Metastatic Malignant Gastric Glomus Tumour: Multidisciplinary Diagnosis & Treatment of a Rare Clinical Entity

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Abstract

Glomus tumours are uncommon neoplasms that are usually benign, solitary and most often found in the skin and soft tissue of distal extremities. Primary gastric glomus tumors are rare, but well described. Fewer than 15 cases of gastric glomus tumour have been reported to have malignant behaviour with distant metastases. Although surgical resection is effective if feasible, recurrence can occur and there is a paucity of evidence on medical treatment options.

Here we present the case of a 69-year-old male with a gastric glomus tumour with metastases to abdominal viscera requiring multidisciplinary care for diagnosis, surgical resection, and multiple lines of systemic/radiation therapy guided by available evidence. Genomic analysis revealed a *NOTCH2* rearrangement, described in only two prior works and highlighting future possibilities for targeted therapy.

Introduction:

A glomus tumour is a rare mesenchymal neoplasm arising from glomus bodies, most often found in the skin and soft tissue of distal extremities.[1] They are characteristically benign and solitary lesions.[1] Gastrointestinal involvement is rare but mainly occurs in the stomach. Gastric glomus tumors account for less than 1% of primary gastric mesenchymal neoplasms.[2] Clinically, gastric glomus tumours can present asymptomatically as an incidental finding (29%), with abdominal pain (46%), overt gastrointestinal bleeding (25%) or other non-specific symptoms.[3] Malignant behaviour with distant metastases from the stomach is a rare occurrence of an already rare entity, with fewer than 15 cases described in the literature.[4–16] Here, we present the case of a 69-year-old male with a gastric glomus tumour with significant metastases to abdominal viscera requiring multidisciplinary care for diagnosis, surgical resection, and systemic treatment.

Case Report:

A 69-year-old white male presented to medical attention with 2–3 weeks of dyspnea and melena and a syncopal event. His medical comorbidities included gastroesophageal reflux disease, dyslipidemia, peripheral neuropathy, hypertension, colovesicular fistula with sigmoid resection related to an abdominal abscess, and sepsis following a root canal. By exam, a firm upper midline mass could be palpated. Initial investigations demonstrated profound anemia (hemoglobin 65 g/L) and a 10.5x4 cm gastric submucosal mass on computerized tomography (CT) imaging. Esophagogastroduodenoscopy (EGD) demonstrated 2 gastric ulcers on the greater curvature with distorted anatomy suggestive of extrinsic compression. A gastrointestinal stromal tumour was suspected, and he underwent exploratory laparotomy which revealed a locally advanced gastric tumour not amenable to immediate resection by the rural general surgery team. He was referred to a tertiary care hospital for consideration of radical resection.

Two weeks later, he underwent endoscopic ultrasound for tissue biopsy by gastroenterology. Endoscopic ultrasound at the area of the gastric mucosal ulceration revealed a hypoechoic mass arising from the 4th

echolayer with internal heterogeneity that was highly vascular. A core biopsy was obtained.

On microscopic examination of the biopsy, neoplastic cells were monotonous with round nuclei and clear cytoplasm (see Fig. 1). A few mitotic figures were seen. Immunohistochemically, the tumour cells stained positive for actin, calponin and synaptophysin in a patchy distribution. The sample was most consistent with a glomus tumour by morphology and immunohistochemistry (see immunohistochemistry results in Table 1).

Table 1
Immunohistochemistry on gastric mass biopsy consistent with a glomus tumour

Test	Result
Smooth muscle markers	Positive
SMA, MSA, calponin, caldesmon	Negative
Desmin	
Neuroendocrine	Positive
Synaptophysin	Negative
Chromogranin, CD56, CDX2, CKAE1/3, CK8/18	
Epithelial markers (CKAE1/3, CK5/6, CK8/18)	Negative
Lymphoid marker (LCA)	Negative
Gastrointestinal stromal tumour markers (CKIT, DOG1)	Negative
Schwanian/Neuroectodermal/melanocytic marker (S100)	Negative
Mesothelial marker (WT1)	Negative
Melanoma markers (MART1, HMB45)	Negative
Vascular markers (CD34, ERG)	Negative*

*Abbreviations: CD, cluster of differentiation; CK, cytokeratin; CKIT, kit oncogene; DOG-1, discovered on GIST-1; ERG, ETS-related gene; HMB-45, human melanoma black 45; LCA, leukocyte common antigen; MART-1, melanoma-associated antigen recognized by T-cells 1; MSA, muscle-specific actin; SMA, smooth muscle actin; WT1, wilms tumor. *Except in a few vessels visible inside the tumour*

Approximately 5 months after his initial presentation, the patient continued to have symptomatic anemia requiring transfusion. Radical surgical resection was performed. Intraoperatively the tumour was localized at the gastric antrum (10.5 x 9.0 x 6.5 cm), invading omentum, pericolic fat, and pancreatic peritoneum with vascular invasion and lymph node involvement. A laparotomy, antrectomy and en-bloc resection of mid transverse colon, right hemicolectomy, Biliroth II gastrojejunostomy, cholecystectomy and biopsy of peripancreatic lesion was performed. Pathologic examination was consistent with malignant glomus tumour (2 of 4 lymph nodes positive for metastasis). The resection specimen had a

high mitotic rate (30 mitoses / 50 high power fields). His clinical symptoms resolved and serial imaging surveillance for recurrence was initiated.

