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Case Report

Gastric glomus tumor: clinical conundrums and potential mimic of gastrointestinal stromal tumor (GIST)

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Abstract: Gastric glomus tumor is a rare neoplasm of the gastrointestinal tract that frequently mimics other mesenchymal lesions clinically and radiologically. We present a 70-year-old woman with an incidentally detected submucosal tumor of the antrum that was thought to be a gastrointestinal stromal tumor (GIST). The lesion measured 1.9 cm radiographically and was monitored over a period of 3 years. Multiple biopsies were attempted but did not yield a clear diagnosis. Over time, the lesion increased in size and developed an area of ulceration, prompting a wedge resection. After surgery, a diagnosis of glomus tumor was reached on the basis of histological and immunohistochemical studies. Glomus tumors are neoplasms of perivascular smooth muscle differentiation that can occur nearly anywhere in the body but exhibit a strong predisposition for the skin and subcutaneous tissue. They usually follow an indolent clinical course, although rare cases of metastasis have been reported. Gastrointestinal involvement is uncommon, and when present, the stomach is almost exclusively involved. Preoperative diagnosis may be impossible given the overlapping features with other mesenchymal tumors of the stomach, as illustrated in our case. A literature review of 210 gastric glomus tumors is provided, and important diagnostic pitfalls are highlighted to prevent misdiagnosis. In an era of precision medicine where incidental lesions are increasingly detected by routine endoscopy and imaging, awareness of this rare entity is important, as gastric glomus tumors are generally benign with a favorable prognosis following complete resection.

Keywords: Glomus tumour, stomach, gastrointestinal stromal tumour, GIST, mesenchymal tumor

Introduction

Glomus tumors are rare mesenchymal neoplasms composed of cells resembling the modified smooth muscle cells of glomus bodies [1-4]. They can occur almost anywhere in the body, but typically present in the skin and soft tissues of distal extremities where glomus bodies are abundant [3, 5, 6]. Gastrointestinal tract involvement is uncommon and when present, the stomach is almost exclusively affected [7, 8]. As in the case being presented, preoperative diagnosis of a gastric glomus tumor can be difficult or even impossible given its rarity and overlapping features with other mesenchymal lesions occurring in this location [4, 9, 10]. Therefore, accurate recognition by the pathologist is critical to ensure that the appropriate therapies are initiated to account for distinctive biological behaviors [4, 11-13]. We report a woman with a gastric glomus tumor presenting clinically as a suspected gastrointestinal stromal tumor (GIST). A literature review of 210 gastric glomus tumors from case series published between 1968 and 2017 is provided, and important diagnostic pitfalls are highlighted to prevent misdiagnosis.

Case presentation

A 70-year-old woman with asymptomatic anemia was found to have a submucosal mass in the gastric antrum following a routine endoscopic examination. A subsequent computed tomographic (CT) scan identified a 1.9 cm lesion along the lesser curvature. Multiple endoscopic biopsies were attempted but did not yield a clear diagnosis; clinically, this was believed to be a gastric gastrointestinal stromal tumour (GIST). Given the small tumor size and lack of symptomology, the patient was man-

