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Cytological-Pathologic Correlation

Cytomorphological features of glomus tumors arising in the stomach: A series of two cases diagnosed on FNA

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1. Introduction

Glomus tumors (GT) are mesenchymal neoplasms that arise from modified smooth muscle cells of the glomus body, a receptor that plays a role in regulation of arteriolar blood flow and temperature regulation. The majority of glomus tumors arise from the extremities with the subungual region of the finger being the single most common site. Other common sites include palm, wrist, forearm and foot [1]. Glomus tumors of the stomach are rare and endoscopic ultrasound-guided fine-needle aspiration cytology (EUS-FNAC) is highly accurate and remarkably helpful in the preoperative evaluation of patients with intramural lesions of the gastrointestinal tract [2]. Moreover, immunocytochemical studies have been helpful in the differential diagnosis of gastric submucosal tumors, including gastrointestinal stromal tumors (GIST), neuroendocrine tumors, and glomus tumors. Herein we report two cases of glomus tumor in stomach with emphasis on cytomorphologic characteristics.

2. Case series

2.1. Case 1

A 75-year-old female with a past medical history of hypertension, hyperlipidemia, coronary artery disease and breast cancer, developed recurrent breast cancer and underwent mastectomy with flap reconstruction and nodal dissection. She underwent a Computed Tomographic (CT) scan for staging purposes prior to planned chemotherapy and was noted to have a 3.3 cm exophytic mass in the gastric antrum. This was thought to be a primary gastric neoplasm but a metastasis from her breast cancer was also in the differential diagnosis. Esophagogastroduodenoscopy identified a submucosal mass in the gastric antrum (Fig. 1A) and endoscopic ultrasound (EUS) showed a 3.3 cm hypoechoic mass arising from the submucosa of the gastric antrum with internal necrosis (Fig. 1B). An EUS guided fine needle aspiration (FNA) was performed.

Examination of the FNA revealed singly scattered and cohesive clusters of small, round to polygonal tumor cells with small amount of cytoplasm and ill-defined borders. The nuclei were uniform, round to oval with fine chromatin (Fig. 2). Cell block showed clusters of bland epithelioid cells with prominent cell borders, thick basement membrane and round nuclei with fine chromatin (Fig. 3A). No cytologic atypia or mitosis were observed. Immunohistochemical stains showed that the tumor cells were positive for smooth muscle actin (SMA) (Fig. 3B), calponin (Fig. 3C) and collagen type IV (Fig. 3D), and were negative for cytokeratin 18, cytokeratin AE1/AE3, synaptophysin, chromogranin, CD56, CD117(c-kit), DOG1, GCDFP-15, GATA3, mammoglobin, melanoma cocktail, S100 and CD45. The morphology and immunoprofile was consistent with a glomus tumor.

A laparoscopic partial gastrectomy and partial omentectomy was performed. Macroscopically, a 1.8 × 1.7 × 1.5 cm rubbery pink-tan nodule was present in the submucosa abutting the mucosal surface. On microscopic examination, tumor involved the mucosa, submucosa, muscularis propria and extended focally to the serosa (4). Microscopic examination showed a tumor composed of sheets of small, round

