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Gastric Gastrointestinal Stromal Tumor with Bone Metastases – Case Report and Review of the Literature

Gastrointestinální stromální nádor žaludku s diseminací do kostí – kazuistika a přehled literatury

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Summary
Gastrointestinal stromal tumors (GISTs) represent rather rare neoplasms. Most GISTs are benign; malignant tumors account for 20–30% of cases (overall, approximately 10–30% of GISTs exhibit malignant behavior). GISTs most commonly metastasize to the liver and abdominal cavity. Distant metastases to other sites, especially to the bones, are relatively rare. We report a case of a 62-year-old man with metastatic spread of GIST to skull, ribs and both sacroiliac joints manifesting six months after surgical resection of a gastric tumor. Although bone metastases from GISTs are rare and there are only a few reported cases in the literature, this case emphasizes that metastatic disease should always be considered in a patient with gastric GIST and suspicious bone lesions.

Key words
gastrointestinal stromal tumors – bone – metastasis

Souhrn
Gastrointestinální stromální nádory (GISTy) patří mezi vzácné diagnózy. Většina GISTů je považována za benigní, nicméně asi ve 20–30 % případů se můžeme setkat s maligním typem růstu (celkově literatura udává rozmezí 10–30 % případů). GISTy se nejčastěji šíří do jater a břišní dutiny. Jiné vzdálené metastázy, obzvlášť do kostí, jsou poměrně vzácné. Tato práce uvádí případ 62letého muže s GISTem, u kterého po šesti měsících od resekce primárního tumoru žaludku došlo k metastatickému rozsevu nádoru do kostí lebečních, několika žeber a obou sakroilických kloubů. Přestože kostní diseminace GISTů je vzácná a literatura uvádí pouze několik podobných případů, autoři této práce zdůrazňují jejich význam v diferenciální diagnostice podezřelých kostních infiltrací.

Klíčová slova
gastrointestinální stromální nádory – kost – metastázy

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Most GISTs are benign; malignant tumors account for 20–30% of cases **(instead of classifying lesions as either benign or malignant, current guidelines categorize GISTs as low-, intermediate-, and high-risk based on size and mitotic index; overall, approximately 10–30% of GISTs exhibit malignant behavior)**. Most frequently, GISTs arise from the stomach (60–70%), small intestine (20–25%), colon and rectum (5%), or esophagus (< 5%). GISTs may also develop as primary tumors of the omentum, mesentery or retroperitoneum. Tumor resection is the treatment of choice for localized disease. Selective tyrosine kinase inhibitors (imatinib, sunitinib) are the standard therapy for metastatic or unresectable GISTs. The risk of recurrence is estimated from the mitotic index, size and the intial site of the tumor [1–3].

GISTs most commonly metastasize to the liver and abdominal cavity. Distant metastases to other sites, such as the bones or the lungs, are relatively rare [4–6]. Bone metastases have been reported, but their actual prevalence is unknown [7,8]. We report a case of bone metastases in a patient with **gastric** GIST supplemented by scintigraphic and radiologic findings.

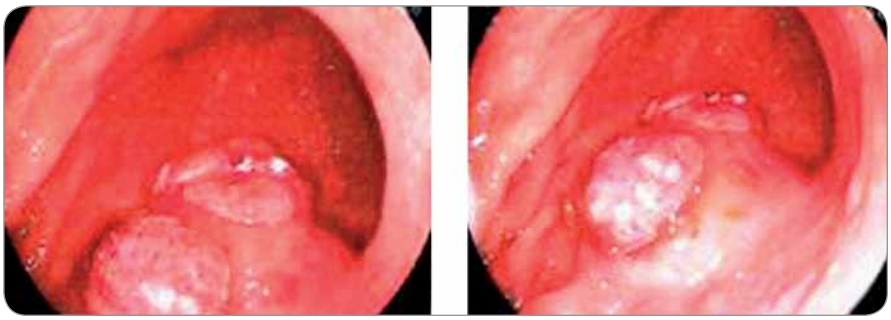

Fig. 1. An endoscopy showing antral gastric ulcerovegetan mass.

