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PHOTO QUIZ

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Gastric granular cell tumor masquerading as gastrointestinal stromal tumor: a rare concept

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Case

A 42-year-old female presented with dysphagia to solids, intermittent vomiting, and weight loss for 3 months, without appetite loss. Vitals and physical exam were normal. Upper gastrointestinal endoscopy (UGIE) revealed a well-defined submucosal lesion (~2x2 cm) at the cardia of the fundus with central umbilication [Figure 1A]. Because of characteristic overlying umbilication, a clinical diagnosis of gastrointestinal stromal tumor (GIST) was initially made, and the patient was further subjected to contrast-enhanced CT (CECT) and endoscopic ultrasound (EUS) with targeted biopsy [Figure 1B-D]. Although the lesion appeared to originate from the submucosal region on EUS, the histopathology of the retrieved tissue was inconclusive. As the tumour was > 2cm and well localized regionally on CECT, a wedge resection was performed. The excised tissue was a submucosal nodular mass (2.5x1.5x0.7 cm) with bulging, slightly indurated mucosa. On sectioning, it appeared firm, yellowish, and homogeneous without necrosis.

Microscopy showed a submucosal infiltrating tumor with intact overlying gastric mucosa [Figure 2A]. It had infiltrated into the lamina propria and extended into the subserosal fat through the muscularis propria, keeping the serosal surface free of tumor invasion. Tumor cells were arranged in sheets and nests separated by thin-walled blood vessels and wavy collagen [Figure 2B-C]. It comprised large polygonal cells with oval to spindle-shaped nuclei with fine granular chromatin, and a few cells showing conspicuous nucleoli and abundant eosinophilic granular cytoplasm, which are Periodic Acid Schiff (PAS) positive [Figure 2D-E]. Mild nuclear pleomorphism and occasional binucleate cells were noted, without significant mitotic activity. A panel of immunohistochemistry was performed for characterization of tumor phenotype [Figure 3A-C].

What is your diagnosis?

What to do next?

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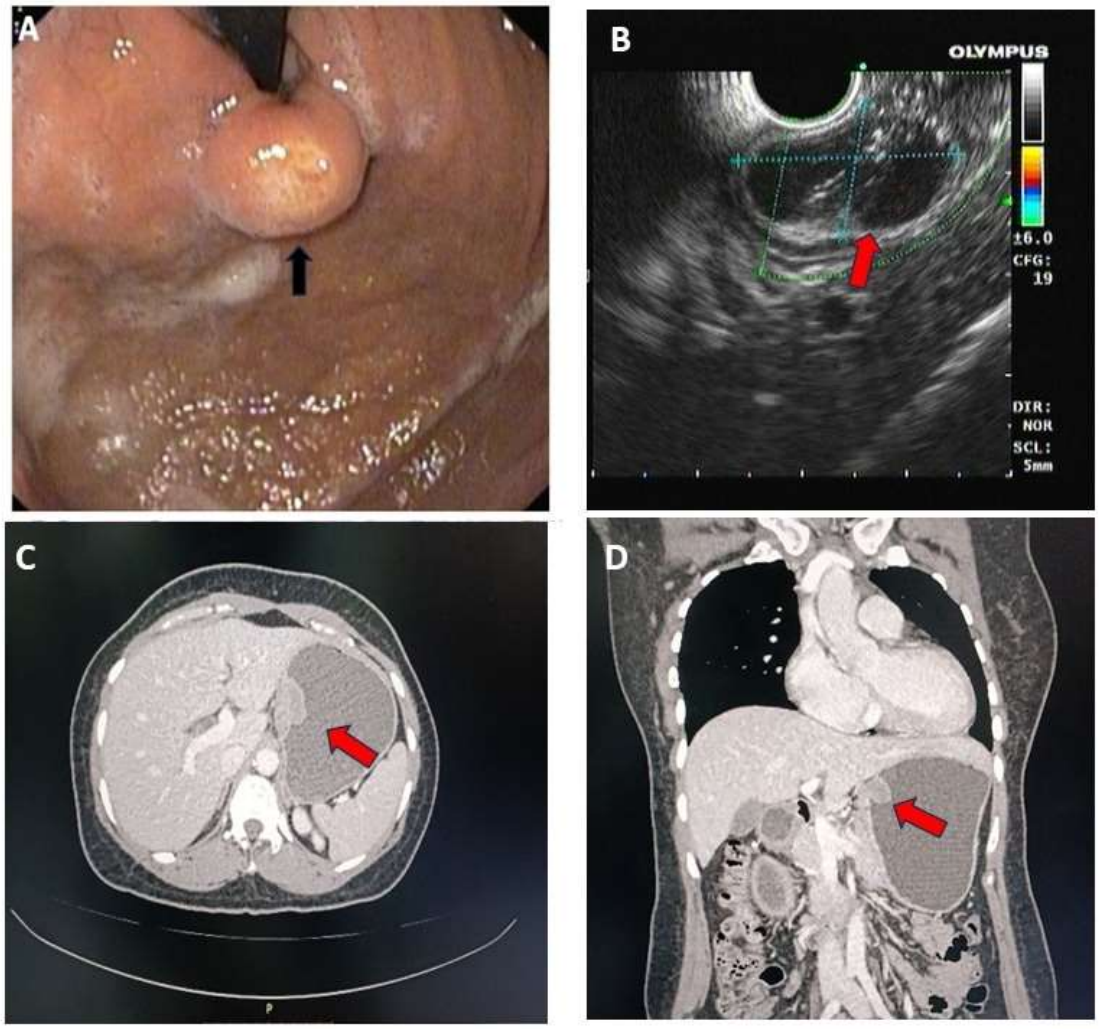