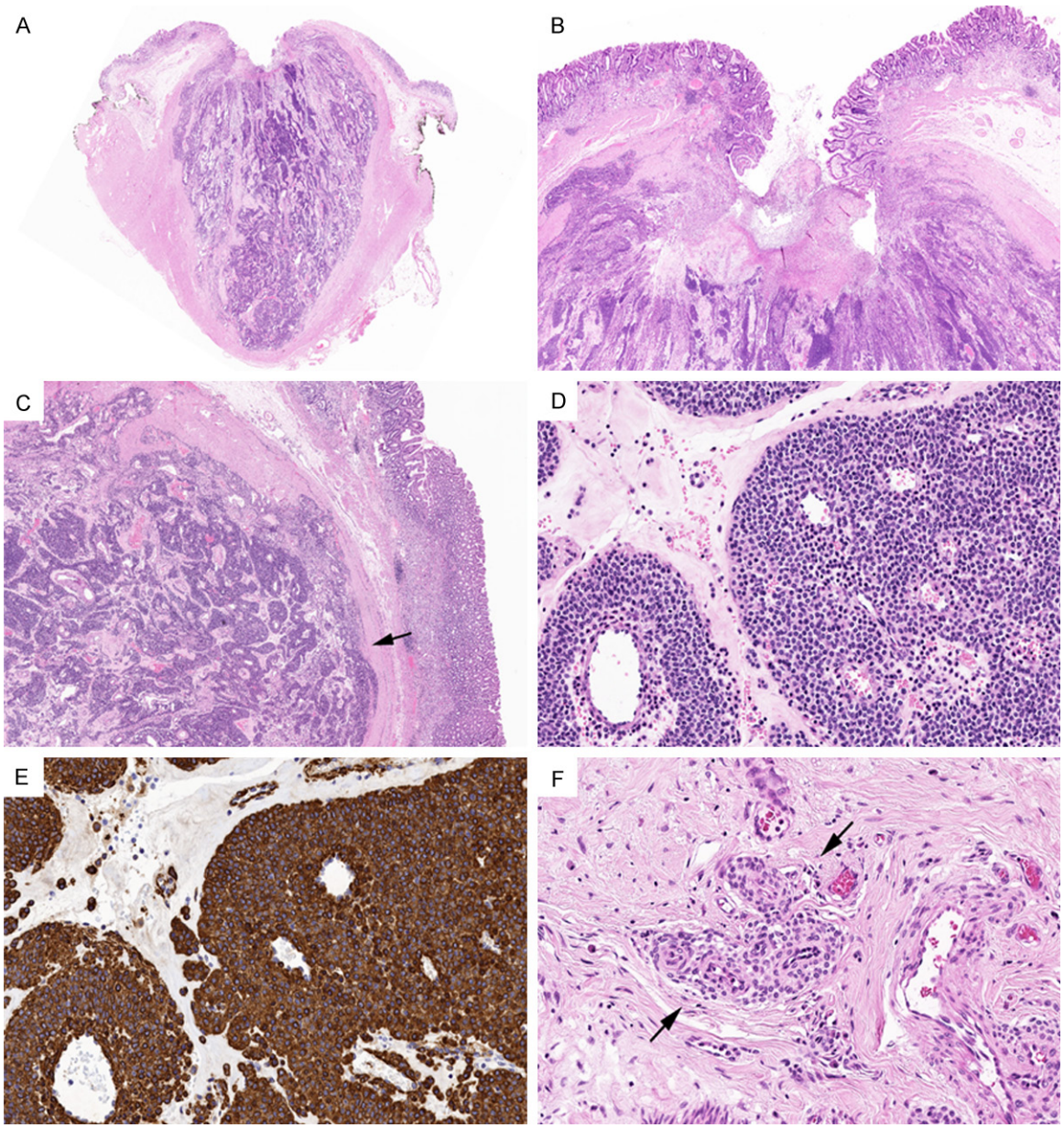

Figure 1. Gastric glomus tumor. A. These generally present as a circumscribed intramural mass that arises in the muscularis propria and frequently mimics a gastric GIST clinically and radiologically. B. Overlying mucosal ulceration is noted in about 27% of cases and can result in significant gastrointestinal bleeding. C. At scanning magnification, gastric glomus tumors exhibit a multinodular appearance. D. The classic morphology of small uniform round cells proliferating around vascular channels is virtually diagnostic of this entity. E. In keeping with their smooth muscle origin, gastric glomus tumor cells show strong, intense and diffuse smooth muscle actin immunoreactivity. Pathogenetically, they are thought to arise from the neuromyoarterial canals (i.e. glomus bodies) which are responsible for thermoregulation. F: Normal glomus body from skin.

aged with routine imaging and clinical surveillance for a period of 3 years. Over time, the mass increased in size and developed an area of ulceration, at which point it was decided to proceed with definitive treatment in the form of a wedge resection with clear margins.