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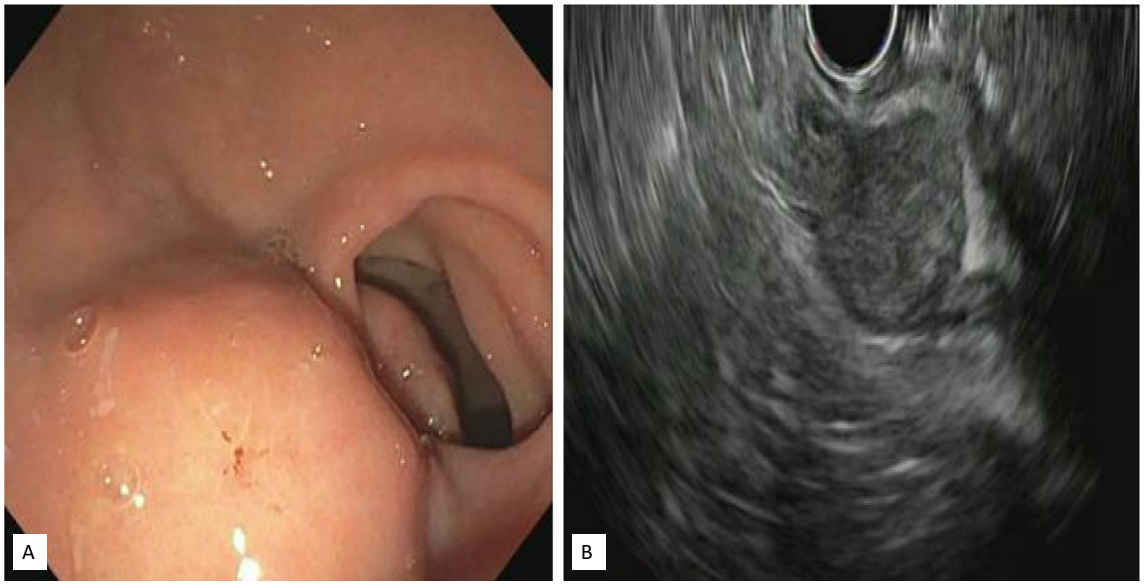

Fig. 1. A, Upper gastrointestinal endoscopy shows a well-circumscribed submucosal mass in the gastric antrum. B, Endoscopic ultrasound shows a 3.3 cm hypoechoic mass arising from the submucosa of gastric antrum with internal necrosis.

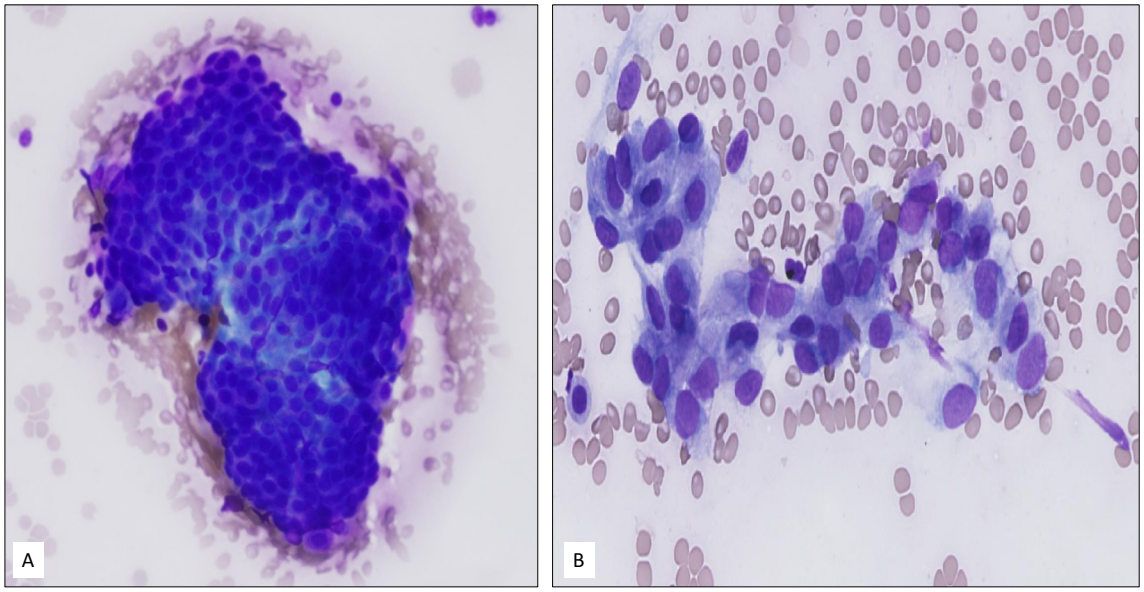

Fig. 2. A and B, Fine-needle aspiration of glomus tumor: Uniform small round to ovoid cells with scant cytoplasm, indistinct cell borders, round hyperchromatic nuclei, homogenous chromatin and inconspicuous nucleoli (A. Diff-Quik, original magnification 200× and B. Diff-Quik, original magnification 400×).

monotonous cells arranged around thick walled vessels (Fig. 5A). The tumor cells were small, uniform, round with centrally-located round nuclei and small amount of cytoplasm (Fig. 5B). No necrosis or mitotic figures were identified.

