A 68 year-old male presented with an incidentally discovered gastric submucosal mass measuring 3.1 cm. A fine needle aspiration biopsy was performed and a diagnosis of "neoplasm consistent with a well-differentiated neuroendocrine tumor" was made. The resection specimen is demonstrated below.

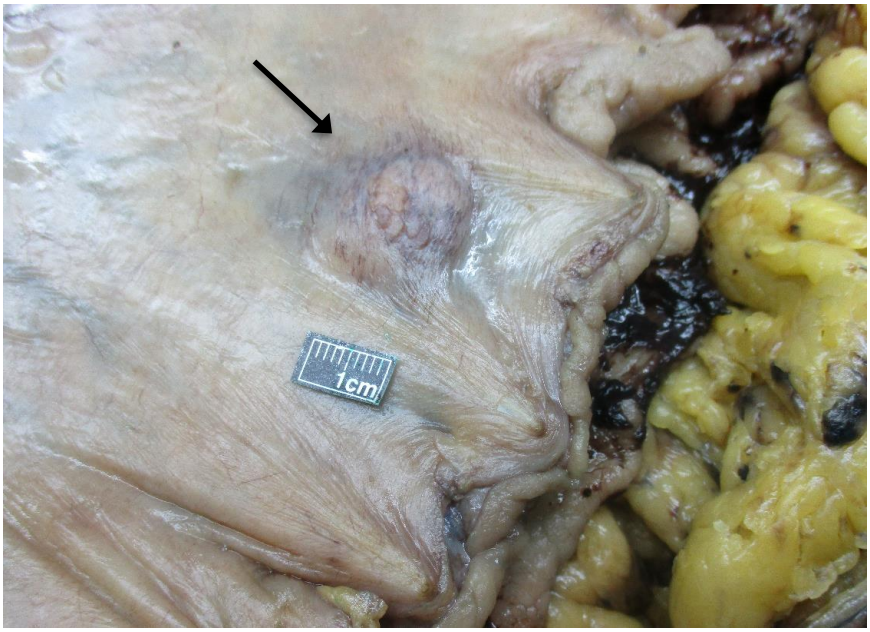

Figure 1. Stomach, gross specimen: left-serosal surface; right-mucosal surface. On cut section the tumor was tan, lobulated, and well circumscribed (images not available).

