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Malignant Glomus Tumors of the Stomach – A Report of 2 Cases with Multiple Metastases –

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Glomus tumors are mesenchymal neoplasms usually developing in the dermis or subcutis of the extremities. The majority of glomus tumors are entirely benign, and malignant glomus tumors are very rare, especially those arising in the visceral organs. Here, we are presenting two cases of malignant glomus tumor, initially diagnosed in the stomach by endoscopic biopsy. Case 1 was found in the stomach, right kidney, brain and humerus of a 65-year-old woman, and Case 2 in the stomach and liver of a 63-year-old man. Histologically, the tumor was composed of solid sheets and nests of round and short-spindle shaped tumor cells with vesicular nucleus and prominent nucleolus. The tumor cells were closely admixed with blood vessels of varying size. Immunohistochemically, the tumor cells showed diffuse and strong positive staining for smooth muscle actin and paranuclear, dot-like staining for synaptophysin, but negative for desmin, c-kit, CD34 and S-100 protein. These two are rare cases of a malignant glomus tumor with widespread metastases.

Key Words : Glomus tumor; Stomach; Kidney; Brain; Neoplasm metastasis

Glomus tumor arises from a modified smooth muscle cell located in the wall of specialized arteriovenous anastomosis and involved in temperature regulation. Most glomus tumors are benign neoplasms that occur in the dermis or subcutis of the extremities.[1] However, malignant glomus tumors do occur, but are rare,[2-6] and malignant glomus tumors involving visceral organs are much rarer.[6,7] Here, we are presenting two cases of malignant glomus tumor arising in the stomach with multiple metastases.

CASE REPORTS

Case 1

A 65-year-old woman was presented to our hospital with a 3-week history of epigastric pain and a loss of appetite. Upon laboratory examination, her hemoglobin level was 9.3 g/dL with a hematocrit of 28.6%. The gastrofiberscopy revealed a well-circumscribed elevated lesion located in the fundus (Fig. 1A). The mucosal surface of the lesion was focally eroded. An abdominal CT scan demonstrated a 3 cm-sized oval mass in the fundus. It also revealed a 4.5 cm-sized renal mass with thrombi of the renal vein and inferior vena cava (Fig. 1B, C). In addition, a 4 cm-sized brain mass was identified in the right inferior temporal area by MRI (Fig. 1D). After endoscopic biopsy of the gastric lesion, a wedge resection of the gastric mass and a right radical nephrectomy were simultaneously performed. The submucosal gastric tumor was white, soft to rubbery and extended to the perigastric adipose tissue (Fig. 1E). The right kidney showed a 4.5 cm-sized, gray-white, soft tumor in the lower pole with a renal vein thrombus (Fig. 1F). One month later, she had an additional operation for the brain tumor. The removed brain tumor was 3 cm in size and multinodular with hemorrhagic areas.

The three tumors from the stomach, kidney and brain appeared nearly identical in the histological and immunohistochemical