2.2. Case 2

A 68-year-old male presented with dysphagia for a few months. Upper gastrointestinal endoscopy showed a 1.25 × 1.25 cm non-mucosal nodule in the gastric fundus (Fig. 6A). EUS showed a 0.7 × 0.5 cm oval hypoechoic, homogenous intramural (subepithelial) lesion in the fundus of the stomach, 3.0 cm distal to the gastroesophageal junction (Fig. 6B). The lesion appeared to originate from the submucosa.

FNA showed uniform small round to ovoid cells with scant cytoplasm, indistinct cell borders, round hyperchromatic nuclei, homogenous chromatin and inconspicuous nucleoli (Fig.7). No mitotic activity was seen. There was no necrosis, but background of blood and fibrin was present.

A cell block showed cells arranged in small lobules and separated by vascular channels and dense, hyalinized stroma (Fig. 8A). Tumor cells were positive for SMA (Fig. 8B), vimentin, calponin, h-caldesmon while negative for desmin, c-kit, CD34, chromogranin, synaptophysin, cytokeratin, S100, CD45. This supported a diagnosis of glomus tumor.

3. Discussion

Glomus tumors are mesenchymal tumors composed of modified smooth muscle cells. They most commonly occur in the peripheral soft tissues, especially in the distal extremities [1,3]. Rare glomus tumors have been reported in almost every location, including the gastrointestinal tract, genitourinary tract, lung, joints, mediastinum, bone, liver and pancreas [1,4]. Glomus tumors of the stomach are rare benign