Gross examination of the gastric antrum revealed a polypoid mass with overlying surface ulceration and a tan fibrotic cut surface measuring 2.2 cm in maximum diameter. Microscopic evaluation revealed a well-circumscribed submucosal lesion composed of small

uniform round cells proliferating around blood vessels in a "hemangiopericytoma-like" pattern (**Figure 1**). No cytologic atypia, mitosis or necrosis were identified. By immunohistochemistry, the small round cells stained diffusely for smooth muscle actin, confirming the histopathological impression of a glomus tumour.

Discussion

Glomus tumours are rare mesenchymal lesions of perivascular smooth muscle differentiation that can occur almost anywhere in the body [3, 5, 14]. They generally follow an indolent clinical course, although rare cases with atypical or malignant behavior have been described [3, 7, 15].

The molecular biology of glomus tumors has begun to be unravelled recently [3, 14, 16]. Inherited truncating mutation in the glomulin gene (*GLMN;* 1p22.1) are now attributed to a significant proportion of glomus tumors that present as multifocal lesions [3, 14, 17-20]. Although the exact mechanisms remain unclear, this familial form appears to follow an autosomal-dominant inheritance with variable expressivity and incomplete penetrance [3, 14, 20]. Furthermore, rare hereditary cases of multifocal glomus tumors have also been reported to arise in the setting of neurofibromatosis type 1 syndrome, due to bi-allelic inactivation of the *NF1* tumor suppressor gene (17q11.2), encoding neurofibromin [21-25]. The latter is a GTPase-activating protein implicated in the regulation of the RAS signaling pathway [21]. In light of these findings, the identification of multifocal glomus tumors (especially in association with syndromic manifestations) has clinical implications, as it may be a harbinger of an underlying genetic predisposition syndrome [23, 25]. In contrast, the molecular biology of solitary glomus tumors remains unclear at this time [3]. Rare *BRAF* and *KRAS* mutations have been described [26]. A recent study of 33 glomus tumors by Mosquera and colleagues identified novel *MIR143-NOTCH* fusions in 52% of cases (including 2 gastric glomus tumours); the mechanism of tumorigenesis is thought to be related to oncogenic activation of the NOTCH signaling pathway, which serves a putative function in the regulation of vascular smooth muscle development [14, 27].

Pathogenetically, glomus tumors are thought to arise from the neuromyoarterial canals (also known as Sucquet-Hoyer canals or glomus bodies) which are normally responsible for thermoregulation, via arteriovenous shunting of blood [3, 5, 11, 16]. This is further supported by the observation that they predominantly occur in the skin and subcutaneous tissue of distal extremities where glomus bodies are abundant [3-5, 7, 11]. Gastrointestinal tract (GIT) involvement is exceedingly rare [3, 5, 7, 8]. However when present, the stomach is almost exclusively involved, with rare reports in the small and large bowel [7, 8]. A literature review between 1968 and 2017 revealed at least 210 cases of gastric glomus tumors published to date (**Table 1**) [2, 4, 7, 28-35]. The overall median age at presentation was 54 years (range 18-90 years). A female predominance was noted, with a male-to-female ratio of 86:124.

Clinically, gastric glomus tumors can present with a variety of symptoms, ranging from asymptomatic anemia to ulcer-like pain and frank melena due to overlying mucosal ulceration [2, 4, 7, 28-35]. Including our case, our literature review revealed that 23% of cases (49/210) were asymptomatic and/or detected incidentally at the time of operation for another suspected lesion [2, 4, 7, 12, 28-35]. In contrast, epigastric pain was noted in 46% of cases (92/198), and gastrointestinal bleeding was a presenting complaint in 25% of cases (51/204). The antrum is by far the most frequent site of involvement, accounting for 82% of gastric glomus tumors (120/146) [2, 4, 7, 28-35].