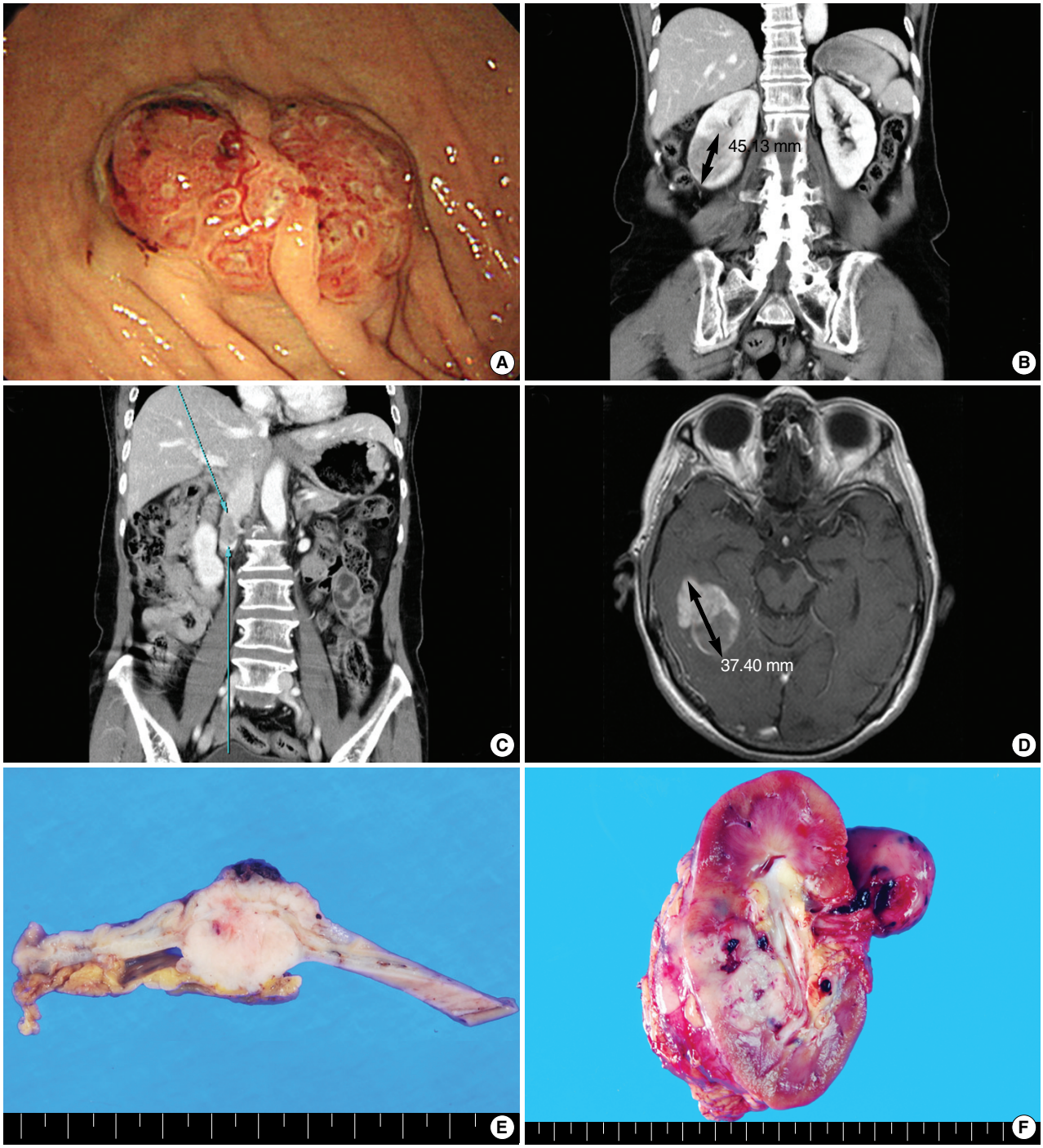

Fig. 1. Case 1: Gastrofiberscopy reveals a 3 cm-sized, well-circumscribed elevated lesion in the fundus (A). Abdominal CT scan demonstrates a 4.5 cm-sized mass located in the lower pole of the right kidney (B) with thrombi of renal vein and inferior vena cava (C), and MRI shows a 4 cm-sized brain mass in the right inferior temporal area (D). Grossly, the gastric tumor is a relatively well-circumscribed mass extending mucosa to perigastric adipose tissue (E), and the renal tumor is found in lower pole with renal vein thrombus (F).