Figure 1. A: Upper gastrointestinal endoscopic picture showing a polypoid lesion with central umbilication, below the gastroesophageal junction, measuring approximately 2x2 cm (indicated by black arrow). **B:** Endoscopic ultrasound (EUS) showing a well-circumscribed hypoechoic lesion of size 2.3 x 1.5 cm just below the gastroesophageal junction arising from the submucosa (indicated by red arrow). **C&D:** CECT abdomen axial section and coronal section showing a well-defined, broad-based intraluminal heterogeneously enhancing soft tissue lesion involving the cardia of the stomach along the lesser curvature (indicated by red arrow).

Discussion

Granular cell tumor (GCT) is a rare benign solitary neoplasm of neural origin, arising from Schwann cells. Abrikossoff first reported it and named it Abrikossoff's tumor or granular cell myoblastoma (1). The granular appearance of the tumor is due to cytoplasmic lysosome accumulation (2). Gastrointestinal tract (GIT) involvement is uncommon (5–11%), with the distal esophagus and large intestine being the most frequently involved sites. Gastric GCTs are rare, accounting for only 4% of GIT GCTs (3). Atypical gastric GCTs are extremely rare. In the GIT, GCT typically arises from the submucosal nerve plexus (4).

They predominantly affect females between 40 and 60 years of age. They are usually asymptomatic unless the size is too big or the location is in the GE junction, which can cause significant dyspepsia, dysphagia, and heartburn (1). Radiologically, they appear hypoechoic, homogeneous, and smooth-edged, resembling cysts or polyps. Grossly, GCTs are smooth, white, grey, or yellowish submucosal lesions without ulceration or nodularity (5).