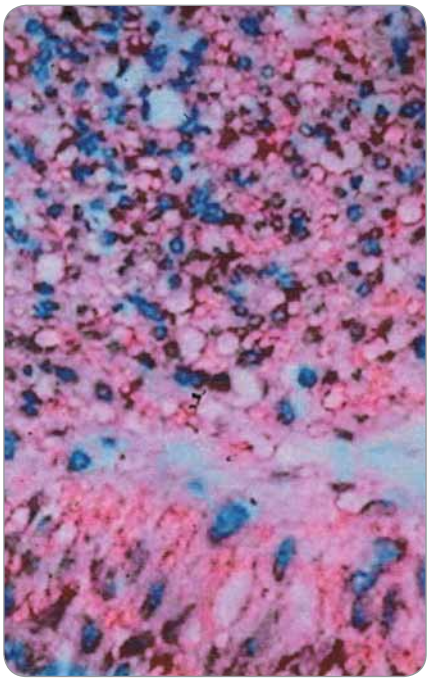

Fig. 2. Histopathological findings showed gastrointestinal stromal tumors (GISTs) (hematoxylin and eosin).

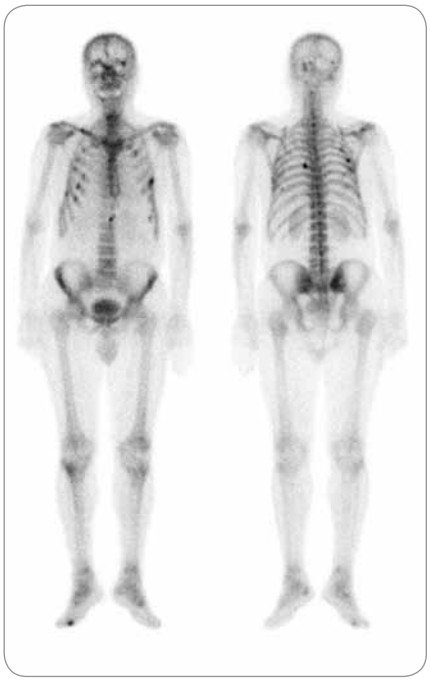

Fig. 3. GISTs metastatic bone lesions in bone scintigraphy.

Case Report

A 62-year-old male patient was referred to the hospital with abdominal pain, nausea and vomiting two years ago. A gastric endoscopy detected an ulcero-vegetan mass in his antrum (Fig. 1). A pathological examination of the biopsied specimens revealed a GIST. Abdominal computed tomography did not prove any other abnormality except for this gastric lesion. The patient subsequently underwent a partial gastric resection. By further histopathological analysis the tumor size concluded to be 4 cm, the mitotic index was 7/50 High Power Field (HPF), the lesion belonged to moderate-risk group according to the NIH and AFIP criteria, with mixed cell type (epithelioid and spindle) and high cellularity (Fig. 2). **Using an immuno-histochemical staining the tumor was confirmed to overexpress c-kit (CD117) and CD34 protein. It should be noted, that this analysis was performed extramurally due to its unavailability at our institutehence there is no pathology documentation included.** Following the resection, the patient had not received any adjuvant treatment. He was clinically stable and had no record of any untoward mediacal event during the follow-up period.

Six months after the operation he was presented to the hospital with complaints of weakness in the lower limbs. **After physical examination, a lumbar MRI was performed, however, it yielded no specific results. Thus, bone scintigraphy was carried out for further clarification.** It showed an increased tracer uptake localized in the skull, ribs and both sacroiliac joints (Fig. 3). Bone metastases of primary malignancy were suspected and the examination was supplemented by Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET/CT) scan for re-staging.

In accordance with bone scintigraphy, FDG PET/CT confirmed the hypermetabolic lesions in patient's ribs and sacroiliac joints (Fig. 4 A, B). **The bone metastases showed increased FDG uptake with mean SUVmax: 4.3 (range 3.6–5.8). The overall character of the bone lesions appeared osteolytic with a small portion of mixed activity de-**