Endoscopically, gastric glomus tumor is generally described as a well-circumscribed elevated mass lesion with normal or ulcerated overlying mucosa [2, 4, 7, 28-35]. Our literature review revealed the presence of mucosal ulceration in 27% of cases (35/130). Currently, endoscopic ultrasonography (EUS) and computed tomography (CT) represent the most widely used diagnostic modalities to characterize subepithelial lesions preoperatively [4]. On EUS, gastric glomus tumors show distinct borders and are localized in the 4th EUS layer (muscularis propria); involvement of the 3rd EUS layer is occasionally noted [4, 30, 33, 36]. The mass is usually heterogeneous and can be either hypo- or hyperechoic depending on its content; hetero-

Table 1. Clinicopathologic features of 210 gastric glomus tumors from published case series between 1968 and 2017

		Present case	Appelman et al. 12 cases (1969)	Kanwar et al. 52 cases (1975)	Miettinen et al. 31 cases (2002)	Lee et al. 13 cases (2006)	Yan et al. 5 cases (2007)	Fang et al. 57 cases (2010)	Zhang et al. 6 cases (2011)	Kang et al. 10 cases (2012)	Baek et al. 7 cases (2013)	Wang et al. 11 cases (2014)	Mengoli et al. 5 cases (2014)	Summary of all 210 cases
Demographics	Median age (age range)	70 years	55 years (30-74)	53 years (18-89)	56 years (19-90)	54 years (30-68)	32 years (31-69)	45 years (28-79)	48 years (32-58)	48 years (37-72)	55 years (33-71)	52 years (35-64)	67 years (51-86)	53.5 years (18-90)
	Sex predominance (male:female ratio)	Female	Male (7:5)	Female (25:27)	Female (9:22)	Female (3:10)	Female (0:5)	Female (22:35)	Female (2:4)	Male (8:2)	Female (2:5)	Male (7:4)	Female (1:4)	Female (86:124)
Symptoms	Gastrointestinal bleeding	0/1	5/12	12/52	11/31	4/13	0/5	14/57	----------	1/10	0/7	3/11	1/5	51/204 (25%)
	Epigastric pain	0/1	----------	18/52	9/31	9/13	4/5	35/57	6/6	5/10	1/7	4/11	1/5	92/198 (46%)
	Incidental/asymptomatic	1/1	3/12	16/52	5/31	0/13	1/5	8/57	0/6	4/10	6/7	2/11	3/5	49/210 (23%)
Tumor	Median size (size range)	2.2 cm	2.6 cm* (1.0-4.0)	3.0 cm (0.8-22)	3.0 cm (1.5-6.5)	2.5 cm (1.2-3.8)	2.0 cm (1.7-3.4)	---- (0.8-11 cm)	2.0 cm (1.2-3.0)	2.0 cm (1.0-3.6)	2.4 cm*** (1.2-2.9)	2.7 cm* (1.5-8.0)	2.5 cm (1.5-3.5)	2.5 cm (0.8-22)
	Antral Location	1/1	----------	----------	21/31	13/13	4/5	53/57	3/6	7/10	7/7	7/11	4/5	120/146 (82%)
	Ulceration	1/1	6/12	4/52	14/31	6/13	----------	----------	----------	1/10	----------	3/11	----------	35/130 (27%)
	Metastasis or recurrence (length of follow-up)	0/1 (3 mo)	0/12 (limited)	----------	1/13 (median 219 mo, range 33-291 mo)	----------	----------	0/15 (range 1-7 years)	0/6 (mean 9 mo, range 3-17 mo)	0/10 (median 44.5 mo, range 15-116 mo)	0/7 (median 25 mo, range 14-51 mo)	0/11 (range 1-144 mo)	0/5 (mean 68 mo)	1/80**

*Average given instead of median; **At least 3 other cases of malignant gastric glomus tumors have been described in the literature as isolated reports, usually ≥5 cm in size; ***Based on imaging findings.