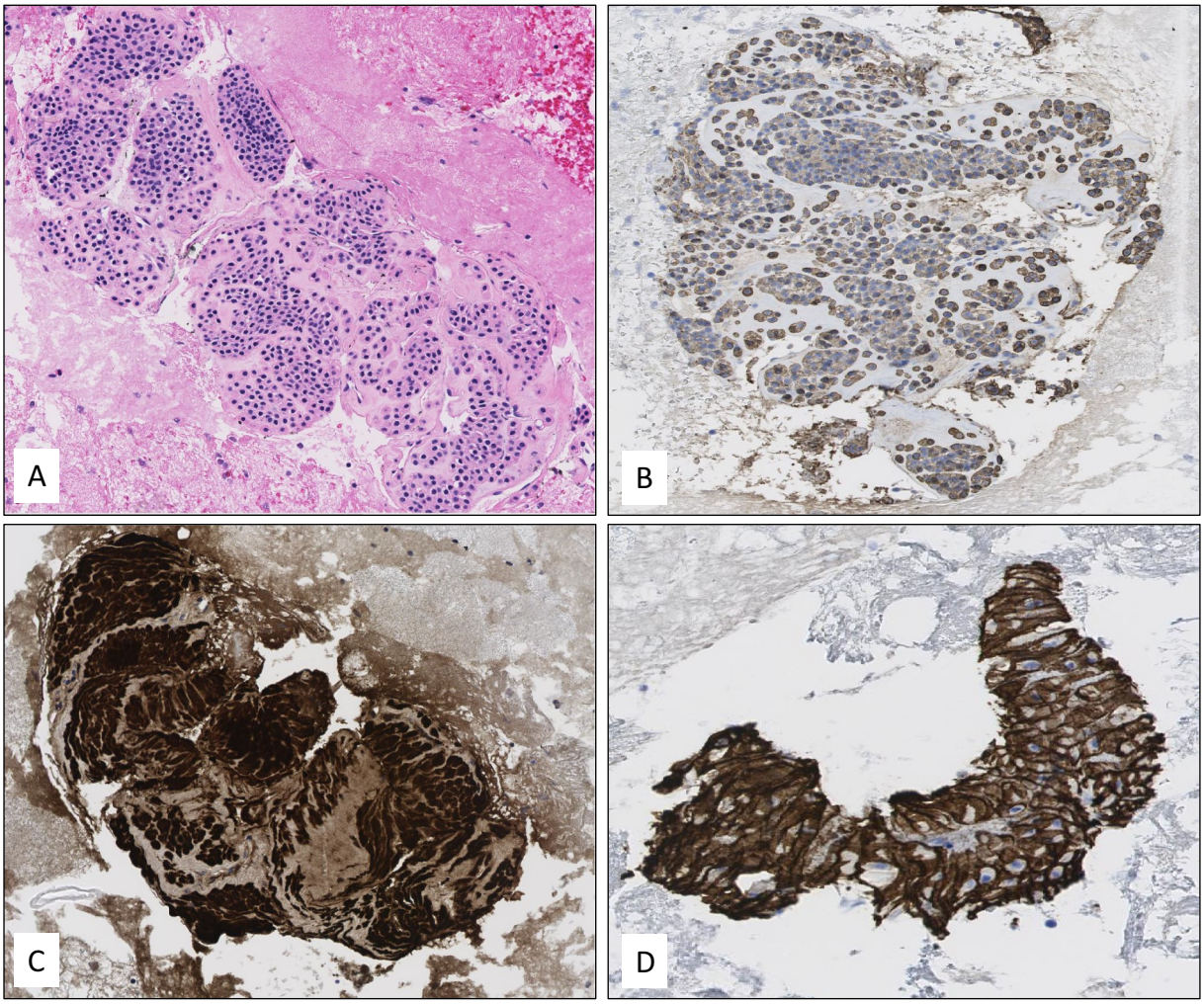

Fig. 3. A, Cell block (CB) showing cells arranged in small lobules and separated by vascular channels and dense, hyalinized stroma. B, Tumor cells show strong and diffuse staining with smooth muscle actin. C, Tumor cells show strong and diffuse staining with calponin. D, Tumor cells show strong and diffuse staining with collagen type IV.

lesions often found as a submucosal or intramuscular mass [5]. There is no sex predilection for gastric glomus tumors even though the subungual glomus tumors are more frequent in females [4]. The median age is 56 years (19–90 years) [6].

The most common site for gastric glomus tumors is the antrum and occasionally the body of stomach [7]. They are mostly solitary, usually 2–3 cm in size [6]. Patients usually have non-specific symptoms like gastrointestinal bleeding, epigastric pain, dyspepsia or can be asymptomatic and the tumor is found as an incidental finding [7].

EUS and CT scan are the main modalities for evaluating gastric submucosal tumors. EUS helps in identifying the layer of origin and CT helps in characterization of the tumor with contrast enhancement. CT generally shows strong homogenous enhancement for glomus tumors. EUS usually detects homogenous and well-demarcated usually hypoechoic lesion. Some glomus tumors may appear heterogenous due to internal hemorrhage and calcification on EUS. However, EUS AND CT findings by themselves are insufficient to establish a preoperative diagnosis of glomus tumor [8].

EUS-FNA is an effective diagnostic method that can help distinguish glomus tumors of the stomach from other gastric tumors. Preoperative recognition of this tumor can prevent an extensive surgical resection in a patient. Aspirate smears of glomus tumors show mixtures of well-demarcated nests or clusters and loosely cohesive sheets of small-to-medium sized, uniform, round to polygonal cells with scant to moderate pale cytoplasm. Nuclei are centrally located and round to oval with fine chromatin. The cells very rarely contain nuclear inclusions and have occasional small, central nucleoli [9-11].

As shown in the reported cases, the differential diagnosis of glomus tumor from other submucosal lesions is not easy based on cytologmorphologic features alone. Cell block architecture and immunohistochemistry are key to diagnosis. Because glomus tumors are derived from modified smooth muscle cells, their immunohistochemistry and ultrastructure are similar to those of smooth muscle tumors. Vimentin and muscle actin isoforms can be identified in nearly all glomus tumors. Heavy-caldesmon may be expressed. However, desmin immunoexpression is highly variable. Corresponding to the ultrastructural features of the neoplasm, laminin and type IV collagen, two constituents of basal lamina, outline the cells or small groups of cells [1,6].

Most glomus tumors are benign. Rare malignant cases of glomus tumors have been reported [12]. Glomus tumors usually require and are cured by conservative local resection. The differential diagnosis of gastric glomus tumor includes neuroendocrine tumor, paraganglioma, hemangiopericytoma, epithelioid GIST, epithelioid leimyoma/leiomyosarcoma and lymphoma.