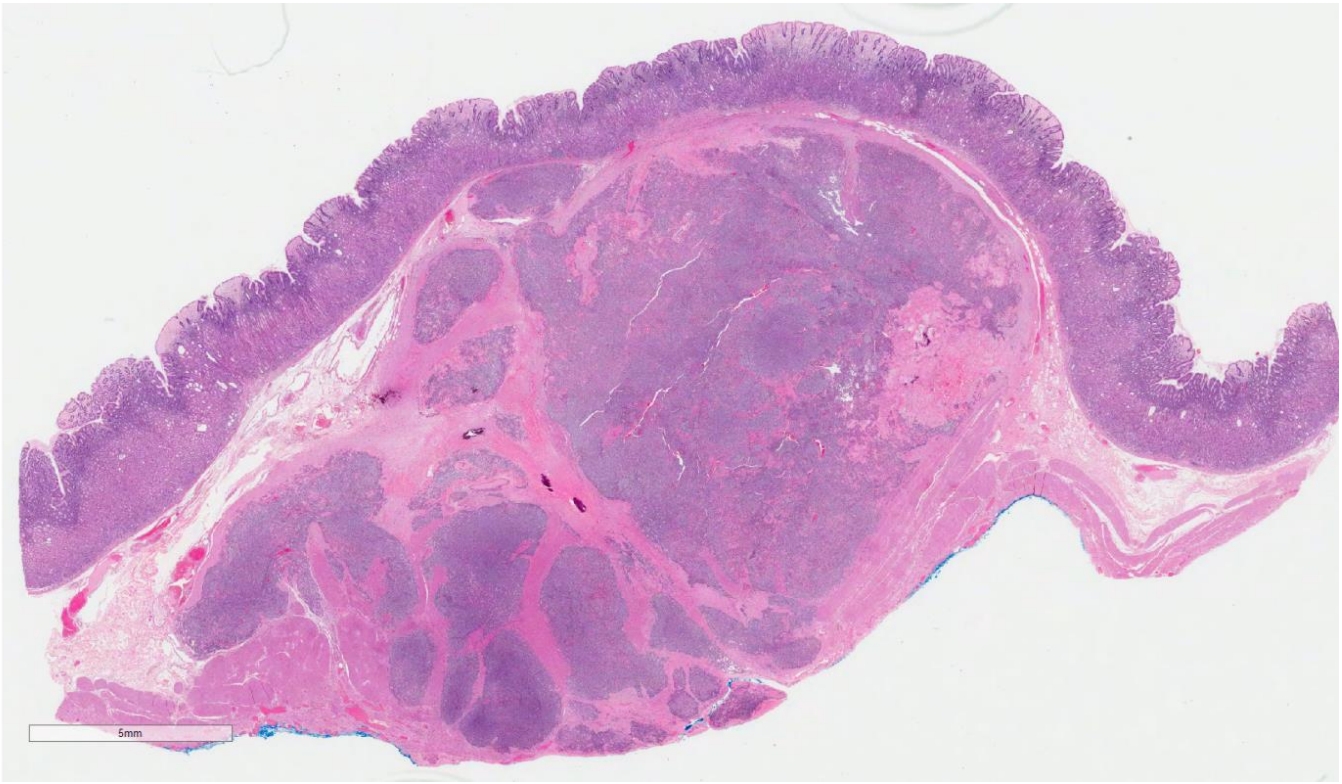

Figure 2. Gastric neoplasm, H&E (1x magnification).