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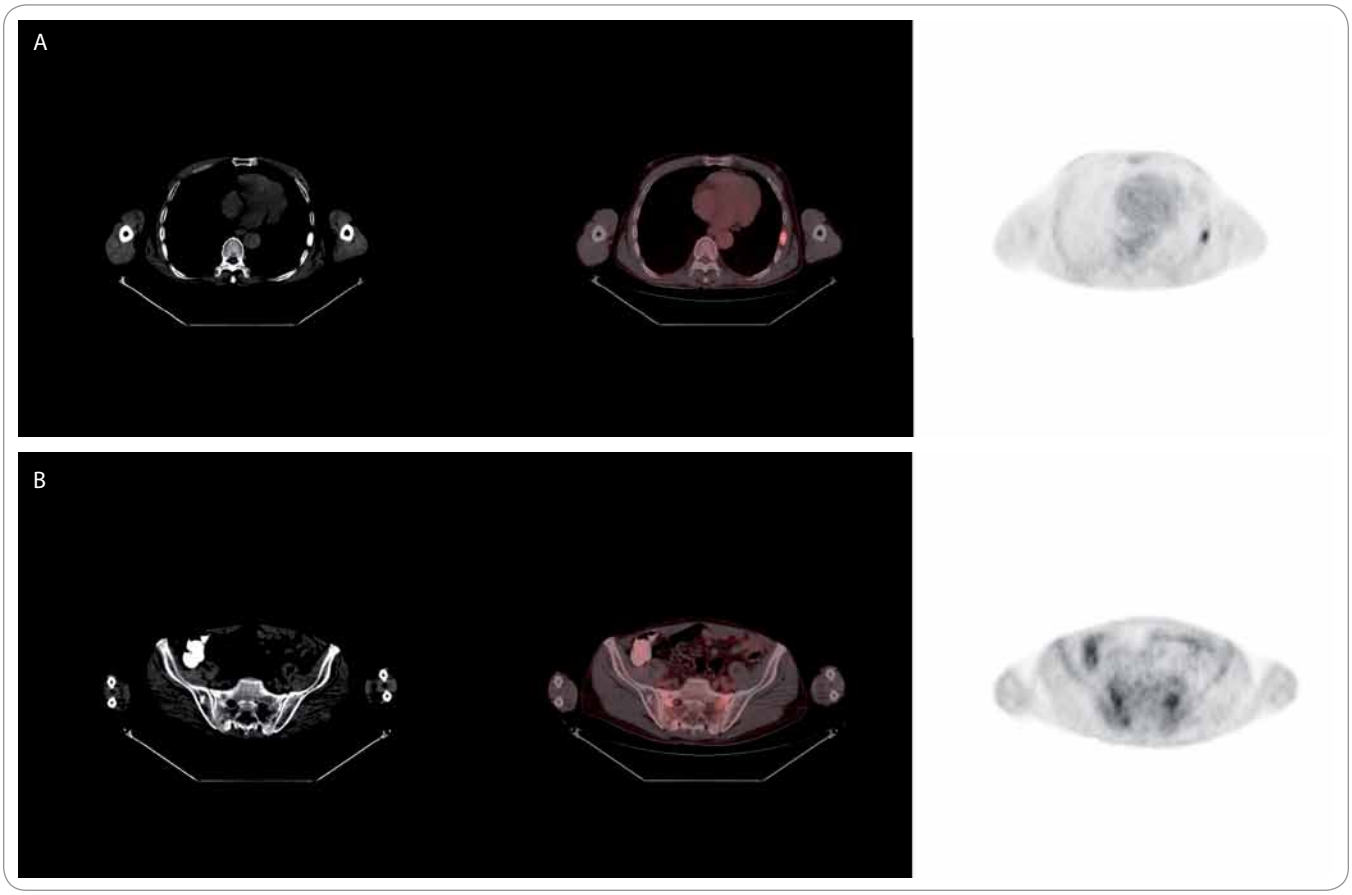

Fig. 4 A, B. GISTs metastatic bone lesions in PET/CT.

tected by CT scans). The patient was commenced on oral imatinib mesylate at a dose of 400mg/day. At the time of this report writing, he has still been receiving the treatment.

Discussion

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. The term GIST was first coined by Mazur and Clark in 1983 to denote a heterogeneous group of non-epithelial neoplasms of the gastrointestinal tract. GISTs originate from interstitial cells of Cajal – intestinal pacemaker cells that arise from the muscularis propria of the gastrointestinal tract wall [9–11].

