Malignant stromal tumor of the stomach with giant cystic liver metastases prior to treatment with imatinib mesylate

Maligni stromalni tumor želuca sa ogromnim cističnim metastazama u jetri pre lečenja imatinib mesilatom

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Abstract

Introduction. Gastrointestinal stromal tumors (GISTs) are rare and account for 0.1%–3% of all gastrointestinal neoplasms. GISTs are most commonly located in the stomach (60%) and 20%–25% are malignant, with metastases involving the peritoneum or the liver. Cystic liver metastases are extremely rare. Only two previous cases of patients with cystic liver metastases, prior to treatment with imatinib mesylate, have been described so far. Case report. We reported a 52-year-old woman presented with a history of abdominal fullness and discomfort. Clinical examination revealed two palpable masses, first in the right upper abdomen and second left to the umbilicus. Examinations revealed 4 cystic metastases in the liver, 3 in the right lobe (including a huge one measuring 20.5 × 16 cm), and 1 in the left lobe, together with a primary tumor on the greater curvature of the stomach. Gastric tumor was removed with a Billroth II gastrectomy. Partial excision of the largest liver metastasis was performed for histopathology. Immunohistochemistry confirmed the diagnosis of a GIST in both tissue samples. After an uneventful recovery the patient was commenced on imatinib mesylate therapy. The patient remained symptom-free at 24 months follow-up. Conclusion. This was the third reported case of gastric GIST with giant cystic liver metastases prior to treatment with imatinib mesylate. Although extremely rare, GISTs may present with cystic liver metastases prior to treatment with imatinib mesylate, and should be considered in the differential diagnoses of patients with liver cysts of uncertain aetiology.

Key words: gastrointestinal stromal tumors; stomach; diagnosis, differential; liver; neoplasm metastasis.

Apstrakt

Uvod. Gastrointestinalni stromalni tumori (GIST) su retki tumori koji čine ukupno 0,1%–3% svih gastrointestinálnih neoplasmi. Najčešća lokalizacija GIST je u želucu (60%). Oko 20–25% ovih tumora je maligno, dok su metastaze najčešće lokalizovane po peritoneumu ili u jetri. Pojava cističnih metastaza GIST u jetri je veoma retka i do sada su u literaturi opisana samo dva bolesnika sa ogromnim cističnim metastazama GIST u jetri pre lečenja imatinib mesilatom. Prikaz bolesnika. Prikazana je bolesnica stara 52 godine, koja se javila lekaru zbog osećaja napetosti u trbuhu. Kliničkim pregledom nađena su dva palpabilna tumeća ispod desnog rebarnog luka i paraumbilikalno sa leve strane. Kompletnom radiološkom pretragom utvrđeno je postojanje stromalnog tumora velike krivine želuca i četiri krupne cistične promene u jetri, tri u desnom i jedna u levom lobusu jetre. Najveća od ovih promena bila je dimenzija 20,5 × 16 cm. Bolesnica je operisana kada je urađena resekcija želuca tipa Billroth II i parcialna ekscizija najveće promene iz desnog lobusa jetre. Patohistološka i imunohistohemijska analiza potvrdile su dijagnozu GIST u želuču i jetri. Nakon uspešnog postoperativnog oporavka ordinirana je terapija imatinib mesilatom na koju je bolesnica dobro reagovala. Dve godine nakon operacije bolesnica je dobro i bez znakova recidiva bolesti. Zaključak. Ovo je tek treći opisani bolesnik sa gastričnim GIST, sa ogromnim cističnim metastazama u jetri pre lečenja imatinib mesilatom. Mađar veoma retko, GIST se mogu prezentovati sa cističnim metastazama u jetri pre lečenja imatinib mesilatom i treba da budu razmotreni u diferencijalnoj dijagnozi bolesnika sa osim tumača u jetri neopozate etiologije.

Ključne reči: gastrointestinalni stromalni tumori; želudac; dijagnoza, diferencijalna; jetra; neoplazme, metastaze.
Introduction

Gastrointestinal stromal tumors (GISTs) are rare and account for 0.1%–3% of all gastrointestinal tumors, and 5.7% of gastrointestinal sarcomas. They are mesenchymal in origin, defined as c-kit (CD 117) positive tumors, and have a characteristic set of histological features including spindle or epitheloid cells.

Around 20%–25% of gastric GISTs are malignant and frequently metastasize to the liver and peritoneum. Liver metastases are typically solid, and cystic lesions are extremely rare in these patients at presentation. Cystic liver metastases appear in colorectal, ovarian and pancreatic mucinous adenocarcinomas, usually as a result of an accumulation of mucin/serous fluid produced by the tumor itself or from cystic degeneration consequent to ischemic necrosis or infarction of the tumor mass. Solid GIST liver metastases can also develop cystic changes following targeted therapy with imatinib mesylate, which inhibits c-kit and causes tumor shrinkage.

Only two patients with cystic GIST liver metastases prior to treatment with imatinib mesylate have been described so far. This is the third patient with gastric GIST and huge cystic liver metastases.

