Liver metastases as a first manifestation of gastrointestinal stromal tumour (GIST)

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Abstract
Gastrointestinal stromal tumours (GIST) are the most common mesenchymal tumour of the gastrointestinal tract. Liver metastasis and diffuse intraabdominal spread are typical manifestation of advanced malignancy. A 59-year-old female patient was admitted to the Internal Department with synchronous liver metastases. Clinical examination revealed a palpable abdominal mass in the left epigastrum. Gastroscopy examination revealed an advanced neoplasmatical tumour of the stomach. The histological findings showed GIST with strong CD117 and CD34 reactivity. GIST was characterised by oncogenic mutations of the KIT receptor tyrosine kinase. Imatinib (tyrosine kinase inhibitor) was used in the treatment of metastatic GIST.

Key words
GIST, liver metastases, stomach tumour

INTRODUCTION

GIST is the most common mesenchymal tumour of the gastrointestinal tract. 10-30% of GISTs are asymptomatic and found incidentally at radiographic imaging or endoscopy. Liver metastases of GIST are more frequently detected synchronously with the primary tumour than metachronously [1]. Liver metastasis is usually thought to be a symptom of end-stage disease. The exception seems to be colonorectal cancer, a disease where oligometastases occurs early, and is usually the only site of metastasis. It should be noted that at the time of colonorectal cancers (CRC) diagnosis, 15% of patients have liver metastases, and in 75% of cases the metastases are confined to the liver. Because it is well known that the liver is a common site to which cancer spreads, physicians are extremely vigilant for liver involvement during follow-up care of patients with certain primary cancers.

CASE STUDY

A 59-years-old female patient was seen at the Internal Department due to liver metastasis diagnosed accidentally in ultrasonography of abdominal cavity. Nine years before this diagnosis, the patient had been treated for local bifrontalis plasmocytoma. The treatment comprised craniectomy and chemotherapy. The patient regularly saw a physician because of hypertension and diabetes mellitus. The patient had been well until approximately 1 month earlier, when she had a check-up, including ultrasonography of abdominal cavity. A few weeks earlier, the patient had noted progressive weakness, unusual tiredness, chronic dry cough and frequent hiccups. Two weeks before the diagnosis, the patient saw a gastroenterologist. She reported an unexplained weight loss (about 27 kg) in the last year, no diarrhoea, vomiting, nausea, disturbance in swallowing, dyspepsia, indigestion, or lack of appetite. The patient did not notice any blood in her stools. Colonoscopic examination was performed and did not reveal any pathology.

On examination, blood pressure was 110/60 mmHg, heart rate 78 beats per minute, respiratory rate 18 breaths per minute, temperature 36.6°C, weight 62 kg, and height 170 cm. The skin and mucous membranes were pale, without any pathological efflorescences. The oropharynx was normal. In examination of the head, asymmetry of the cranium was found, caused by craniectomy bifrontalis performed 9 years earlier. The abdomen was soft. In deep palpation in the left epigastrum a pathological tumour was detected. The tumour was about 5 cm, irregular, and painful when pressed. Liver in examination was enlarged; the spleen was normal size.

In laboratory tests, deeper anaemia with haemoglobin about 7.5 g% and raised level of CRP (150 mg/l) without leucocytosis were discovered. The level of CEA, CA 19-9, AFP were normal. The level of Chromogranin A was 63.97 U/l (reference value 2-18 U/l). Results of other laboratory tests: coagulation, kidney and liver function, were normal. Stool specimen was guaiac negative.

Computed tomography (CT) of the abdomen and pelvis showed a stomach mass about 99 mm by 88 mm with a few lymph nodes of sizes about 12 × 11 mm, 18 × 11 mm, 12 × 5 mm (Fig. 1-3). Chest radiography was normal. Gastroscopy examination revealed an advanced neoplasmatical tumour of the stomach, covering especially the front wall. Pathological examination of biopsy specimens of the stomach mass showed neoplasma fusocellulare probabiliter GIST. Next, immunohistochemical reactions were performed for precision diagnosis. Finally, the patient was diagnosed with GIST; CD 117 +, DOG +, IM -7/30 HPF, CD 34+ and was
qualified for Glivec therapy. The patient had transfusion of 2 units of red blood cells. She felt well. The patient took antidiabetic and antihypertensive medications, had no allergies to medications, and had quit smoking 8 years earlier.