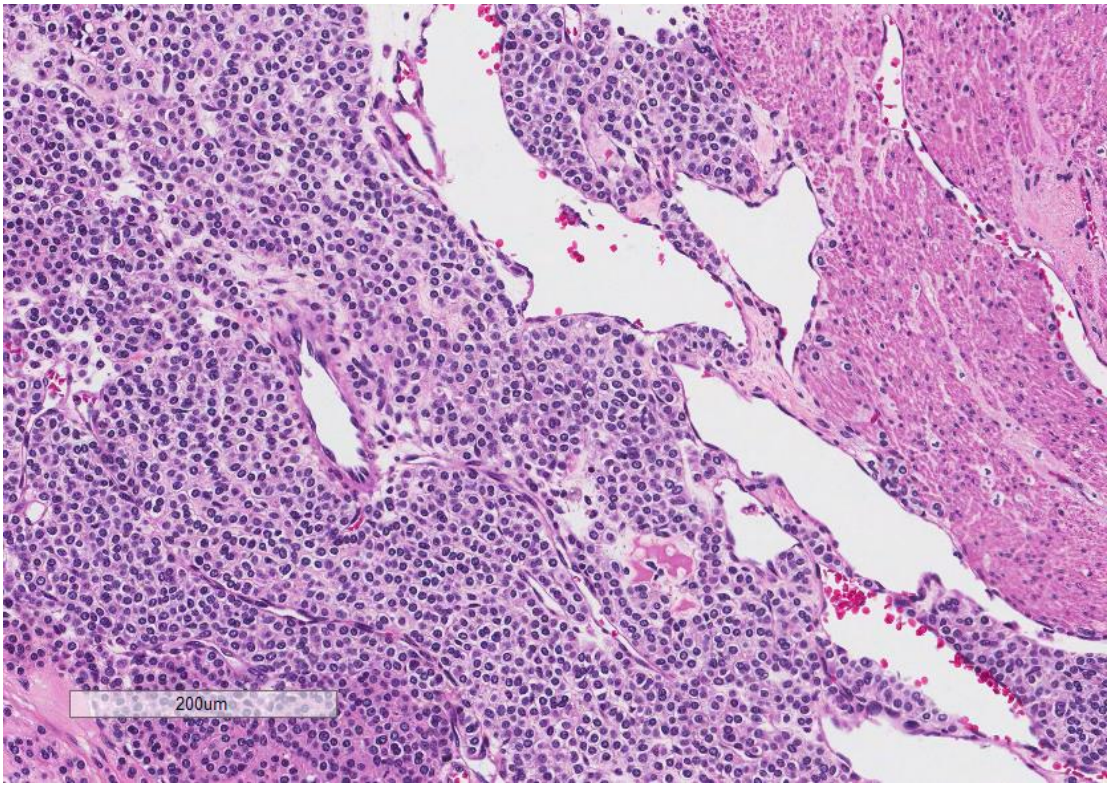

Figure 3. Gastric neoplasm, H&E (10x magnification).

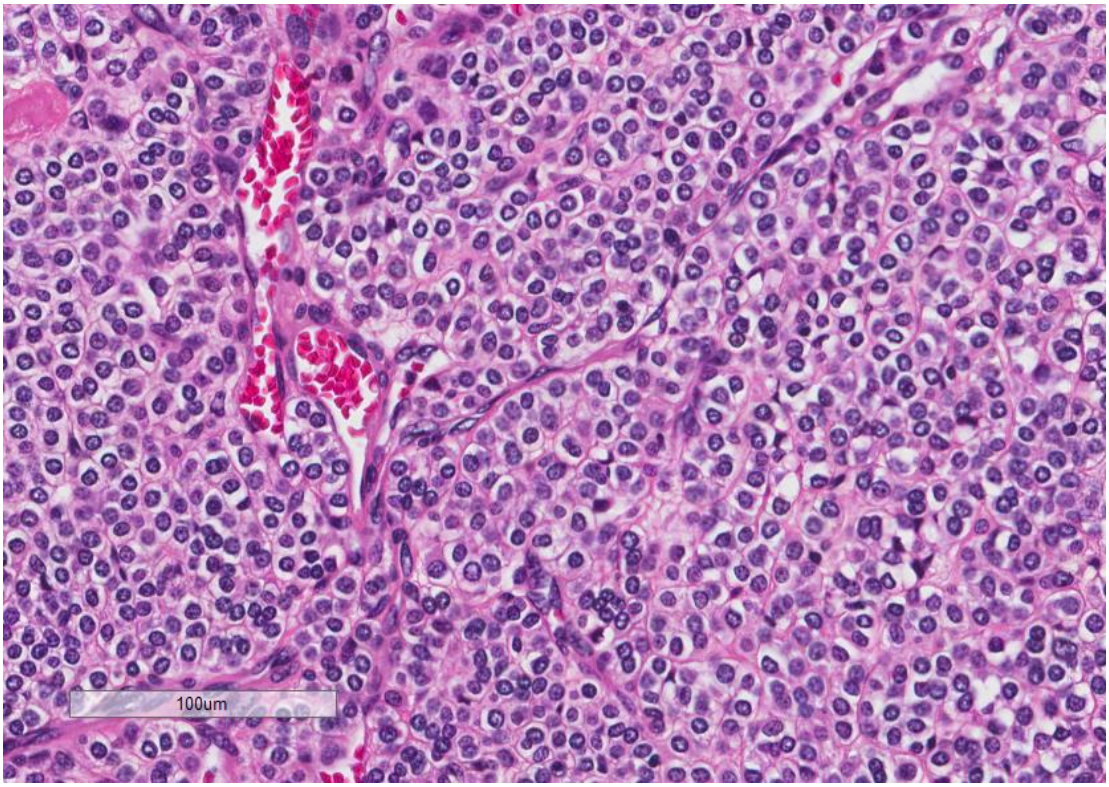

Figure 4. Gastric neoplasm, H&E (20x magnification).