Neuroendocrine tumors exhibit cellular smears with single or loosely cohesive clusters of round to polygonal cells with minimal to moderate amount of cytoplasm, round to ovoid nuclei with finely granular salt and pepper chromatin with inconspicuous nucleoli. Chromogranin, synaptophysin, neuron specific enolase (NSE) and

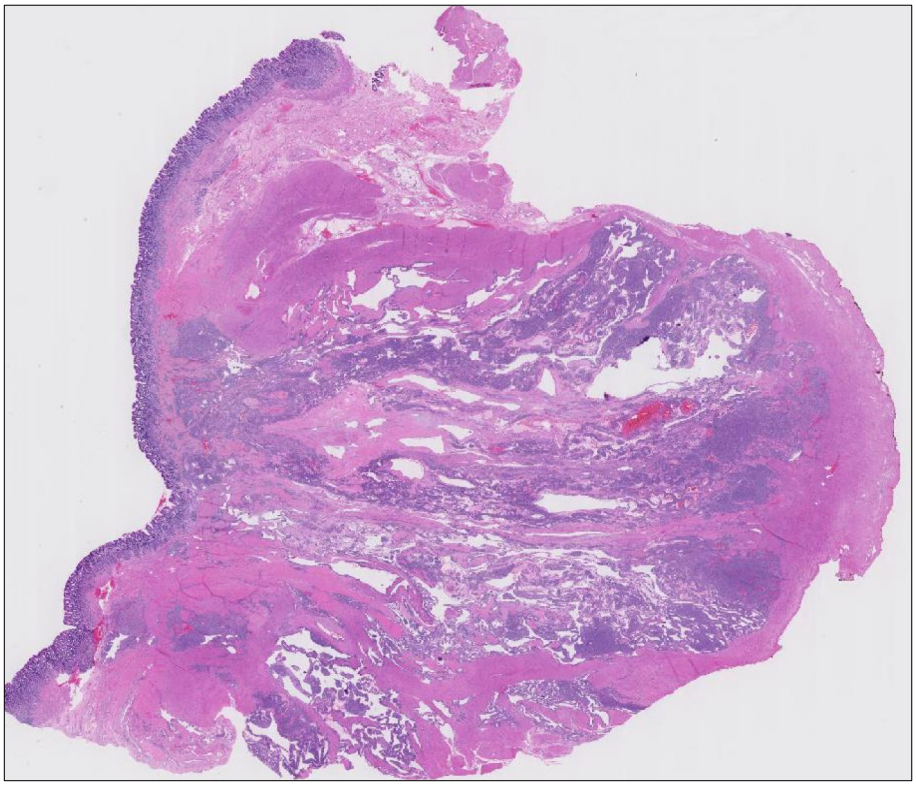

Fig. 4. Whole mount slide of partial gastrectomy specimen showing glomus tumor involving mucosa, submucosa, muscularis propria and extending to serosa.