(IHC) staining patterns. Histologically, the tumors had a multinodular growth pattern with a perivascular arrangement (Fig. 2A). The tumor cells were round or polygonal, and had oval or slightly elongated central nuclei, moderate amount of pale cytoplasm and distinctive cell borders (Fig. 2B). They had diffuse cytologic atypia with anisonucleosis, nuclear membrane irregularities, prominent nucleoli and multinucleated giant cell formation (Fig. 2C). Mitotic figures were two per 50 high power fields, and atypical

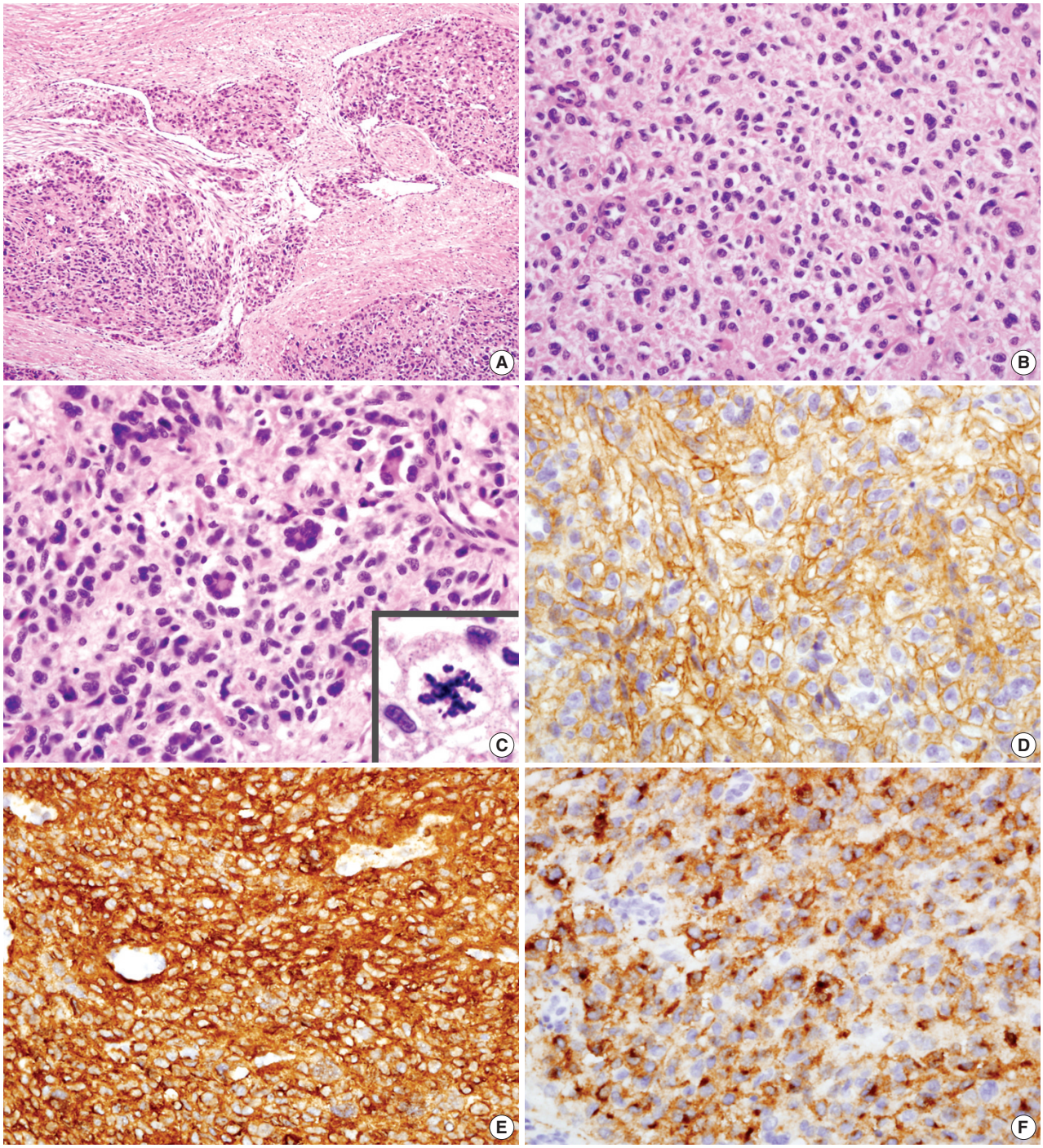

Fig. 2. Case 1: Histologically, the tumor reveals a multinodular growth pattern with perivascular arrangement of tumor cells (A). The tumor cells are round to polygonal with distinctive cell borders (B). The cells show cellular atypia (C) and atypical mitoses (C, inlet). The immunohistochemical staining, the tumor shows pericellular net-like staining for type IV collagen (D), strong positive reaction for SMA (E) and paranuclear dot-like staining for synaptophysin (F).

