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High-grade undifferentiated pleomorphic sarcoma of pelvis treated with curettage and bone graft after complete remission following caffeine-potentiated chemotherapy

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Introduction

Undifferentiated pleomorphic sarcoma (formerly known as malignant fibrous histiocytoma: MFH) is a relatively rare primary malignant bone tumor first described by Norman and Feldman as a malignant histiocytoma.¹ It comprises approximately 6 % of all bone tumors.^{2,3} It is reported that the osteosarcoma adjuvant or neoadjuvant chemotherapeutic regimen is beneficial⁴ and a good pathological response predicted better disease-free survival.⁵ Caffeine is a xanthine analogue that has a biochemical modulating effect as an inhibitor of DNA repair, and may inhibit post-replication repair of sublethally damaged DNA.^{6,7} Caffeine-potentiated chemotherapy has been administered to patients with high-grade bone and soft tissue sarcomas since 1989, because caffeine enhances the cytocidal effects of anticancer drugs through the inhibition of DNA-repair. Approximately 15% of primary malignant bone tumors involve the pelvic girdle.⁸ Periacetabular lesions are the most difficult site to reconstruct because of the complicated anatomical structure and complication rates including deep infection (12–47%), implant dislocation (2–22%), or local recurrence (28–35%) is still high in pelvic lesions.^{9,13}

In this study, we present a case of high-grade pleomorphic sarcoma involving the right acetabulum, which was successfully treated with curettage and a a bone graft after complete remission following caffeine-potentiated chemotherapy. The patient and her parents were informed that her data would be submitted for publication and gave their consent.

Case report

A 14-year-old Japanese female patient was referred to our university hospital with pain in the right hip that had been present for 2 weeks after she slipped and fell on an icy road. The patient was previously diagnosed with multiple neurofibromatoses (Neurofibromatosis type1; NF1) in her childhood, but had no other disorders. The physical examination revealed no soft tissue swelling or mass around the hip joint, despite her limp. A plain radiograph of the pelvis showed an osteolytic lesion around the right acetabulum (Fig. 1-a). Computed tomography (CT) showed the lucent expansile lesion at the acetabulum (Fig. 2-a). Magnetic resonance images (MRI) of the lesion showed low intensity in the T1-weighted images (Fig. 3-a) and mixed iso and high intensities in the T2-weighted images (Fig. 3-b), and the tumor was highly enhanced by Gadolinium (Gd) (Fig. 3-c). There was no abnormal soft tissue mass. Technetium-99m and Thallium-201 scintigrams revealed area of strong accumulation in the right acetabulum (Fig. 4-a). Distant metastasis was not detected. Open biopsy was performed, and the tumor was diagnosed as high-grade undifferentiated pleomorphic sarcoma (Fig. 5-a, b, c). Immunohistochemical analysis revealed that α SMA (Fig. 5-c), CD31, CD68, and vimentin were focally positive, and Cam 5.2, AE1/3, HHF35, CD34, and S100 were negative. Five courses of intra-arterial administration of cisplatin (120 mg/m², for 4 hours) and doxorubicin (30 mg/m²/day for 2 days) combined with caffeine (1.5 g/m²/day for 3 days continuously) and 2 courses of intravenous ifosfamide (3 g/m²/day for 3 days) and etoposide (60

mg/m²/day for 3 days) combined with caffeine (1.5 g/m²/day for 3 days continuously) were performed at three weeks intervals. Preoperative chemotherapy yielded a dramatic patient response. A plain radiograph of the pelvis (Fig. 1-a) and a CT showed a sclerotic change of the cortex (Fig. 2-b). MRI showed that the tumor size was unchanged following chemotherapy in the T1-weighted images (Fig. 3-d). The signal intensity in the T2-weighted images changed to high intensity (Fig. 3-e), and the Gd-enhanced images revealed the weak marginal enhancement around the tumor (Fig. 3-f). The Thallium-201 scan revealed no accumulation on the right acetabulum (Fig. 4-b). Thereafter, we performed a second multi-sampling biopsy to confirm whether the viable tumor cells still existed. Microscopically, no viable tumor cells were detected, and total tumor necrosis was expected. We additionally performed one course of intravenous administration of ifosfamide and etoposide combined with caffeine.

We proposed to the patient's legal guardians that the treatment options were wide excision and pelvic reconstruction, hemipelvectomy, thorough curettage in conjunction with artificial bone graft, and heavy ion radiotherapy. After careful discussion, the patient's guardians chose thorough curettage combined with artificial bone graft to preserve the patient's normal limb function. Seven months after the initial diagnosis, the patient underwent surgery. We made a small incision and created a 3 × 4 cm bony window. Intraoperative frozen sections revealed no viable tumor cells. We proceeded to perform a thorough curettage using high speed-burr with the adjuvant use of phenol

and ethanol. The cavity was filled with artificial bone paste (α -tricalcium phosphate, BIOPEX; Mitsubishi Materials Corporation, Tokyo, Japan) impregnated with 30 mg of doxorubicin as a local adjuvant treatment to prevent local recurrence. In the permanent section, no viable tumor cell was seen after surgery (Fig. 5–b). The patient underwent two courses of postoperative chemotherapy, consisting of cisplatin and doxorubicin combined with caffeine, and ifosfamide and etoposide combined with caffeine. The patient was permitted to place partial weight on the right leg 3 weeks after surgery. Full weight-bearing was permitted 2 months after surgery. The patient has been free of disease for 36 months after surgery. Although the artificial bone has not been replaced by newly formed bone, incorporation with the host bone has been obtained (Fig. 1–c). Moreover, the patient has been highly satisfied with the normal activities of her right lower limb.