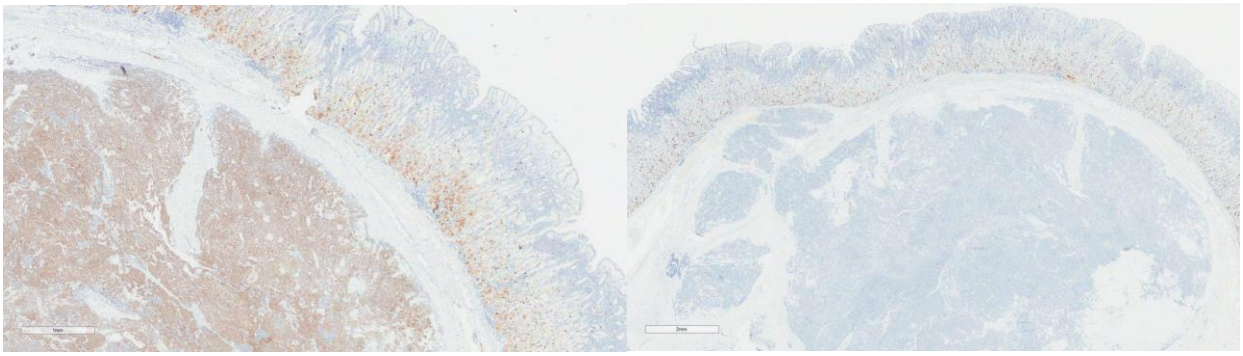

Figure 5. Left: Synaptophysin (1x magnification); Right: Chromogranin (1x magnification)

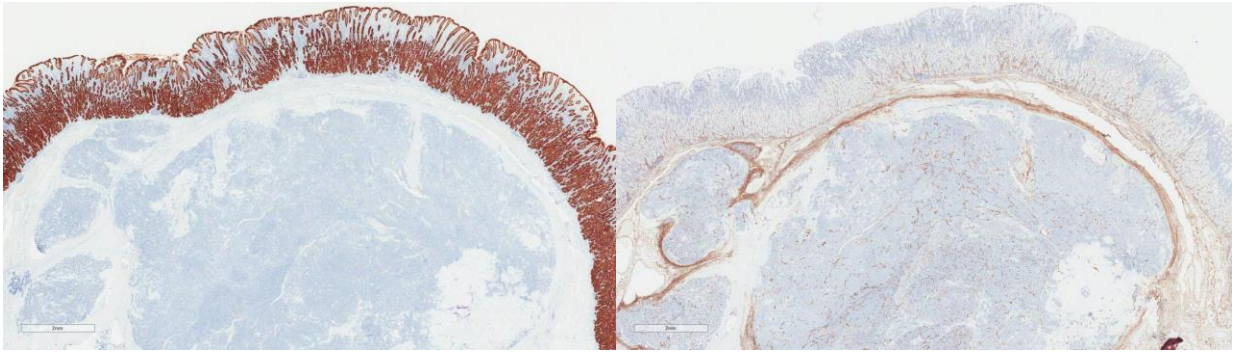

Figure 6. Left: Pan-cytokeratin (1x magnification); Right: CD34 (1x magnification)

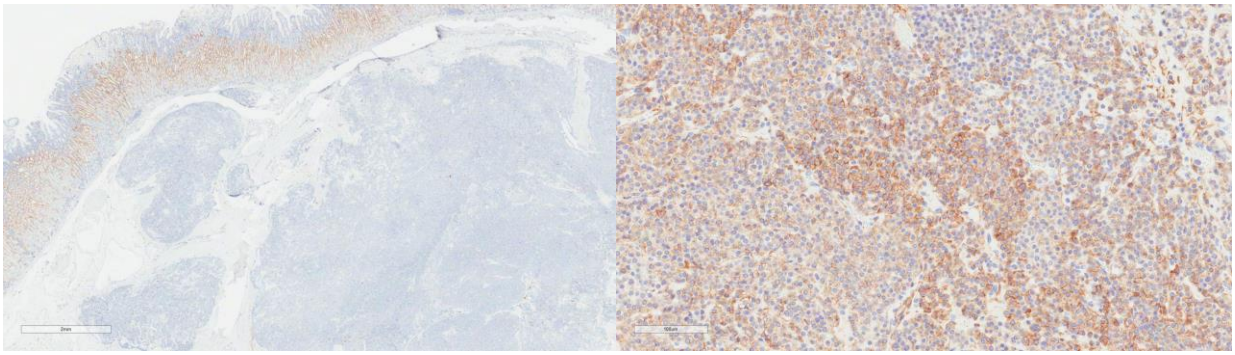

Figure 7. Left: CD117 (1x magnification); Right: DOG1 (20x magnification)