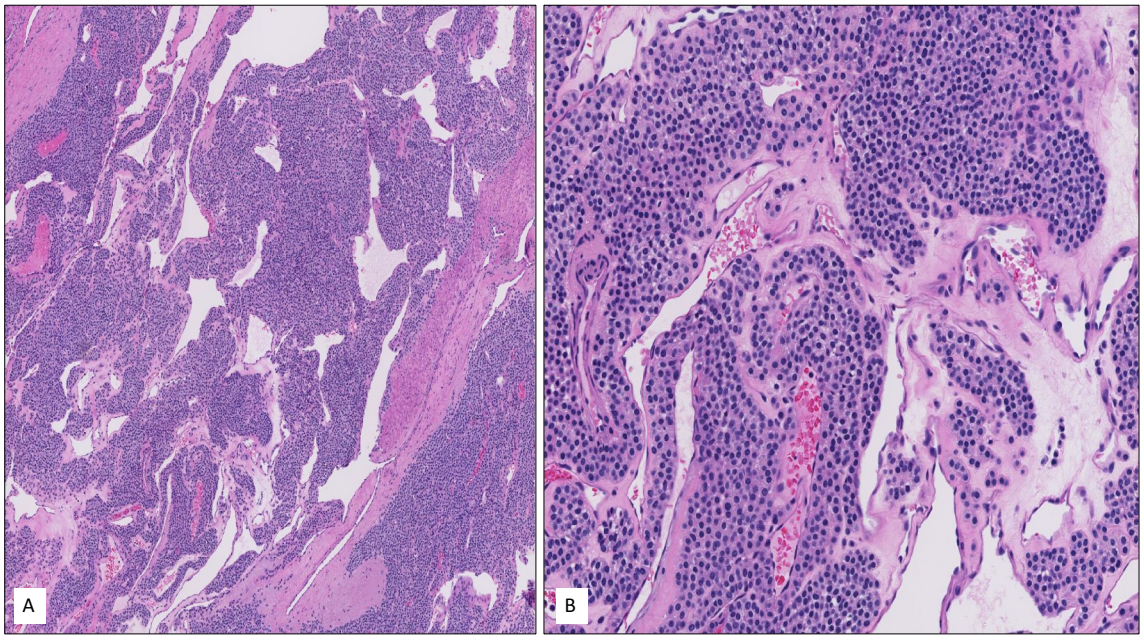

Fig. 5. A, Partial gastrectomy specimen showing tumor composed of sheets or nests of small, round monotonous cells arranged around thick walled vessels (original magnification 100×). B, The tumor cells are small, uniform, round with centrally-located round nuclei and small amount of cytoplasm (original magnification 200×).

cytokeratins are positive [13].

Epithelioid GISTs show smears with loosely cohesive groups and single cells with round to ovoid tumor cells with abundant eosinophilic cytoplasm, hyperchromatic nuclei, irregular nuclear membranes with coarsely granular or clumped chromatin. The tumor cells are CD117, DOG-1 and CD34 positive [14].

Smooth muscle tumors, like epithelioid leiomyoma can be confused with a glomus tumor. Smooth muscle tumors are usually positive for desmin whereas glomus tumors are most often desmin negative. Conventional leiomyoma/leiomyosarcoma of the gastrointestinal tract mostly presents as a spindle cell lesion. Epithelioid leiomyosarcomas usually exhibit nuclear pleomorphism, increased mitotic activity, necrosis and fewer vessels and thus can be distinguished from the glomus tumors [15,16].