geneity often correlates with hemorrhage or calcification, whereas internal hyperechoic spots are often associated with internal calcification [4, 30, 33]. Another characteristic finding of gastric glomus tumor is a peripheral halo sign, representing tumor cells that are partially or completely surrounded by muscularis propria [12, 33, 37]. On unenhanced CT, gastric glomus tumors often appear as circumscribed submucosal masses with homogeneous density and occasional flecks of calcifications [4, 10, 33]. On contrast-enhanced CT, an important feature is the presence of strong enhancement on arterial phase images and prolonged enhancement on portal venous phase images, reflecting their hypervascular nature which was also noted in our case [4, 10, 38]. On MRI, the tumor may appear hypointense on T1-weighted images and slightly hyperintense on T2-weighted images, with hypervascularity suggested by persistent enhancement after gadopentetate dimeglumine administration [10]. Nonetheless, it should be noted that all of the previously described EUS, CT and MRI findings in gastric glomus tumors can also be seen to some degree in other hypervascular submucosal tumors of the stomach, including GISTs and neuroendocrine tumors [4, 10]. Given the intramural location of gastric glomus tumors which precludes a diagnosis by endoscopic biopsy, some investigators have explored the role of endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA) with varying degree of success [4, 9, 30, 39]. Further studies are required to clarify the optimal method (including needle gauge selection) for tissue acquisition and assess the risk of bleeding and/or other complications which represent major limitations when biopsying this highly vascular tumor [4, 9, 30].

Given the aforementioned conundrums in the preoperative setting, gastric glomus tumors are frequently diagnosed unexpectedly following surgery [2, 4, 7, 12, 28-35]. As with other submucosal lesions of the stomach, the differential diagnosis varies according to the location within the mural layers. For gastric glomus tumors, the most important differential diagnoses to consider are an epithelioid GIST and a neuroendocrine tumor [7, 11-13]. Other considerations include paraganglioma, hemangiopericytoma and lymphoma [7]. Based on our literature review, the most common initial diagnosis for gastric glomus tumor is a GIST [9, 12, 34, 35, 40-42]. Which is approximately 100 times more common in this location [7]. In a recent large series of gastric glomus tumors, 6 of 11 cases (55%) were initially thought to be GISTs [34].

The gross appearance of gastric glomus tumor is typically described as a circumscribed oval or spherical intramural mass [7, 12, 13]. Our literature review of 210 published gastric glomus tumors revealed a median size of 2.5 cm (range 0.8-22 cm) [2, 4, 7, 28-35]. The cut surface may appear soft to rubbery, fibrotic or calcified, and frequently show a hemorrhagic component [7, 12, 13]. The tumor can bulge into the mucosa and/or externally towards the serosa [7, 12, 13]. Microscopically, gastric glomus tumors often exhibit a multinodular appearance at scanning magnification [12, 13]. The tumor nodules are composed of solid sheets of uniform round cells with sharply defined cell membranes, round nuclei and delicate chromatin, and generally surround large vessels in a hemangiopericytoma-like pattern (**Figure 1**). Furthermore, gastric glomus tumors almost exclusively arise in the muscularis propria and usually lack submucosal involvement [12, 13]. This is an important clue to differentiate glomus tumors from its mimickers, particularly neuroendocrine tumors which arise in the deep lamina propria [12, 13]. Although the classic morphology of small uniform cells proliferating around well-formed vascular channels is virtually diagnostic of a gastric glomus tumor, immunohistochemistry may be helpful in borderline cases [7, 11-13]. In keeping with their smooth muscle origin, gastric glomus tumor cells show strong positivity for smooth muscle actin (SMA; our case), calponin and h-caldesmon and negativity for desmin [7, 12, 13]. Focal expression of CD34 and synaptophysin have been described, however gastric glomus tumors tend to lack chromogranin, keratin and CD117/c-kit expression, distinguishing them from neuroendocrine tumors and GISTs [7, 12, 13].