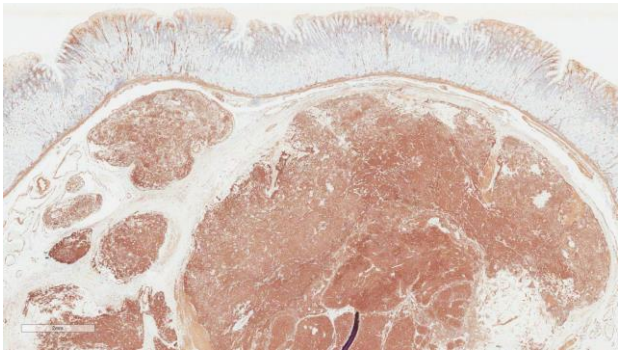

Figure 9. Smooth Muscle Actin (1x magnification)

Other markers:

Vimentin – Positive
Calponin – Positive
Caldesmon – Patchy positive
AE1/3 – Negative
HMB45 – Negative
Calretinin – Negative
Inhibin – Negative
Desmin – Negative
S100 – Negative

Question: Based on the gross features, morphology, and immunophenotype, what is the most appropriate diagnosis?

A) Well-differentiated neuroendocrine tumor
B) Epithelioid gastrointestinal stromal tumor
C) Glomus tumor
D) Paraganglioma

Answer: C)

Discussion:

C) Glomus tumors (GTs) arise from specialized vascular smooth muscle cells (pericytes) and classically present as painful lesions on the subungual finger[1-2]. Glomus tumors of the stomach are uncommon lesions, which have been described in numerous case reports and series[3-5]. These tumors can clinically and morphologically mimic more common gastric neoplasms, and therefore knowledge of this entity, along with a high index of suspicion, are necessary for correct diagnosis[3].

Clinically, patients with gastric GTs frequently present with epigastric pain, ulceration, or upper gastrointestinal bleeding, which can be severe[3]. Incidental presentations have also been reported[3]. A wide age range can be affected (median age 54 years), and a slight female predominance has been shown[3]. A wide variation in tumor size has been described, with a median size of 2.7 centimeters[3]. Larger gastric GTs may have an increased risk of metastasizing[3.]

Morphologically, GTs typically demonstrate well-circumscribed and sheet-like growth with prominent vascular spaces[1, 3]. The cells are usually monotonous and rounded with round-oval nuclei and eosinophilic to clear cytoplasm[1, 3]. Cell membranes are typically well-defined and the nuclei are centrally placed with delicate chromatin[3]. Correct diagnosis generally requires morphologic assessment along with a panel of immunohistochemical markers.

Glomus tumors of the gastrointestinal tract are usually positive for smooth muscle actin (SMA), calponin, and vimentin[3]. Peri-cellular net-like positivity is seen with Collagen type IV and Laminin[3]. One series found synaptophysin and CD34 positive in 18% and 20% of gastrointestinal glomus tumors, respectively[3]. Caldesmon is also positive in more than half of cases[3]. Cytokeratins, CD117 (c-kit), S100, desmin, chromogranin, and CD45 are consistently negative in these lesions[3]. Reports of DOG1 positivity in GTs (not restricted to the GI tract) have varied, with one series demonstrating 0/14 positive cases and another demonstrating 6/7 positive cases[6-7]. In the study by *Wong et al.* evaluating DOG1 positivity in numerous tumor types, glomus tumors were the only neoplasms to stain CD117 negative and DOG1 positive[7].