mitoses were also observed (Fig. 2C). Areas of hemorrhage were present. The staining for type IV collagen showed pericellular net-like positive fibers (Fig. 2D), and the staining for CD34 revealed abundant vascular spaces wrapped in the nests of tumor cells. Also, the tumor cells were diffusely and strongly positive for smooth muscle actin (SMA) (Fig. 2E). Interestingly, the tumor cells showed paranuclear dot-like staining for synaptophysin (Fig. 2F). However, the tumor was negative for c-kit, S-100 protein,

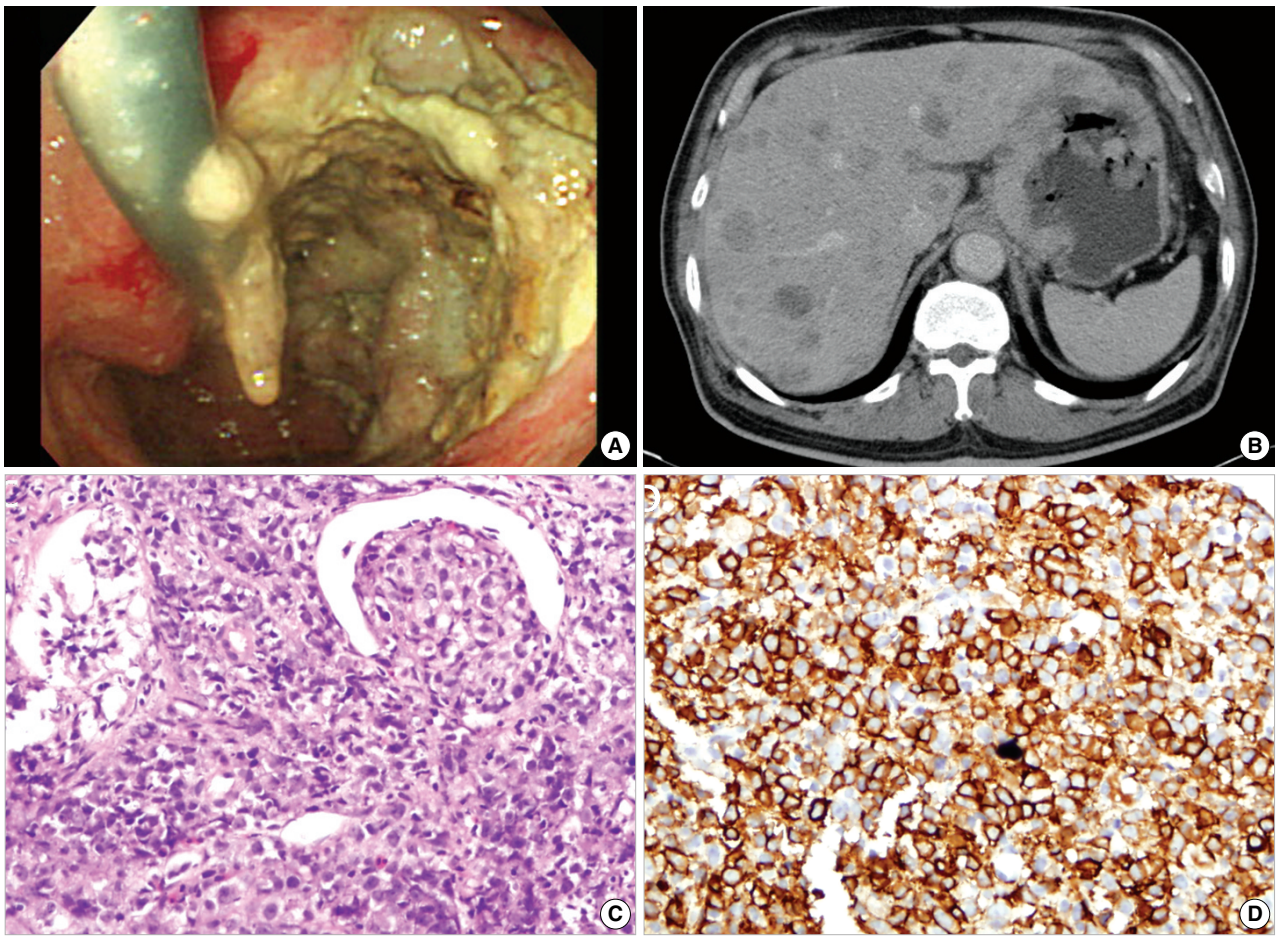

Fig. 3. Case 2: Gastrofiberoscopy reveals a large ulceroinfiltrative mass extending from the lesser curvature of the body to the cardia of the stomach (A). A abdominal CT scan shows a thickened wall of the gastric fundus and body, multiple hypodense lesions in the liver, and paraaortic lymphadenopathy (B). Histologically, the endoscopic biopsy shows polygonal epithelioid cells, which have round nucleus with prominent nucleoli and abundant cytoplasm, and protrude into the vascular spaces (C). Immunohistochemically, the tumor cells are positive for SMA (D).

desmin, and cytokeratin. In the brain, the tumor cells were negative for glial fibrillary acid protein. Based on histological and immunohistochemical staining results, the tumor was diagnosed as a malignant glomus tumor of the stomach with metastases in the kidney and brain.

Four months after brain surgery, MRI study revealed metastatic lesion in the left humeral head and the right occipital lobe of the brain. The patient received radiation therapy, but died of respiratory insufficiency eight months after the initial manifestation of the tumor. An autopsy was not performed.

Case 2

