2% of all cases.<sup>21</sup> The same is true for esophageal GCTs, with only few definitive cases of malignant GCTs reported.

Fifteen cases of infiltrating GCTs of the esophagus have been reported.<sup>2</sup> Like typical tumors, the mean age of the patients is about 40 years, and most complained of dysphagia (from a range of months to years). The tumors measured between 1.6 and 3 cm and were characterized by deep infiltration. The GCTs infiltrated the muscularis in 7 cases, the adventitia in 4, and regional organs (trachea, pharynx, or larynx) in another 4 patients.<sup>2, 3, 5, 7, 10-12, 15, 19, 20, 25</sup> Morphologically, the tumor cells are similar to typical cases, although nuclear atypia and mitosis can be seen. Although several of these tumors were originally considered to be malignant on the basis of the infiltrative growth pattern, no metastasis or death has been reported for them. On the contrary, patients can experience extended survival. In addition to the case presented today one patient was reported to be alive and well 22 years after incomplete surgical excision.<sup>5</sup>

Few definitive cases of malignant esophageal granular cell tumor have been reported. Mayer and Salzer-Kuntschik reported a case of an esophageal GCT that metastasized to cervical lymph nodes. In this case, the patient died 7 months later.<sup>19</sup> Wyatt et al. reported a 78-year-old female patient with malignant granular cell tumor with mitotic figures and vascular invasion.<sup>27</sup> Yoshizawa presented the case of a 71-year-old man who after complaining of dysphagia for 10 months was diagnosed with a 10x5 cm submucosal tumor with central ulceration of the mid-esophagus.<sup>30</sup> Four years later, the patient developed bilateral pleural metastases and multiple nodular lesions in his liver, and died shortly thereafter. Although the histologic details were sketchy, in several reports the presence of necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity, and pleomorphism seem to indicate malignant behavior, as previously noted with malignant granular cell tumor of the soft part.<sup>6, 19</sup>

### Pathogenesis

Formerly known as granular cell myoblastoma, both immunohistochemical and ultrastructural data support neural differentiation in this tumor. Ultrastructurally, the cytoplasmic granules consist of membrane-bound autophagic vacuoles that contain cellular debris, including myelin-like figures similar to Schwann cells, while the immunohistochemical expression of S-100 protein in both a diffuse and intense pattern is supportive of Schwann cell differentiation.<sup>8, 17, 18</sup> In a recent series, nestin, an intermediate filament protein expressed in neuroectodermal stem cells and skeletal muscle progenitor cells, has been shown to be in GI GCTs, suggesting that these lesions may arise from a multipotential stem cell in the GI tract.<sup>24</sup>

## Treatment

After exclusion of muscularis propria invasion by EUS, small esophageal GCTs can be successfully excised by endoscopic polypectomy.<sup>28,29</sup>

In the case of infiltrative GCTs, surgical resection, even when incomplete, has been associated with prolonged survival.<sup>9,11</sup>

In conclusion, although the infiltrative nature of the tumor and the presence of nuclear atypia suggest an aggressive behavior, they are not diagnostic of malignancy, even when the resection has been incomplete.

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#### Case 12

A 75-year-old woman, previously healthy, presented to her family doctor for general fatigue. Routine tests demonstrated an iron deficiency anemia. A full colonoscopy had been performed in the recent past and had demonstrated 2 hyperplastic polyps. She again was referred to a gastroenterologist, who this time performed an upper endoscopy. The examination demonstrated an atrophic antral mucosa. In addition, a large 2 cm polyp was identified. Of note, the polyp appeared friable when touched by the tip of the endoscope, and bled easily. A polypectomy was attempted.

**Diagnosis:** Gastric Hyperplastic Polyp with Malignant Transformation.

Most gastric polyps are incidental findings found in about 2% of endoscopies performed for other reasons. Occasionally, though, they may become inflamed and eroded, but subsequent bleeding is rarely apparent. Rarely, a large polyp may lead to gastric obstruction.

Hyperplastic polyps are the most or second most common type of gastric polyp.<sup>1-3</sup> Various terminology have used to describe these polyps: "hyperplasiogenous" or "regenerative" polyps.

#### Clinical Features and Pathogenesis

Hyperplastic polyps are randomly distributed throughout the stomach. When distal, the larger polyps also can manifest with gastric outlet obstruction, and there are rare reports of hyperplastic polyps prolapsed into the duodenum, with obstruction of the ampulla of Vater and secondary pancreatitis.

The stimuli for the development of hyperplastic polyps are not known. They are thought to result from excessive regeneration following mucosal damage and, as such, occur in chronic *Helicobacter*-associated gastritis (25% to 37% of the cases),<sup>4, 5</sup> autoimmune gastritis (51.3%) with or without pernicious anemia, adjacent to ulcers and erosions,<sup>5, 6</sup> or at gastroenterostomy sites.

They also occur in gastric remnants adjacent to gastro-jejunostomy stomas and in the gastric cardia/GE junction of patients with chronic esophageal reflux.