Gastric GTs almost always follow a benign clinical course, however notable exceptions do exist in the literature. *Song et al*. reported the case of a 65 year-old woman presenting with a malignant gastric GT and multi-organ metastases[8]. In a case series of 32 patients, *Miettenen et al*. identified one patient with a gastric GT metastatic to the liver, who eventually died of their disease[3]. In another series by *Folpe et al*, the only case arising in the stomach had metastasized to the liver[9].

In the study by *Folpe et al.*, they looked at 52 atypical and malignant GTs (from all body sites), and classified them as 1) malignant GT, 2) symplastic GT, 3) GTof uncertain malignant potential, and 4) glomangiomatosis[8]. This classification was based on features that included: size, site (superficial vs. deep), nuclear grade, presence of atypical mitotic figures, and mitotic rate[8]. Metastases were observed in 38% of tumors classified as malignant, and were not observed in the other three categories[8]. Of note, this classification scheme may not accurately predict the behavior of gastric GTs, which generally behave less aggressively than other deep-seated lesions, and may require a site-specific grading scheme[3-4]. Interestingly, BRAF V600E mutations have recently been identified in a subset of atypical/malignant GTs[10].

A) One of the primary considerations in this case was a well-differentiated neuroendocrine tumor (NET). Morphologically, well-differentiated NETs have monotonous round-polygonal cells with round nuclei containing coarse 'salt and pepper' chromatin[1, 7]. They are more commonly centered in the mucosa or submucosa, and architectural patterns can include nested, trabecular, and acinar[1, 7]. By immunohistochemistry, well-differentiated NETs are typically positive for cytokeratins, CD56, chromogranin, and synaptophysin[1, 7]. Lesions that are cytokeratin negative but synaptophysin and/or

chromogranin positive should prompt consideration for alternate diagnoses including GT or paraganglioma.

B) Another strongly considered differential in this case was an epithelioid gastrointestinal stromal tumor (GIST). Morphologically, epithelioid GISTs can also have clear cytoplasm and stromal hyalinization, similar to a GT[3]. However, they typically have more polygonal or oval cells, and do not usually have such prominent dilated veins or capillaries[3]. Among all GISTs (including spindled and epithelioid), roughly 60-70% will be positive for CD34, 95% will be DOG1 positive, and 95% will be CD117 positive. Both DOG1 and CD117 have similar sensitivities for diagnosing GISTs, and only approximately 1% of cases will be negative for both[1]. While multiple different tumor types can express either CD117 or DOG1, only GISTs will show strong expression of both[1]. However, it is important to remember that epithelioid GISTs can have markedly decreased or absent DOG1 and/or CD117 expression[7]. The majority of GISTs will have either KIT or PDGFRA mutations, which can be tested for in diagnostically challenging cases[7].

d) Paragangliomas of the stomach are exceedingly rare tumors, though cases have been reported[11]. Morphologically, extra-adrenal paragangliomas often show anastomosing cell cord or trabecular arrangements[1]. Other variants include organoid (Zellballen) and solid/diffuse patterns[1]. Cytoplasm is relatively abundant and finely granular, while nuclear pleomorphism is common[1]. By immunohistochemistry, paragangliomas are usually positive for neuroendocrine markers, including synaptophysin and chromogranin, and negative for cytokeratins (though not always)[1, 3]. S100 positive sustentacular cells are another helpful clue to making the diagnosis[1, 3].

Key Points:

- Glomus tumors of the stomach are uncommon lesions that can mimic more common tumors, especially on small biopsy specimens. A high index of suspicion is required.

- These tumors can be positive for synaptophysin but should always be negative for cytokeratins; a feature which can help to differentiate them from well-differentiated neuroendocrine tumors.

- Glomus tumors can also be positive for DOG1 and CD34, potentially mimicking an epithelioid gastrointestinal stromal tumor (GISTs). However, CD117 should be negative. PDGFRA or KIT mutation testing can be performed in difficult cases.

- Most gastric glomus tumors follow a benign clinical course, however notable exceptions do exist in the literature. Features that include increased size and mitotic rate may predict aggressive behavior.

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