Approximately 1 year after his initial presentation, CT imaging revealed new lesions in the liver (largest 4.2 x 4.1cm) and thickening of the pancreatic tail/body suspicious for local recurrence. A liver biopsy confirmed recurrent malignant glomus tumour.

Gene sequencing and genomic profiling was performed (see Table 2). A 15-gene next-generation sequencing panel (TruSight15, Illumina, San Diego, CA) did not identify any mutations. Subsequent comprehensive genomic profiling (FoundationOne CDx, FoundationOne Medicine, Cambridge, MA) revealed a *NOTCH2* rearrangement at exon 26 (partner gene not reported) and frameshift mutation in *ATRX* (C605fs*16). Tumor mutation burden was low (2/Mb) and there was no evidence of microsatellite instability, both suggesting a low probability of sensitivity to immuno-oncology drugs. Given evidence that ATRX plays a role in homologous recombination repair, it was hypothesized that a tumour lacking ATRX function may respond to a PARP inhibitor and to conventional platinum-based chemotherapy. Although clinical trials of NOTCH inhibitors were enrolling patients at the time, it was not feasible for the patient to travel for eligibility assessment.

Table 2
Summary of tumor genomic profiling and predictive response to therapy

Gene/Biomarker	Mutation/Result	Predictive response to therapy
NOTCH2	*NOTCH2* rearrangement at exon 26, partner gene not reported	Notch inhibitor (clinical trial)
ATRX	C605fs*16	Pt-based conventional chemotherapy, PARP inhibitor (clinical trial)
Tumor mutation burden	Low (2/Mb)	Low sensitivity to immune-oncology drugs
Microsatellite instability	Negative	Low sensitivity to immune-oncology drugs

Guided by medical oncology, palliative chemotherapy was pursued. His treatment course included: (1) doxorubicin, 4 cycles, stopped due to minimal response and cardiotoxicity; (2) ifosfamide, 3 cycles, stopped due to disease progression; (3) docetaxel/gemcitabine, 3 cycles, stopped due to disease progression; (4) dacarbazine, 3 cycles, stopped due to disease progression; (5) pazopanib, 6 weeks, stopped due to disease progression. At that point systemic therapies were stopped, and palliative care involved. He soon died from complications of his metastatic cancer approximately 2 years and 10 months after initial presentation.

Discussion:

Less than 1% of glomus tumours have malignant behaviour.[5] Only 15 prior cases of gastric glomus tumour with metastases to extra-gastric sites have been reported.[5–11, 13–16] Metastases have been reported to the colon, liver, pancreas, kidney, skin, and brain. Metastases have been documented as occurring at the time of initial presentation to 6 years after diagnosis of the primary gastric glomus tumour.[4]

Gastric glomus tumours are a diagnostic challenge, as they are difficult to differentiate from other submucosal tumours on conventional imaging and endoscopy.[17] Biopsy by EUS is an established tool to facilitate histopathological diagnosis of gastric submucosal tumors, including glomus tumours.[18] A potential pitfall in the pathologic diagnosis of this case was the expression of synaptophysin, a marker most commonly associated with neuroendocrine tumors. However, a small proportion of gastric glomus tumors (3 of 21 cases in one study) express synaptophysin.[19] In the present case, the immunoreactivity for SMA, MSA, and calponin with negative staining for all keratins, CD56, chromogranin, and CDX2 ruled out neuroendocrine tumor despite the synaptophysin result.[19]

Surgical resection with curative intent remains the mainstay of treatment, especially for single solitary lesions.[3, 4] However, the management of locally advanced disease and metastatic disease remain less clear. This includes ambiguity in choosing treatment agents, timing of initiation, and duration of therapy. Negahi and colleague advocate for tumour debulking and systemic chemotherapy.[14] They administered doxorubicin, bevacizumab and paclitaxel – chosen due to the vascular nature of the neoplasm.[14] Radiotherapy with concomitant cisplatin has also been tried.[20] In the present case, guided by the limited evidence that exists, five lines of palliative chemotherapy were tried including: doxorubicin, ifosfamide, docetaxel/gemcitabine, dacarbazine, and pazopanib. All were unsuccessful in slowing disease progression.