A 63-year-old man was presented with a five month history of epigastric pain. Upon physical examination, his face was pale and he had hepatosplenomegaly. Laboratory analysis showed a hemoglobin level of 10.2 g/dL and normal liver function. Gastrofiberscopy revealed a large ulceroinfiltrative mass extending from the lesser curvature of the body to the cardia of the stomach (Fig. 3A). A CT scan of the abdomen showed multiple hypodense lesions within the liver parenchyma accompanied by extensive paraaortic lymphadenopathy (Fig. 3B). The gastric mass was approximately 9 cm in the maximal diameter.

Histopathologic examination of the endoscopic biopsy specimens demonstrated an infiltration of polygonal epithelioid cells in the gastric mucosa. The tumor cells had round nuclei with prominent nucleoli and abundant cytoplasm (Fig. 3C). Vascular invasion of tumor cells was also present (Fig. 3C). IHC profiles were the same as of Case 1 (Fig. 3D).

The patient was treated by combination chemotherapy comprised of ifosfamide, adriamycin and dacarbazine because of the distant metastasis to the liver. However, the patient died after

completion of the first cycle of chemotherapy due to extensive bleeding from the main tumor mass, which was related to angiographic embolization therapy.

DISCUSSION

The glomus tumor is a distinctive neoplasm that resembles the normal glomus body, which is a specialized form of arteriovenous anastomosis and regulates heat.[1] The glomus body is mostly well-developed in the subungual region, where glomus tumor most frequently occurs.[1] The glomus body is normally present in the submucous layer of the stomach chiefly along the lesser curvature of the pylorus and on the posterior wall of the cardia.[8,9] Therefore, a glomus tumor of the stomach may occur anywhere in the stomach, although the incidence is much lower than in the digits.