The majority seat in gastric mucosa, showing some degree of chronic atrophic gastritis and intestinal metaplasia.<sup>7</sup>

Hyperplastic polyps have a wide age range but are more common with increasing age (mean age: 57.3 to 66 years). Notably, all series report a peculiar predisposition in women that represents between 58 and 63.5% of patients. Depending on various series, 32 to 60% of hyperplastic polyps are located in the antrum, 29 to 49% are in the body fundus, and only about 2.5% in the cardia.

#### Gross and endoscopic features

Hyperplastic polyps are single in about two thirds of cases. The small polyps are smooth-surfaced, dome-shaped, sessile lesions, while the large ones are frequently lobulated and sometimes pedunculated. Superficial erosion commonly occurs. Their size ranges from less than one centimeter up to an exceptional 13 cm. However, most cases measure less than 1 cm, and polyps larger than 2 cm represent only 10%.

#### Microscopic Appearance

Histologically, hyperplastic polyps are characterized by two features: a) Marked elongation of the pits with branching, resulting in a corkscrew appearance or in cystic dilatation of foveolae lined by tall mucin-secreting cells, and 2) excess of edematous lamina propria with inflammation characterized by an infiltrate composed of plasma cells, lymphocytes, eosinophils, mast cells, macrophages, and variable numbers of neutrophils. Interspersed wisps of smooth muscle fibers are quite commonly seen between the gastric pits and arise from thickened split and fragmented muscularis mucosae. The gastric glands do not normally participate in the formation of the polyps.<sup>8</sup> The glands are lined by a single layer of hyperplastic foveolar-type epithelium, though pyloric-type glands, chief cells, parietal cells, and foci of intestinal metaplasia may be found, especially in the deeper zones.

The surface of the polyp may be ulcerated and acutely inflamed, showing degenerative and regenerative atypia in the epithelial and stromal cells within a prominent reparative granulation tissue with numerous capillaries. There also may be invagination of the surface mucosa with budding, which may produce a back-to-back appearance, as well as the appearance of pseudo-invasion;<sup>9</sup> this can cause major diagnostic problems, since true carcinoma<sup>3</sup> may be found in hyperplastic polyps.

Polypoid hyperplasia or hyperplastic polyps of the cardia and gastro-esophageal junction, either of foveolar type or mixed with squamous epithelium, can be observed. They are believed to represent a regenerative response to surrounding mucosal injury, such as ulcers, erosive esophagitis, or "junctitis" of the gastro-esophageal junction.<sup>10, 11</sup> They have been observed variably in the setting of gastroesophageal reflux disease. Histologically, they are mostly comprised of cardiac-type mucosa. Admixed squamous mucosa also can be seen and, rarely, parietal cells. Intestinal metaplasia is variably seen and dysplasia is rare (<3%).<sup>10</sup>

#### Differential Diagnosis of Hyperplastic Polyps

The differential diagnosis is that of Ménétrier's disease, Cronkhite-Canada syndrome, and juvenile polyposis. Hyperplastic polyps are easily distinguished from Ménétrier's disease by their smaller size and the presence of intervening normal mucosa (unless they are numerous). The distinction from juvenile polyposis rests entirely on the clinical diagnosis and the demonstration of juvenile polyposis in the large bowel. The differentiation from Cronkhite-Canada may be difficult, and unless diffuse, may depend on the typical ectodermal features clinically.

Among the diagnostic challenges that may occur when evaluating hyperplastic polyps, distinguishing between regenerative changes and dysplasia may be the most difficult. When attenuated epithelium is seen actively growing over an ulcerated surface, then it reasonably can be presumed that the pits in the immediate vicinity of the ulceration, as well as the attenuated epithelium, are all showing regenerative changes. In some polyps, however, the typical appearance of dysplasia may be seen, and very rarely one is surprised to find a focus of carcinoma.

#### Evolution/Prognosis of Hyperplastic Polyps

Over time, hyperplastic polyps can increase in number or regress, either spontaneously or following *Helicobacter* eradication.<sup>7</sup>

Historically, they were believed to confer no risk of malignant transformation. However, malignant transformation, although rare, is well-documented. Malignant degeneration has been reported to occur in 0.3% to 7.1% of hyperplastic polyps (average 2.1%),<sup>12-14</sup> and dysplasia has been reported in 1.8% to 16.4% of hyperplastic polyps.<sup>3, 13-15</sup> In one study, dysplasia was identified in 19.4% of hyperplastic polyps, but this figure may be inflated, since polyps smaller than 5 mm in diameter were excluded.<sup>16</sup> Polyp size greater than 2 cm is associated with an increased risk of its harboring dysplastic or malignant foci. Thus, larger polyps should be completely excised for histologic exclusion of neoplasia. The molecular genetics of carcinoma arising in gastric hyperplastic polyps are likely to follow the classical gastric adenocarcinoma. An immunohistochemical analysis showed that p53 reactivity was observed in the adenomatous foci of all transformed polyps, while it was negative elsewhere.<sup>17</sup>

Also, given the frequent surrounding background of intestinal metaplasia and dysplasia, an association with a synchronous carcinoma elsewhere in the stomach is recognized,<sup>1-3</sup> and therefore, careful endoscopic assessment of the surrounding mucosa is important.

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