Case report

A 52-year-old woman with no significant past medical history presented to our unit with a 2-month history of fullness and discomfort in the right upper abdomen. On examination the patient had a large spherical, painless, fluctuant mass palpable in the right upper abdomen, extending up behind the right costal margin. Another, smaller, hard, painless and mobile mass was also found to the left of the umbilicus. There was no splenomegaly or ascites, and there were no dilated veins on the abdominal wall. The patient had an elevated white blood cells (WBC) (18.9 x 10^9/L), mild anemia and mild thrombocytosis (516 x 10^9/L). Blood proteins were elevated (93 g/L) as were fibrinogen (9.0 g/L), alkaline phosphatase (199 u/L) and y-GT (120 u/l). All other laboratory data including tumor markers (ALP, CA 19-9, CA 72-4, CEA) were within normal limits.

Ultrasonography showed that much of the right lobe of the liver was taken up by 3 cystic lesions. The largest of these measured 20.5 cm x 16 cm and contained several tissue layers (Figure 1); two smaller cysts measuring 5.7 cm x 6.3 cm and 6.7 cm x 8 cm were located in segments VII and VIII of the liver. A fourth cyst measuring 3 cm in diameter cm was present in the left liver lobe. A gastric tumor measuring 9.5 x 7.5 cm x 6.5 cm was present in the left mesogastrum. Computed tomography scan confirmed the ultrasonography findings (Figures 2, 3 and 4).

We performed the operation through right subcostal laparotomy. A firm, mobile, rough tumor was found attached to the greater curvature of the antral part of the stomach. The tumor had not created any defect of the gastric mucosa and was removed by way of a Billroth II gastrectomy. Frozen section histology of the tumor was suggestive of GIST. The...
The well of the cyst wall was excised and sent for histology. The antral gastric tumor had predominantly extramural growth, and measured up to 95 mm in diameter. Macroscopically, it appeared pseudocystic as most of the central areas were necrotic and hemorrhagic. This soft, fragile internal tissue was surrounded by a more firm, partly sclerotic and calcified pseudocapsule. Histology revealed mesenchymal neoplastic proliferation which was mostly hypercellular and epithelioid, but with many additional microcystic and pseudohemangiomatous areas (Figure 5a). The periphery contained the areas of mixed spindle and epithelioid cells with a vacuolar and sclerosing appearance, suggestive of gastric GIST. The liver cyst specimen had a very thin rim of neoplastic tissue at its periphery, which was sharply demarcated from hepatic parenchyma (Figure 5b). Its histology was identical to that of the gastric tumor confirming that it was a liver metastasis.

Immunohistochemistry showed strong PDGFRA immunostaining of the epithelioid areas but only focal and weak "dot-like" cytoplasmic CD117 immunostaining in the mixed spindle and epithelioid areas, in both the primary and secondary lesions (Figure 5c and d). Vimentin immunostaining was also positive, however CD34, desmin, αSMA, S-100 protein, WT-1, calretinin and markers for other epithelial, neuroendocrine and other non-mesenchymal markers were all negative.

The patient’s postoperative recovery was uneventful. Following histological confirmation of a malignant GIST of the stomach with cystic liver metastases the patient was commenced on imatinib mesylate treatment, and remained clinically well at 24 months.

Discussion

GISTs encompass a wide spectrum of tumors with varying locations and biological potentials. Previously classified as leiomyomas, leiomyosarcomas, neurofibromas and...
schwanomas, GISTS are now known to be quite different both histologically and immunohistochemically. They predominantly affect middle-aged and older patients (median age of 55–60 years), and while they can occur in different parts of gastrointestinal tract, they most commonly occur in the stomach (60% of cases) and small intestine (35%); they can also occur in the rectum and other parts of gastrointestinal tract, and in those tissues in close proximity to them. GISTS are believed to originate from the intestinal cells of Cajal or related stem cells, and can be divided histologically into 4 spindle cell (70%) and 4 epitheloid variant (30%) subgroups.

A significant proportion of GISTS are malignant, however differences exist according to primary tumor location; 20%–25% of gastric and 40%–50% of small intestine GISTS are malignant. Metastases frequently occur in the peritoneum and liver, and only rarely involve the bones, soft tissues and skin; lymph node and lung metastases are extremely rare. Metastases can develop up to 10–15 years after primary surgery, and thus a life-long clinical follow-up is mandatory.

GIST liver metastases are typically solid, and cystic lesions are extremely rare in these patients at presentation. In 2003 Zonios et al. reported a 73-year-old woman with gastric GIST who presented with low grade fever, weight loss, left-quadrant pain and multiple cyst-like hepatic metastases, while in 2009 Jain et al. presented a 50-year-old man with gastric GIST who had a 12 cm × 9 cm cystic liver metastasis. Both these patients had cystic GIST liver metastases prior to any treatment.

Solid GIST liver metastases are known to develop cystic changes as a result of targeted therapy with imatinib mesylate, which inhibits c-kit and causes tumor shrinkage. Indeed these morphological changes are now regarded as a positive prognostic sign, as the overall survival is significantly better in those patients developing these cystic changes following imatinib mesylate treatment.

This is only the third documented case of gastric GIST with cystic metastases present prior to any treatment. The presented patient had multiple cystic liver metastases and the largest such reported lesion.

**Conclusion**

Although extremely rare, GISTS may present with cystic liver metastases prior to treatment with imatinib mesylate, and should be considered in the differential diagnoses of patients with liver cysts of uncertain etiology.

**REFERENCES**


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