Glomus tumors are usually benign and solitary, but a few malignant cases have been reported. Gould *et al*.[2] presented four cases of a malignant glomus tumor, involving deep dermis or subcutis, and divided into two categories: glomangiosarcoma arising in a benign glomus tumor and *de novo* glomangiosarcoma. Watanabe *et al*.[4] reported the glomangiosarcoma of the hip, which showed multiple lung and skin metastases two years after the primary tumor had been excised.

Gastric malignant glomus tumors are much rarer than those occurring in dermis or subcutis. In the series of atypical and malignant glomus tumors reported by Folpe *et al.*,[10] the only one gastric glomus tumor metastasized to the liver, which lead to the patient's death in 3 years. Among 32 gastrointestinal glomus tumors studied by Miettinen *et al.*,[11] all but one were benign in a long-term follow-up. The one non-benign patient developed liver metastasis and died of metastatic diseases 50 months after diagnosis. Our two patients had metastatic lesions and died 8 and 2 months after the first histological diagnosis of the tumor, respectively. Glomus tumors involving kidney parenchyma are extremely rare; only four cases have been reported in the English literature so far, and all these tumors were benign without local recurrence or distant metastases after surgical resection.[12,13] The glomus tumors in the brain represent paraganglioma occurring in the skull base, and no primary malignant glomus tumor has been reported in the brain.[14]

Aggressive clinical behavior was expected to some extent in our patients, because both patients already showed multiple metastases at the time of initial presentation to the hospital. The criteria for malignant glomus tumors have been controversial. Recently, Folpe *et al*.[10] defined a new classification scheme and criteria for malignancy in glomus tumors. The features favoring malignant glomus tumors included deep location, a size greater than 2 cm, atypical mitotic figures, moderate to high nuclear grade and $\geq$5 mitotic figures/50 HPFs. Our patients had a large tumor size (more than 3 cm), visceral locations (stomach, kidney, and liver), and showed a high nuclear grade and atypical mitotic figures. According to the above criteria, our cases were considered as malignant glomus tumors, and were histologically or clinically confirmed by the presence of metastases. Additionally, both cases were considered to be *de novo* glomangiosarcoma defined by Gould *et al*.,[2] as there was no area representing a typical glomus tumor.

Because of the characteristic histology, glomus tumors usually do not present a diagnostic difficulty, especially when it presents with the classic symptoms, e.g., a small, painful, cutaneous nodule of the extremity.[15] However, the rarity of glomus tumors arising in the stomach, concurrent involvement of multiple organs and the limitation on small endoscopic biopsies caused some confusion with other primary or metastatic gastric lesions. With respect to the differential diagnosis of the present cases, gastrointestinal stromal tumor (GIST) was initially considered because endoscopic biopsy showed that the gastric mucosa and submucosa were infiltrated with nests and sheets of round or epithelioid cells. However, immunohistochemical stainings showed that the tumor cells were positive for SMA, but negative for c-kit and CD34, which excluded the possibility of GIST.

Interestingly, Case 1 showed focal paranuclear dot-like positivity for synaptophysin, which led to some confusion with neuroendocrine tumors. Miettinen *et al*.[11] reported 32 cases of gastrointestinal glomus tumors, three of which demonstrated a focal positivity for synaptophysin with a similar staining pattern as our case, while 30 cases of peripheral glomus tumors did not. Jundi *et al*.[16] also reported a case of duodenal glomus tumor, in which the neoplastic cells stained focally for synaptophysin.

Based on that malignant glomus tumors have not been reported in either the kidney and brain, and the paranuclear dot-like immunohistochemical staining pattern for synaptophysin has not been observed in glomus tumors of other organs except the gastrointestinal tract, the primary site of our cases was considered to be the stomach. Even though the majority of gastric glomus tumors are considered to be benign, the possibility of malignant glomus tumors should not be overlooked. Workup on metastatic disease needs to be done because gastric malignant glomus tumor can present multiple metastases at the time of diagnosis.

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