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CASE REPORT

Imatinib-induced bone marrow necrosis detected on MRI examination and mimicking bone metastases

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Abstract Imatinib has revolutionized the treatment and prognosis of patients with gastrointestinal stromal tumors (GIST). In contrast to liver and/or abdominal involvement, bone metastases are an uncommon event in GIST. We report here two patients with metastatic GIST who developed pelvic bone marrow focal lesions visible on MRI examinations, while Imatinib dramatically improved other tumor sites. A biopsy in one patient diagnosed bone marrow necrosis. The other patient had a favorable follow-up over several years, without bone metastases. Focal bone marrow abnormalities, detected on MRI examinations and mimicking bone metastases in patients who were otherwise responding, should be considered as probable bone marrow necrosis.

Keywords Bone marrow · Necrosis · MRI · GIST · Metastases

Introduction

Imatinib has become the worldwide front-line standard treatment for patients with metastatic gastrointestinal stromal tumors (GIST). GIST is frequently characterized by a gain-of-function mutation of the Kit receptor [1] and was the first solid tumor model to be treated efficiently with therapy targeting the initial genetic alteration typifying this disease [2, 3]. Imatinib is a small molecule tyrosine kinase inhibitor that is active against Kit, inducing partial tumor necrosis. Patients with advanced GIST (bearing liver and/or abdominal implants) benefit from Imatinib in 90% of cases during the first year of treatment and 75% of patients are alive after 2 years of treatment [3]. Synchronous or metachronous bone lesions are a rare event in advanced GIST and clinical guidelines do not recommend routine bone explorations at diagnosis or during therapy. We report two cases of focal bone marrow abnormalities detected on MRI examinations that appeared in the pelvic bones of two patients who were responding to Imatinib.

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Case reports

Case 1

A 44-year-old male patient underwent a marginal resection of a rectal tumor that was initially diagnosed histologically as a leiomyosarcoma. He received six cycles of chemotherapy, followed by 45 Gy of radiation therapy. Four months later, local recurrence was treated with chemotherapy and wide surgery. Histological analysis and rereading of the initial specimen diagnosed a GIST. Three months later, local recurrence (Fig 1a) and pulmonary metastases were discovered. Imatinib was started at a dose of 400 mg per day. After 3 weeks, shrinkage of the pelvic masses exceeded 50%, according to response evaluation criteria in solid tumors (RECIST), and pulmonary metastases had disappeared. Five months after the initiation of Imatinib, bone marrow changes of the iliac bones (Fig 1b,c) and proximal femurs appeared on the pelvic MRI examination while all other tumor targets were controlled. The patient underwent a CT-guided biopsy of one of the pelvic bone marrow lesions. The lesions were not visible on CT, and their location was deduced from MRI. The biopsy did not