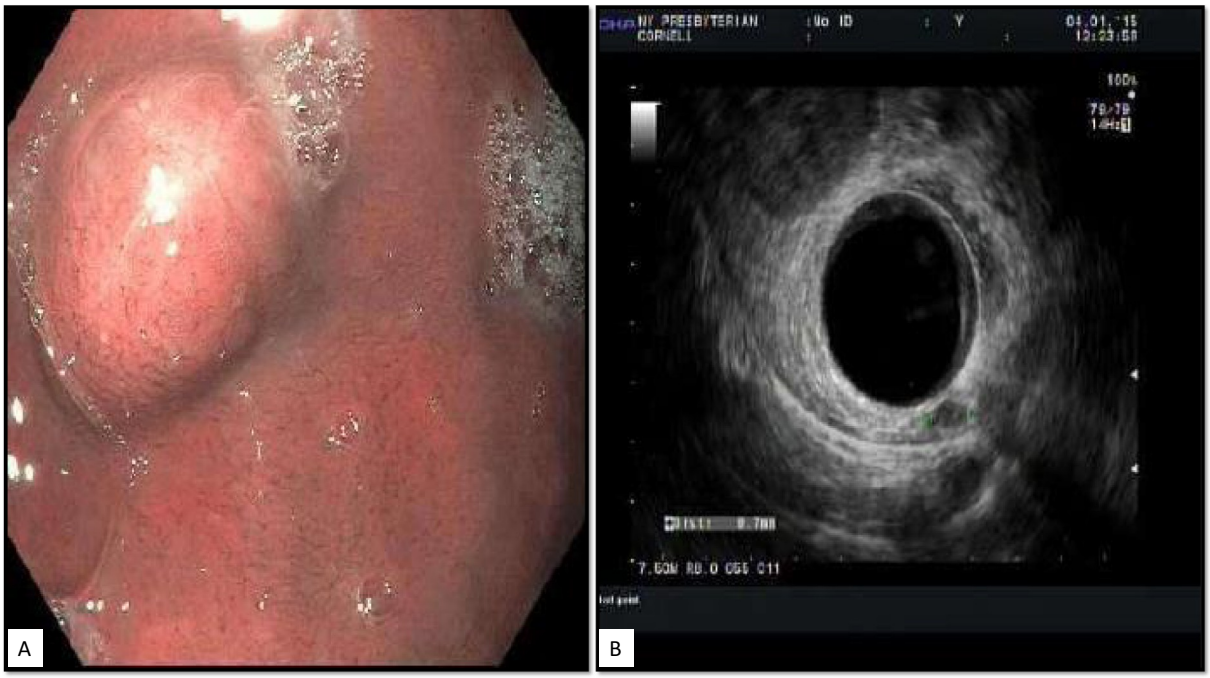

Fig. 6. A, Endoscopy showing a nodule in the fundus of the stomach. B, Endoscopic ultrasound showing a hypoechoic, homogenous lesion in the fundus of the stomach. The lesion appears to originate from the submucosa.

Lymphomas show sheets of monotonous discohesive cells. Cell size varies depending on the lymphoma type with scant cytoplasm and clumped chromatin. The cells stain positive with CD45 and T- or B-cell specific markers [17].

FNAs of paragangliomas are usually highly cellular, consisting of loose clusters and isolated single cells with a large amount of blood in the background due to tumor vascularity. The cells show moderate nuclear pleomorphism and intranuclear cytoplasmic pseudoinclusions. Chromatin is finely textured to coarsely "salt and pepper". Romanowsky stained smears of these tumor cells show fine, red metachromatic granules in the cytoplasm, whereas alcohol fixed Papanicolau stained preparations display dark purple-red granularity [18,19]. Glomus tumors show a greater degree of cell cohesion, yielding larger sheets as compared to the small clusters and nests of a paraganglioma. The nuclear and cytoplasmic appearance of these two tumors is otherwise too similar to distinguish on morphology alone. Immunohistochemistry is diagnostically useful. Both glomus tumor and paraganglioma are cytokeratin negative, requiring additional stains. Neuroendocrine markers stain positively in the epithelioid component of paraganglioma, and S100 stains the spindled sustentacular cells, though these may not be as readily identified in FNA specimens. Glomus tumors are negative for these markers.