**DISCUSSION**

Gastrointestinal stromal tumours are defined as pleomorphic mesenchymal tumours of the gastrointestinal tract that express the KIT protein, and often CD34 on immunohistochemistry. They are a subset of mesenchymal tumours and represent the most common mesenchymal neoplasms of the gastrointestinal tract. Diagnoses of GIST dramatically increased after 1998, most probably due to greater awareness and improved histological detection, but the increasing incidence also cannot be excluded. GISTs are KIT-expressing (tyrosine kinase receptor – CD 117) and KIT-signalling driven mesenchymal tumours. Less than 1% of GIST tumours have an activating mutation in either KIT or PDGFRα. Initially, the origin of GISTs was attributed to Cajal cells; nowadays, it is considered to originate from multipotential mesenchymal stem cells [2]. The incidence of GISTs is estimated to be 10–20 per million people per year. However, its actual incidence is difficult to assess because of incomplete classification and definition. GIST cases have been reported in all ages, including children; however, over 90% of tumours occur in adults aged over 40 (median age of patients – 63). In the presented case, the patient was 59 years old. It has been proved that there is a slight predominance of males. On the other hand, there is no association between the incidence and geographic location, ethnicity, race, or occupation. The most common location of a GIST seems to be the stomach (50–60%) and the small intestine (30–40%). It may also be found in the colon and rectum (5–10%), and in oesophagus (5%). There have also been reports of some rare locations, e.g. mesentery, rectoperitoneum, omentum, gallbladder, pancreas, liver, and urinary bladder. GISTs that occur outside the GI tract are usually called EGISTs [3].

The clinical presentation of a GIST is not disease-specific and is usually related to the presence of a mass or bleeding. As a consequence, 50% of patients with a GIST, as in the presented case, have metastases already at the time of diagnosis. About 10% of cases remain asymptomatic, usually because of their small size (<2cm). GISTs can grow very large before producing symptoms, because they tend to displace adjacent structures without invading them. Bleeding attributed to the erosion of...
the GI lumen remains the most common symptom of a GIST. Bleeding can also take place into the GI lumen and cause such symptoms as haematemesis, melena, or anaemia. Vomiting, nausea, abdominal discomfort, early satiety or weight loss may be the most common symptoms of an abdominal mass. Cases of rupture of GISTs into the peritoneal cavity are rarely reported, but it may be associated with life threatening intraperitoneal haemorrhage. Different symptoms may be related to the location of the tumour: dysphagia in the oesophagus, biliary obstruction in the ampulla of Vater, or even intussusception in the small bowel.

Scientists in Spain have reported a clinical case of a 70-year-old female with liver metastases from a GIST. Hepatomegaly, tumour in epigastric region and elevated liver enzymes (LDH, GGTP), were the first symptoms of the disease [4]. It should also be mentioned that lymph node metastases are not very common for GISTs. Distant metastases most commonly occur in GISTs of the peritoneum, omentum, mesenteric areas and liver. One of the most important characteristics of a GIST is its high tendency to seed. Intra-abdominal lesions may cause the seeding of tumour cells into the abdominal cavity; the patients may also present metastases in surgical scars. GISTs vary greatly in size from a few millimetres to over 30 cm, although the median size is 5-8 cm. In the presented case, the stomach mass was about 7 cm × 9 cm. GISTs usually have an exophytic growth and as a result the intra-operative appearance commonly resembles a mass attached to the stomach, projecting into the abdominal cavity and displacing other organs. Mucosal ulceration is reported to be present in 50% of cases. Macroscopically, GISTs are smooth grey tumours, well circumscribed, usually with a pseudo-capsule. Sometimes, some areas of haemorrhage, cystic degeneration, or necrosis can be observed. Another characteristic is the eosinophytic structures composed of collagen which stain brightly with PAS (periodic acid-Schiff stain) [2].