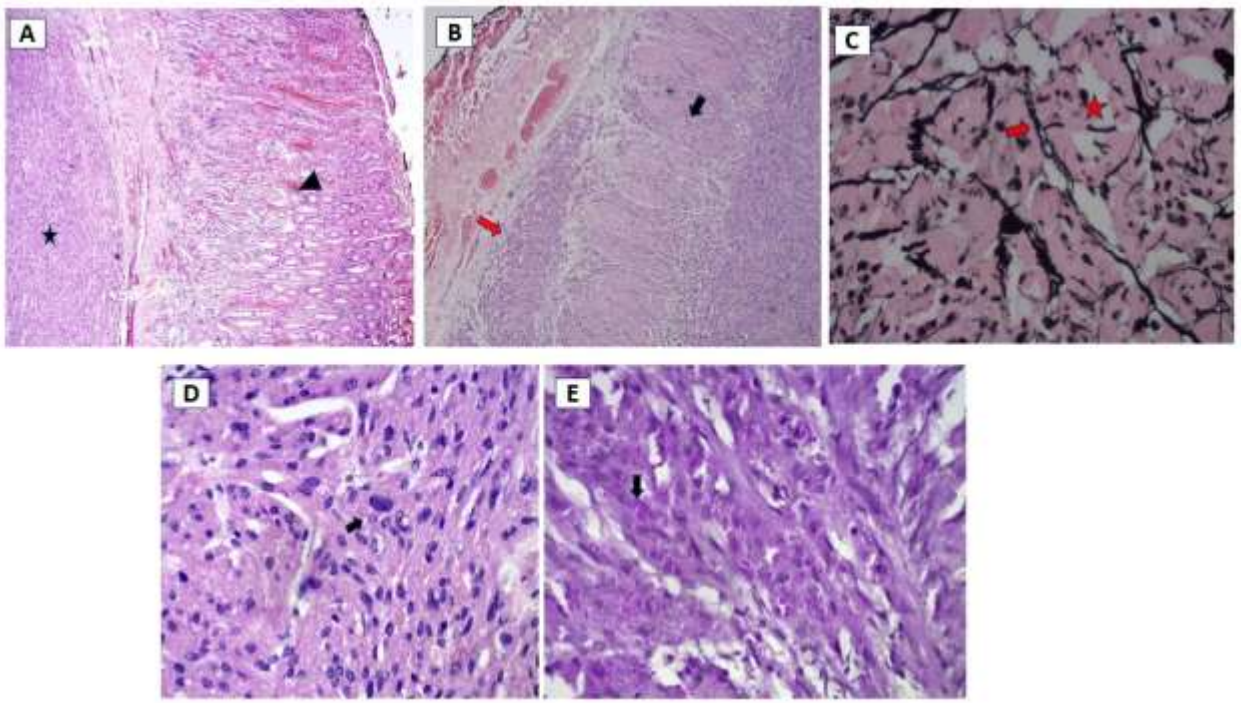


Figure 2. A: Submucosal tumor (indicated by black asterisk) with intact overlying gastric mucosa (indicated by black arrowhead) (H&E, 40x). **B:** Nests of tumor cells infiltrating the muscularis propria (indicated by black arrow) and present in the subserosal fat (indicated by red arrow). (H&E, 100x). **C:** Nests of tumor cells (indicated by red asterisk) surrounded by reticulin fibers (indicated by red arrow) (Reticulin stain, 400x). **D:** Nests of tumor cells separated by thin-walled blood vessels and wavy collagen. The tumor cells are large, polygonal with oval to spindle-shaped nuclei with fine granular chromatin and an abundant amount of coarse, eosinophilic granular cytoplasm (H&E, 400x). **E:** Cells with abundant eosinophilic granular cytoplasm, which are PAS positive (indicated by black arrow) (PAS, 400x).