Approximately 90% of GISTs stain positively for the receptor tyrosine kinase, KIT (or CD117). Eighty-five percent of tumors harbor mutations in KIT and 5% in platelet-derived growth factor receptor alpha (PDGFRα) domain. In fact, targeting this receptor with a c-kit tyrosine kinase inhibitor is of great clinical significance in the treatment of patients with unresectable or metastatic GIST, by reducing the tumor burden and improving survival rate [12–14].

Instead of classifying lesions as either benign or malignant, current guidelines categorize GISTs into low-, intermediate-, or high-risk group, depending on the tumor size and mitotic index. Prediction of the biological behavior of GIST at the time of the initial diagnosis may be difficult, however, large (> 5 cm) tumors, high mitotic activity (> 5 mitoses per highpower field), high cellularity, the presence of necrosis, prominent nuclear pleomorphism, and certain activating c-kit mutations are predictive of malignant behavior [1,14,15].

According to the largest epidemiological analysis to date, which included 1,458 recorded cases [16], or as reffered in a study by Miettinen and Lasota [17], GIST have a predilection to adults between 40–50 years of age [16,17].

The clinical presentation of GISTs is primarily dependent on the size. Small tumors (≤ 2 cm) are usually asymptomatic, often detected incidentally via endoscopy or at radiographic examination. The most common symptoms, though not specificaly GIST-related, include bleeding, upper abdominal pain, bloating or abdominal pressure and obstipation. Occasionaly, urgent abdominal complaints, such as massive gastrointestinal bleeding, perforation or bowel obstruction, may ocur [18].

Metastatic spread is a hallmark of a malignant behavior of the GIST. Overall, approximately 10–30% of GISTs exhibit malignant behavior. The most frequent site of occurrence is the stomach (60–70%), small intestine (20–25%), colon and rectum (5%), or esophagus (< 5%). GISTs may also develop as primary tumors of the omentum, mesentery or retroperitoneum [2,9].

Bone metastases in GISTs are rare, though nowadays, they are encountered

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far more frequently than in the past. This might be due to the advances in imaging techniques and the improvement of patients' overall survival rate following the introduction of tyrosine kinase inhibitors [19].

In the literature, there are only a few reported cases of patients with GIST metastases to the bone [20,21]. Bertulli et al reported 13 out of 278 patients (5%) with GIST who developed bone metastases. In four patients this was the only metastasization site and the other nine cases were associated with another organ invasion [22]. In the study of Jati et al comprising 190 GIST patients, six (3.2%) patients were reported to have bone metastases [23]. As rare as they appear, bone metastases are not an exception in patients with metastatic GIST, and any suspicious bone lesion should therefore be carefully evaluated, in order to prevent a serious bone event or other complications [23].

The detection of bone metastases in patients with GISTs is often based on a clinical presentation by itself (i.e. fractures or bone pain) or is an incidental finding on imaging evaluation. Hereby we emphasize the importance of bone metastases incidence for furher clinical practice despite the paradoxical paucity of available data on the sensitivity and specificity of bone scintigraphy and PET [19]. **In this case, the bone metastases showed an increased FDG uptake (mean SUVmax: 4.3; range 3.6–5.8). The overall character of the bone lesions appeared osteolytic with a small portion of mixed activity detected by CT scans). The available literature does not provide consistent data on the treatment of bone metastases in GISTs. In several prospective trials, matinib mesylate has been reported to have activity against recurrent, metastatic, or unresectable GIST in 50% patients, whereas approximately 75–85% patients achieved a stable disease. Imatinib mesylate was proven effective in the treatment of bone metastases of GIST [24]. The patient reffered in this work received oral imatinib mesylate at a dose of 400mg/day. At the time of this report writing, he has been receiving this treatment for 19 weeks. In comparison, Bertulli et al reported a 17-month (3–40 m) median survival in 13 patients with GIST metastatic to bones [22].**

GISTs are not considered as a radiosensitive tumor [25], but radiotherapy can be considered as a palliative treatment option. The effect of biphosphonate administration to a patient with GIST bone lesions is unknown, yet, it is recommended in some of the works[19].

Conclusion

Although bone metastases of GISTs are relatively rare and there are only a few reported cases in the literature, this work gives emphasis on a careful evaluation of any suspicious bone lesions, especially in patients with high-grade (high-risk) GIST.

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