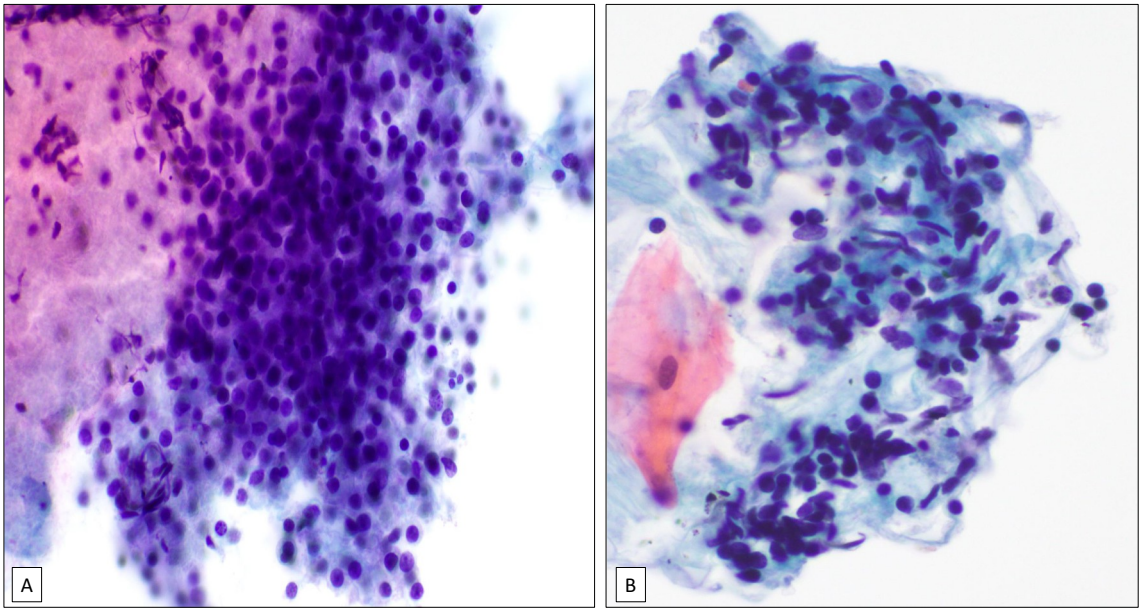

Fig. 7. Fine-needle aspiration of glomus tumor: A, Uniform small round to ovoid cells with scant cytoplasm, indistinct cell borders, round hyperchromatic nuclei, homogenous chromatin and inconspicuous nucleoli. No mitotic activity. No necrosis. Background of blood and fibrin (Diff-Quik, original magnification 200×). B, Uniform small round to ovoid cells with interspersed elongated spindle cells which are possible endothelial cells (Papanicolaou, original magnification 200×).

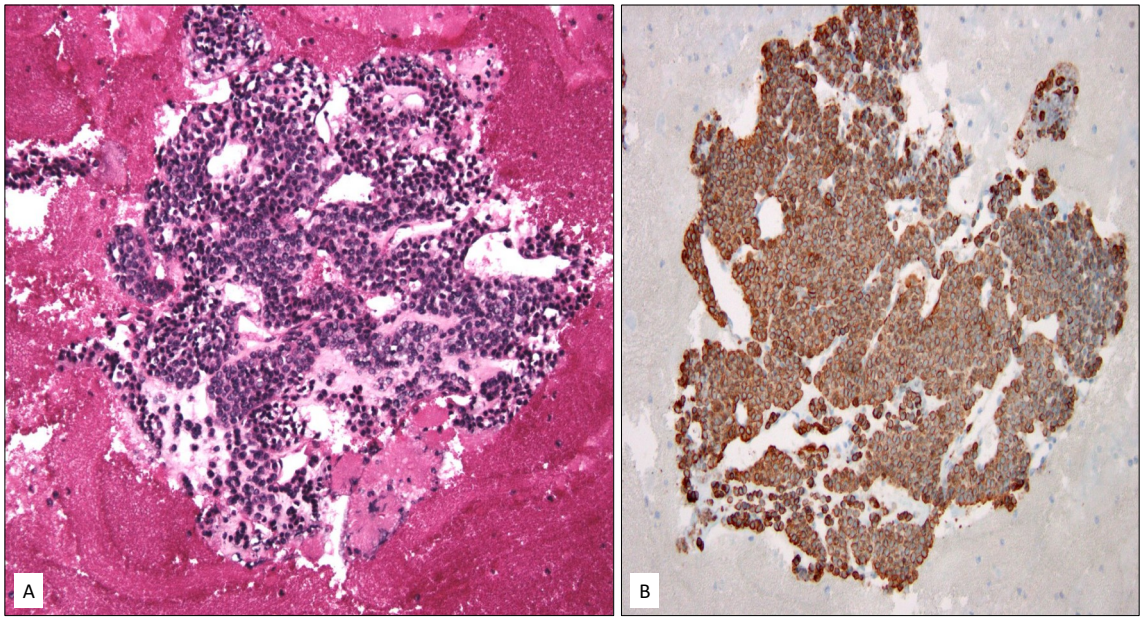

Fig. 8. A, Cell block (CB) showing cells arranged in small lobules and separated by vascular channels and dense, hyalinized stroma. B, Tumor cells show strong and diffuse staining with smooth muscle actin.

In hemangiopericytoma, cellular smears show clusters of oval to spindle-shaped cells with ill-defined, finely granular cytoplasm. The nuclear chromatin is bland, and the number of mitotic figures varies. Further determination of immunophenotype helps to establish the diagnosis. Glomus tumors are positive for SMA, while hemangiopericytomas are SMA negative [20,21].

Glomus tumors should be considered in the differential diagnosis of submucosal masses arising in the stomach. EUS-FNAC is an efficient diagnostic method for submucosal gastric tumors.

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Declaration of Competing Interest

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