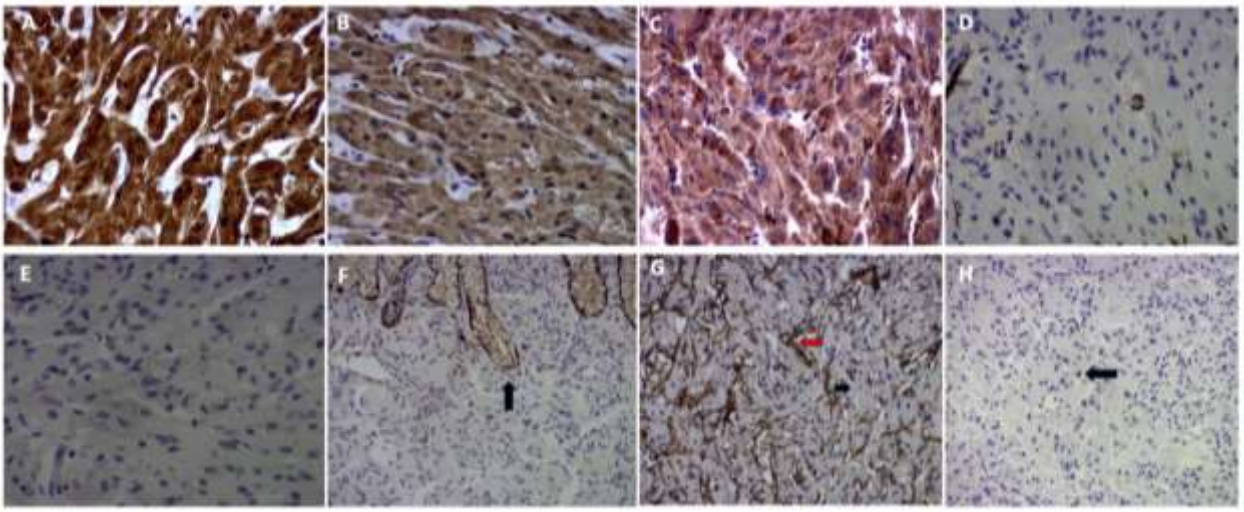


Figure 3. The tumor cells show diffuse and strong immunopositivity for S100 (3A), NSE (3B) & CD68 (3C). The tumor cells show immunonegativity for CD117 (3D), DOG1 (3E), PAN CK (3F), and SMA (3G), which excludes the possibilities of GIST, epithelial tumor, paraganglioma, and leiomyoma, respectively. Smooth muscles of the vessels are indicated by the red arrow (3G). The Ki-67 proliferation index is approximately 2% in the highest proliferating areas (nuclear stain indicated by black arrow) (3H). As per Fanburg-Smith criteria (6), a diagnosis of atypical GCT was made based on the above findings.

The histological diagnosis can be challenging. The microscopy usually shows a solid tumor located in the submucosa or muscularis propria comprising sheets and nests of large polygonal cells with oval to spindle nuclei, bland chromatin, and abundant eosinophilic, coarse granular cytoplasm. The nests are usually surrounded by strips of collagen (2, 3).

According to Fanburg-Smith criteria, GCTs are classified as benign, atypical, or malignant based on six histological features such as necrosis, spindling, high nuclear: cytoplasmic ratio, >2 mitotic figures/10 high-power field, pleomorphism, and vesicular nuclei with prominent nucleoli. Tumors with 1–2 features are labelled as atypical, whereas those with >2 features are classified as malignant (6). Tumor size, growth rate, and invasion into adjacent structures also influence the biological behavior of the tumour. On immunohistochemistry, >10% Ki-67 proliferation index and >50% of p53 positivity have been significantly correlated with malignancy (5). Our case had spindling and moderate pleomorphism, qualifying as atypical GCT.

The differential diagnosis usually includes GIST, leiomyoma, neurofibroma, schwannoma, paraganglioma, neuroendocrine carcinoma, and spindle cell squamous cell carcinoma. The closest differentials are GIST and leiomyoma, which have similar histology, but GCTs are distinguished by PAS-positive granular cytoplasm and collagen strips around nests. Also, immunohistochemistry negativity for CD117, DOG1, and SMA differentiates GCT from GIST and leiomyoma (3, 5). This distinction is crucial, as GCTs are often managed conservatively with an endoscopic approach if diagnosed early, while other submucosal tumours like GIST, schwannoma, or neuroendocrine tumours may require chemotherapy along with endoscopic or surgical resection.

GCTs of size <1 cm in diameter can be treated conservatively, between 1-2 cm can be removed by endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), whereas tumors of larger size > 2cm, or multiple tumors, should be treated with surgery followed by LASER ablation therapy as required. Larger tumors of size >4 cm, atypical and malignant subtype, invading the deeper layer of muscularis propria or surrounding structures, pose therapeutic challenges for complete excision. In our case, surgical resection was chosen over endoscopic management due to the tumour size being >2 cm and uncertain histological nature. Endoscopic follow-up is advised at six months post-treatment, then annually if no recurrence is found (7-8). At the twelve-month follow-up, our patient remained asymptomatic with no recurrence.

Conflict of interests

There is no conflict of interest for authors of this article.

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