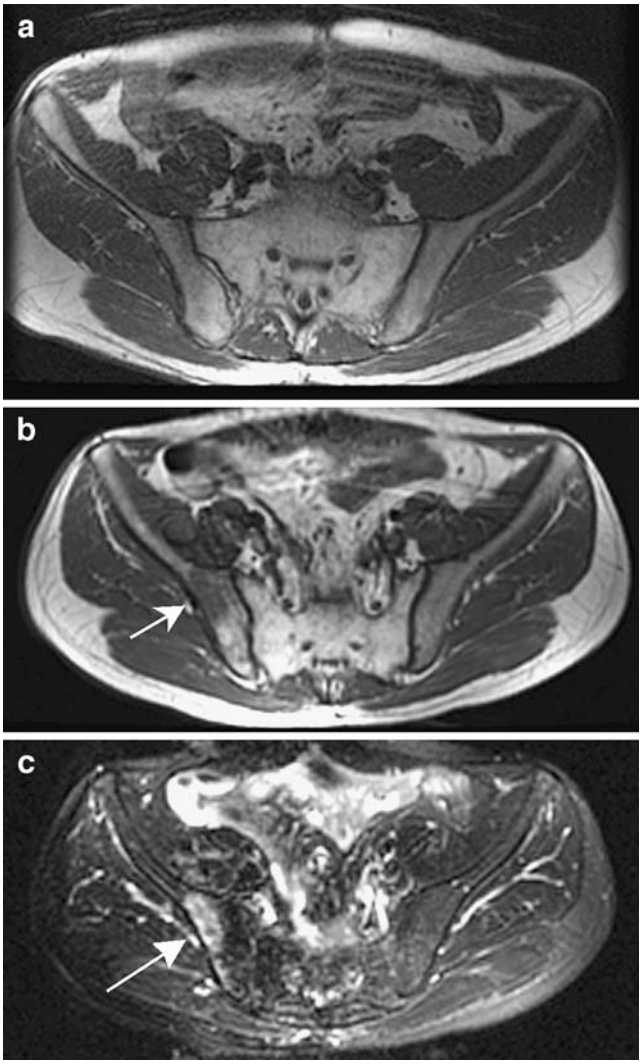

Fig. 1 Case 1. **a** Axial MR T1-weighted image of normal bone marrow. Five months later, a right iliac bone marrow lesion had appeared, on **b** T1 SE (*arrow*) and **c** T1 FSE fat pre-saturated (*arrow*) images

reveal any malignant tissue, but bone marrow necrosis was present. After a 21-month period of remission under Imatinib, the patient developed pleural, pericardial and mediastinal metastases and died.

Case 2

A 28-year-old male patient underwent two surgical procedures and received chemotherapy for a large GIST of the small bowel diagnosed before the Imatinib era. Abdominal recurrence was detected on CT and MRI examinationsI during the Imatinib era. On the initial MRI examinationI (Fig 2a,b) the bone marrow was normal. Imatinib (800 mg per day) was administered and the masses began to shrink within a week of treatment initiation (50% according to RECIST criteria). One month after beginning Imatinib, peritoneal metastases were smaller, but bone marrow changes had appeared in the right sacral ala and the right iliac bone (Fig 2c,d). As a fracture line was visible in the sacrum, the sacral lesion was considered to be a probable stress fracture. Three weeks later, the sacral lesion had disappeared, confirming the diagnosis of a coincidental stress fracture, but bilateral iliac focal bone marrow abnormalities had become visible (Fig 2e,f). The problem was explained to the patient, indicating the low probability of bone metastases. He refused a biopsy, explaining that his life had been too difficult and painful already. He fared well for 2.5 years without any bone problems, before developing general resistance to Imatinib.

Discussion

Imatinib has become the treatment of choice for metastatic GIST. About 90% of patients benefit from this tyrosine kinase inhibitor, despite the occurrence of secondary resistance observed in 20% of patients per year of treatment. Imatinib induces a tissue response with necrosis rather than an objective response using the classical RECIST criteria with changes in tumor size. Thus, the classic RECIST criteria cannot efficiently evaluate the activity/efficacy of Imatinib in GIST [4–6]. In our initial protocol, every patient with a pelvic lesion was followed up with MRI examinations every 2 weeks for 2 months, then every 2 months, in addition to CT. Eighteen patients were followed up with sequential MRI examinations of the pelvis. They always included T1-weighted axial spin-echo images, T2-weighted sequences with fat pre-saturation, and T1-weighted images with fat pre-saturation after contrast medium injection. Bone marrow changes were observed in two patients. In Case 1, the lesion was unilateral. An initially unilateral lesion in the second patient progressed to bilateral lesions. In both cases, these lesions increased in size over time. On MRI examination, they looked like possible bone metastases with well-demarcated foci exhibiting a low intensity signal on T1-weighted images, and a high intensity signal on T2-weighted and on T1-weighted images after contrast injection. The discordance between the favorable impact of Imatinib on the peritoneal metastases and the simultaneous appearance of the marrow lesions suggested that the etiology of the bone marrow changes was unlikely to be metastasis. Treatment-induced bone marrow necrosis has been reported histologically in patients with chronic myeloid leukemia [7, 8] treated by Imatinib. Necrosis of peritoneal or hepatic metastasis is considered a reliable sign of response on CT examinations. It may very probably also occur in normal marrow. If bone marrow focal lesions appear at the same time as disease progression, the problem may be solved by simply