Targeted treatment based on identified mutations remains an evolving field in oncology. This study is only the third published work to describe abnormalities in the NOTCH family of genes (*NOTCH1-4*) in glomus tumours. In the largest of those studies, Agaram and colleagues uncovered NOTCH-gene fusions in 50 of 93 cases (54%), including all but one malignant glomus tumour.[21] Interestingly, all six glomus tumours with gastrointestinal involvement in that study were malignant which does not reflect previous work suggesting gastric glomus tumours are mostly benign.[6, 21] The NOTCH signaling pathway has been implicated in a variety of other cancer types where it might have significant treatment implications. NOTCH inhibitors are under investigation in clinical trials, but unfortunately none were approved or accessible to the patient in this case.[22]

In this case, interdisciplinary collaboration and close follow-up was essential in navigating challenges in diagnosing and treating this rare clinical entity. Gastroenterology was involved soon after presentation for assessment and biopsy by EUS. Radical resection by general surgery was initially successful, but metastatic disease recurred and was detected on surveillance imaging. No longer amenable to surgery, medical oncology pursued multiple lines of palliative chemotherapy guided by the limited evidence that exists. Eventually, palliative care helped transition to symptom-based management.

Overall, this case highlights the rare but important malignant behaviour of glomus tumours and need for long-term follow-up by a multidisciplinary team. Hopefully ongoing research will lead to targeted treatment options using gene sequencing, including those directed at the NOTCH signalling pathway.

DECLARATIONS:

Declarations

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Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Ethics approval

Not required, institutional protocols were followed.

Consent to participate

Informed consent was obtained and documented.

Consent for publication

The participant has consented to the submission of the case report to the journal.

Authors' contributions

TA, MC, KK, CC and GW were involved in patient care and conceived of the case report. GW provided expertise on endoscopic diagnostics. TA and MC provided expertise on pathologic analysis. CC provided expertise on surgical management. KK provided expertise on systemic treatment. JF assembled the case, conducted the literature review, and was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

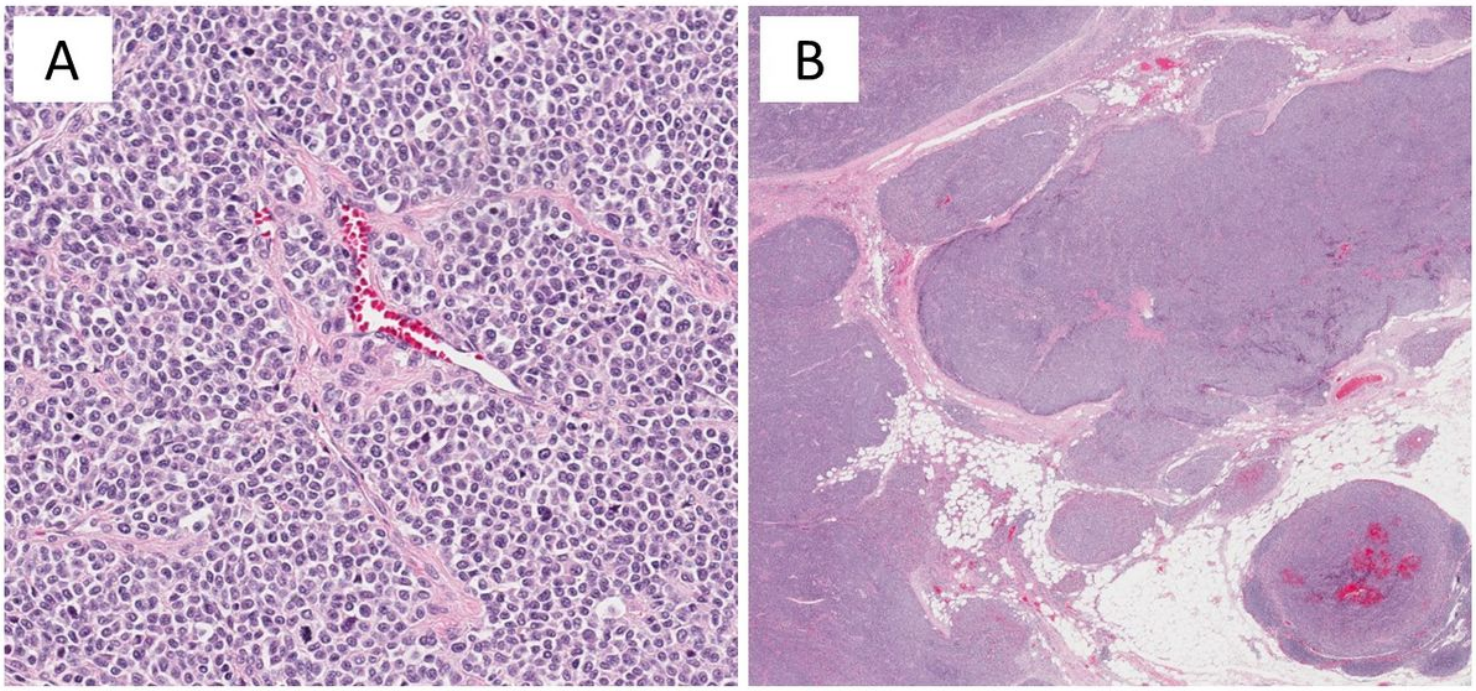

Figure 1

Glomus Tumour. (A) Lobulated tumor composed of round cells with uniform nuclei and limited amounts of pale cytoplasm. (B) Sharply defined borders with lymph node metastasis indicative of malignant behaviour.