Malignant gastric glomus tumors are exceptionally rare, with at least 4 reported cases of distant metastasis in the literature [7, 14, 15, 43, 44]. The liver is the most common distal site affected. With the exception of documented metastatic spread, there is currently no consensus on the diagnostic criteria for malignant

gastric glomus tumors [7]. Furthermore, the distinction between metastatic and multicentric disease can be challenging in some cases [7]. In 2001, Folpe and colleagues proposed the following criteria to predict malignant behavior in glomus tumors: 1) deep location and a size of >2 cm, 2) atypical mitotic figures, 3) moderate to high nuclear grade and ≥5 mitotic figures per 50 high-power fields (HPF) [15]. However, some experts believe that these criteria do not apply to gastric glomus tumors [7, 8]. For instance, in one of the largest case series, Miettinen and colleagues found that only 1 of 13 cases of gastric glomus tumors with follow-up metastasized [7]. Given the marked difference of malignant behavior between Folpe's series of deep glomus tumors of peripheral soft tissues (5/14) and their own series of gastric glomus tumors (1/13), Miettinen and colleagues proposed that the latter should be considered a separate site-related category [7]. Furthermore, a size of 5 cm appears to be a more appropriate indicator of risk, based on the observation that gastric glomus tumors with documented metastatic spread typically measured more than 5 cm, with only rare reports measuring less than this cut-off [7, 15, 43-45]. Mitotic activity and nuclear atypia appear to be poor predictors of malignancy in gastric glomus tumors: for instance, the two cases that metastasized in Folpe's series and in Miettinen's series had only 1-3 mitoses/50 HPF and mild nuclear atypia, a finding commonly seen in non-metastatic cases [7, 15]. The presence of spindle cell change may be of some significance as the only gastric glomus tumor with such change in Miettinen's series did metastasize [7]. Although vascular invasion is an alarming finding in many other tumors, it is frequently seen in benign gastric glomus tumors, and only 1 of 7 patients with follow-up and vascular invasion had evidence of adverse outcome [7].

The most widely used surgical approaches include wedge or segmental resection with clear margins [4, 7, 11, 31, 33, 34]. Enucleation is currently not advocated given the risk of recurrence in incompletely excised lesion and potential complications (bleeding, perforation) [11, 15, 32]. In most cases, complete excision of gastric glomus tumor is curative [4, 7, 11, 31, 33-35]. However, as criteria for malignancy have not been firmly established in gastric glomus tumors, a small possibility of malignant behavior cannot be ruled out [7]. Based on the current data, gastric glomus tumors of larger size (>5 cm), especially if associated with atypical features (spindle cell change, atypical mitotic figures, high nuclear atypia, vascular invasion), likely warrant closer follow-up [7].

Conclusion

To our knowledge, the current study represents one of the largest literature reviews of gastric glomus tumors to date. Gastric glomus tumors are the most common type of gastrointestinal glomus tumors. They pose significant diagnostic challenges in the preoperative setting and are frequently misdiagnosed as GISTs initially, as seen in our case. Almost a quarter of cases are diagnosed unexpectedly after surgery. Preoperative characterization by endoscopy, EUS, CT and MRI can be helpful although definitive classification is hampered by overlapping features with other submucosal tumors in this location. Important differential diagnoses to consider include epithelioid GIST and neuroendocrine tumor. The classic morphology of small uniform cells proliferating around well-formed vascular channels is virtually diagnostic of a gastric glomus tumor; however immunohistochemistry for smooth muscle differentiation can assist in borderline cases. Complete excision is usually curative, as the vast majority of these are clinically benign. Nevertheless, rare cases of metastasis have been described. Based on the current literature, the most important risk factor that warrants closer follow-up is large tumor size (>5 cm), especially if one or more atypical features (spindle cell change, high nuclear atypia, atypical mitotic figures, vascular invasion) are identified.

Disclosure of conflict of interest

None.

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