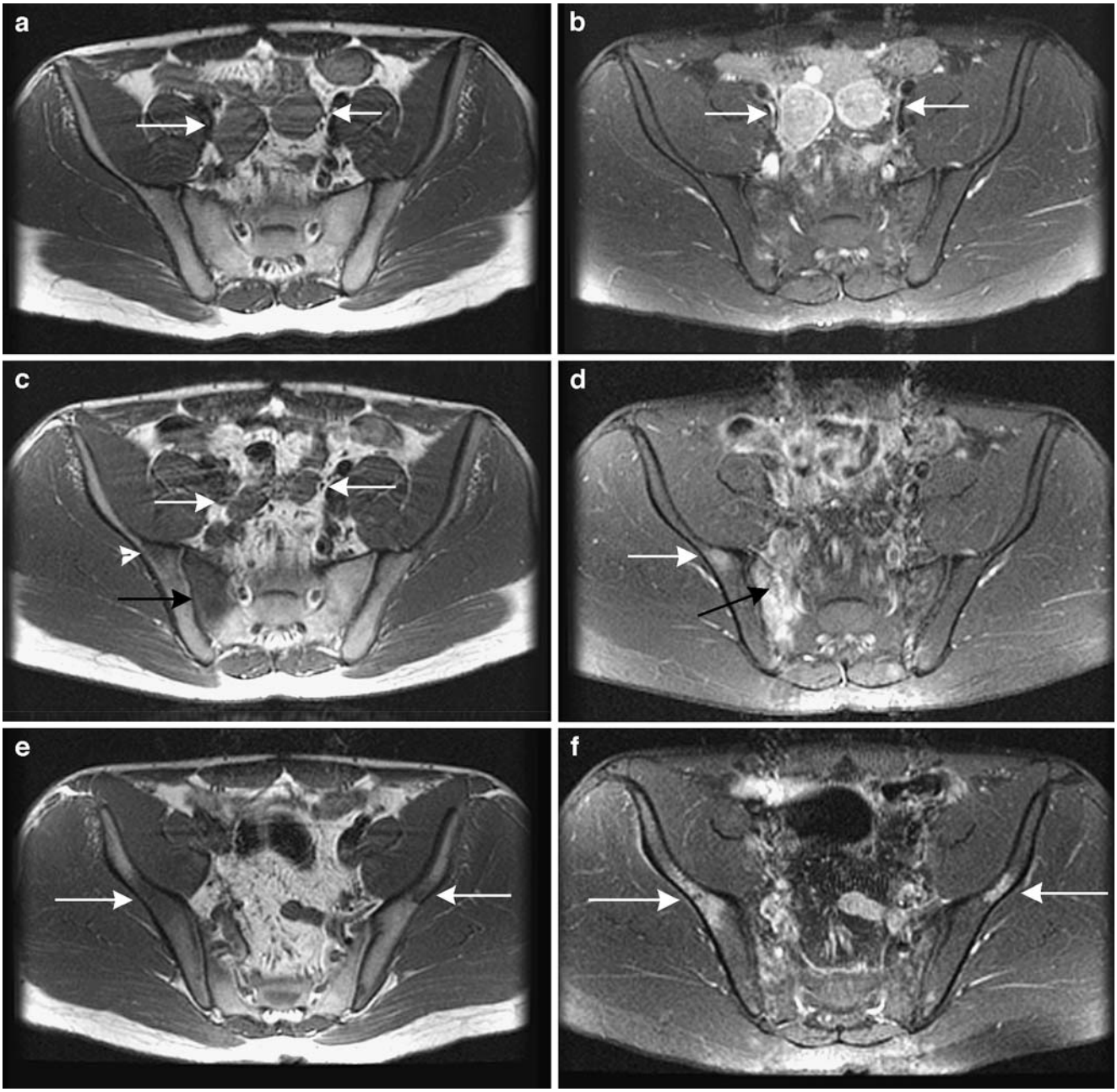

Fig. 2 Case 2. **a** Axial T1W, and **b** T1W FSE MRI with fat pre-saturation and injection of contrast medium before Imatinib was given: two peritoneal metastases (*white arrows*) are visible, and the marrow is normal. One month later (**c** T1W SE and **d** T1W FSE with fat pre-saturation and injection of contrast medium), the peritoneal metastases are much smaller (*white arrows*). Lesions have appeared in the right sacrum ala (*black arrow*), and a smaller one in the right iliac bone (*white arrowhead*). The sacral lesion is centered by a fracture line, and was considered to be a stress fracture. Three weeks later, the sacral lesion had regressed, but marrow focal lesions were visible in both iliac wings (*white arrows*), on **e** T1W SE, and on **f** T1W FSE fat pre-saturated images after injection

performing a biopsy to confirm metastatic lesions, which may alter treatment options. However, the appearance of such bone marrow changes with a simultaneous good response with regard to metastases should suggest bone marrow necrosis. In those cases, biopsy should be discussed, taking into account all the patient's data.

Conclusion

Focal bone marrow abnormalities appearing on MRI examinations in the follow-up of GIST patients responding well to Imatimid are probably foci of bone marrow necrosis.

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