Diagnosis of a GIST is usually delayed due to the vague nature of symptoms. The diagnostic procedure usually includes barium examination of the GI tract, computed tomography and angiography, but none of them can establish the diagnosis. The preoperative percutaneous biopsy is thought to be associated with a high risk of tumour rupture and dissemination. The significance of endoscopic ultrasound-guided fine needle aspiration has been proved, with an accuracy of 80%-85%. Some characteristics of GISTs, shown with the use of EUS (extraluminal growth, size, irregular border, heterogeneity), may be helpful in assessing its malignant potential. It should not be forgotten that GISTs always have a malignant potential, even if they may appear benign, and the clinical outcome is usually unpredictable. The most useful predictors of the behaviour of malignant behaviour seem to be the size and the mitotic count (mitoses < 5 to 50 high-power fields, usually characterized a GIST in the stomach as benign, while GISTs occurring anywhere that measure >10 cm tend to behave in malignant way. The key to pre-operative determination of malignant potential, however, always lies in cytology, immunohistochemistry and histology. Increased expression of MIB-1 and Ki-67 is thought to be connected with a less favourable prognosis [2].

Total surgical resection of the tumour, with the aim of obtaining negative microscopic margins, and avoiding rupture of the tumour rupture is the gold standard therapy, and is connected with 48–65% of five-year survival. Regional lymph nodes resection has no meaning, because GISTs relatively rarely has metastases there. Tumour rupture can lead to local dissemination and peritoneal implants. Partial resection can be only considered for palliative purposes or to control the symptoms or complications (haemorrhage, pain or compression of other organs). GIST’s response to conventional chemotherapy is very poor (<10%); radiotherapy is usually used only for analgic purposes. Imatinib (STI 571, Glivec, Gleevec) is a newly developed tyrosine kinase inhibitor recently tested in clinical trials on patients with unresectable GISTs. Imatinib has dramatically transformed the prognosis of locally advanced inoperable or metastatic GISTs. Imatinib mesylate has been proved to be a very active agent for tumour control in metastatic and advanced GIST. The prospective trial has shown a response in 50% of patients, and 75-85% of them have at least a stable disease. The two-year survival rate after therapy is approximately 70%, and 50% of patients showed no progression. It is worth mentioning, that interruption of the treatment usually leads to relapse, even for patients with complete remission [2]. Clinical trials of recurrent or metastatic GIST showed that the partial response rate is between 47% and 54%. However, a complete response is rarely reported. The initial treatment of a metastatic GIST is aimed at reducing its size by using imatinib mesylate, followed by surgical treatment for complete resection.

Scientists in Japan have reported the case of a patient with a GIST with metachronous liver metastases who underwent complete surgical resection following the IM treatment. The resected specimen was pathologically proved as a complete response. Preoperative radiographic CT, MRI, findings and microscopic findings of the resected specimen were described in terms of the effect of the molecular targeting therapy [5]. The treatment can include mild to moderate adverse effects such as periorbital edema, nausea, muscle cramps, diarrhoea, headache, dermatitis, fatigue, vitiligo, hypothyroidism, or abdominal pain. Treatment with imatinib of patients with large bulky tumours may cause some serious adverse effects, including gastrointestinal or intraabdominal haemorrhages or cardio toxicity [2]. It must be borne in mind that imatinib is not appropriate for all cases of GIST. There are patients who do not respond to the treatment (about 15% of patients), or even present an aggravation within 6 months during such therapy (so-called secondary resistance to Imatinib resulting from secondary kit mutation). It has been proved that about 50% of patients who initially respond, become resistant within 2 years of commencement of treatment [6]. As GISTs behave in an unpredictable manner, and usually tend to recur within 3-5 years, intense follow-up is required during this period. According to the National Comprehensive Cancer Network guidelines, contrast CT of the abdomen and pelvis is recommended every 3-6 months, as most recurrences happen during the first 2 years after surgical treatment. It should also be emphasized that malignant GISTs of the stomach have significantly better prognosis than malignant GISTs of the small intestine. Recent studies have also shown a correlation between age and the malignant potential of tumours [2].
REFERENCES