Discussion

In this case, caffeine combined chemotherapy resulted in the complete remission of high-grade undifferentiated pleomorphic sarcoma of the pelvis, and rendered it possible to perform minimum invasive surgery to preserve limb function. Moreover, the tumor has not recurred 36 months after surgery. To our knowledge, no other attempt at curettage with chemotherapy for high-grade bone sarcoma has been reported to date.

High-grade undifferentiated pleomorphic sarcoma is a relatively rare bone neoplasm that occurs in all age groups.^{2,3} Several reports have described the effectiveness of neoadjuvant treatment with a

regime similar to osteosarcoma.⁴ Improvements in imaging techniques, chemotherapy and surgical techniques has resulted in more limb-saving surgeries over the past three decades for patients with osteosarcoma. The recent literatures showed that the response rate of chemotherapy and the 5-year-survival rate was reported to be 56–62% and 66-76%, respectively.^{13, 14} Capanna R, et al. reported that the 5-year survival rate of patients with MFH improved from 28% to 57% by administrating chemotherapy with surgical treatment.⁹ Picci P, et al. reported that a good pathological response correlated with better disease-free survival with a survival rate that was not different between osteosarcoma and MFH patients, although the patient response rate was significantly worse than in patients with osteosarcoma.⁵ We found only two reported cases of a malignant transformation of a neurofibromatous bone lesion to malignant fibrous histiocytoma.^{15, 16} One patient exhibited irradiation-induced malignant transformation¹⁵ and the other patient had not undergone irradiation.¹⁶ In this case, no neurofibromatous tissue was observed in the tumor and no neurofibromatous bone lesion was detected at other sites. Choudhry M, et al. reported the association of NF1 with malignant bone tumors. They identified 8 of 2900 patients with a primary malignant bone tumor who had coexisting NF1.¹⁷ The histological diagnoses were four cases of osteosarcoma, four cases of spindle cell sarcoma and one case of Ewing's sarcoma. Although the increased risk of bone sarcoma was estimated eight times that of the normal population, they found that the prognoses of these patients were favorable compared to patients who developed soft tissue

sarcomas in association with NF1.

Previously we reported the effectiveness of caffeine-potentiated chemotherapy for bone and soft tissue sarcomas in several studies.^{18,19} In particular, this treatment induced a response rate of more than 90% in osteosarcoma patients and facilitated a reduction in the surgical margin for a majority of the patients who achieved a markedly favorable response.¹⁸

The incidence of primary malignant bone tumor involving the pelvic girdle account for approximately 15% of primary malignant bone tumors.⁸ Periacetabular lesions are the most difficult site to reconstruct because of the complicated anatomical structure. Although a variety of reconstruction methods have been developed including custom-made prosthesis,^{10, 20} saddle prosthesis,^{11, 12} hip transposition,²¹ massive allograft,^{22, 23} recycling tumor-bearing autografts autoclaved,²⁴ irradiated²⁵ or frozen by liquid nitrogen,²⁶ and a bone graft-prosthesis composite,⁹ the resulting limb-function remains unsatisfactory. Complication rates including deep infection (12–47%), implant dislocation (2–22%), or local recurrence (28–35%) are still high in pelvic lesions⁹⁻¹² and result in poor implant-related survival (42%).²⁰ Moreover, any reconstruction methods following a wide excision severely diminish limb function, even if a marginal excision is performed. The pelvis is a technically demanding and challenging site. To our knowledge, this is the first report of successful treatment with curettage in conjunction with chemotherapy for high-grade undifferentiated pleomorphic sarcoma in the acetabulum.

In this case, we implanted an artificial bone graft impregnated with 30 mg of doxorubicin. Although the effectiveness of the anti-cancer drug loaded artificial bone has not been clarified, there are few reports concerned about this approach.^{28,29} We aimed to reduce the risk of local recurrence by this procedure.

Jaffe, et al. reported the clinical outcome of the patients with osteosarcoma treated by chemotherapy without surgical extirpation of the primary tumor.³⁰ Although they indicated this therapy for patients who showed clinical, radiographic, and histological responses, only 3 of 31 patients were cured by the administration of chemotherapy alone. In addition, the inclusion of four additional patients who underwent extirpation of the primary tumor without disease recurrence, and in whom no viable tumor was found in the resected specimens, may increase the number of patients who were potentially cured with chemotherapy to 7 patients (23%). They concluded that the results of their study did not justify the adoption of the current forms of chemotherapy as exclusive treatments for osteosarcoma. Although long-term follow-up examination is necessary in the present case to define the indications of this treatment, we suggest adapting this treatment when complete disappearance of abnormal accumulation is observed on Thallium-201 scan, no enhancement of the tumor on Gd-enhanced MRI, and no viable cells in the second biopsy specimen are obtained, and when the patient strongly desires and consents to receive this treatment after careful discussion.

In conclusion, the caffeine-potentiated chemotherapy showed total necrosis in this case and

enabled us to perform the most conservative function-preserving surgery. The precise evaluation of preoperative chemotherapy effects with a Thallium-210 scan, MRI and biopsy is required to apply this procedure, but long-term follow-up period is necessary to define the indications. This approach will provide a greater benefit to patients with pelvic osteosarcoma.

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Figure legends:

Fig. 1. a AP radiograph on admission of the patient revealed an osteolytic lesion at the right acetabulum, **b** Radiograph after preoperative chemotherapy showed a sclerotic change of the cortex. **c** Radiograph taken at 36 months after surgery shows stable artificial bone graft without evidence of tumor recurrence.

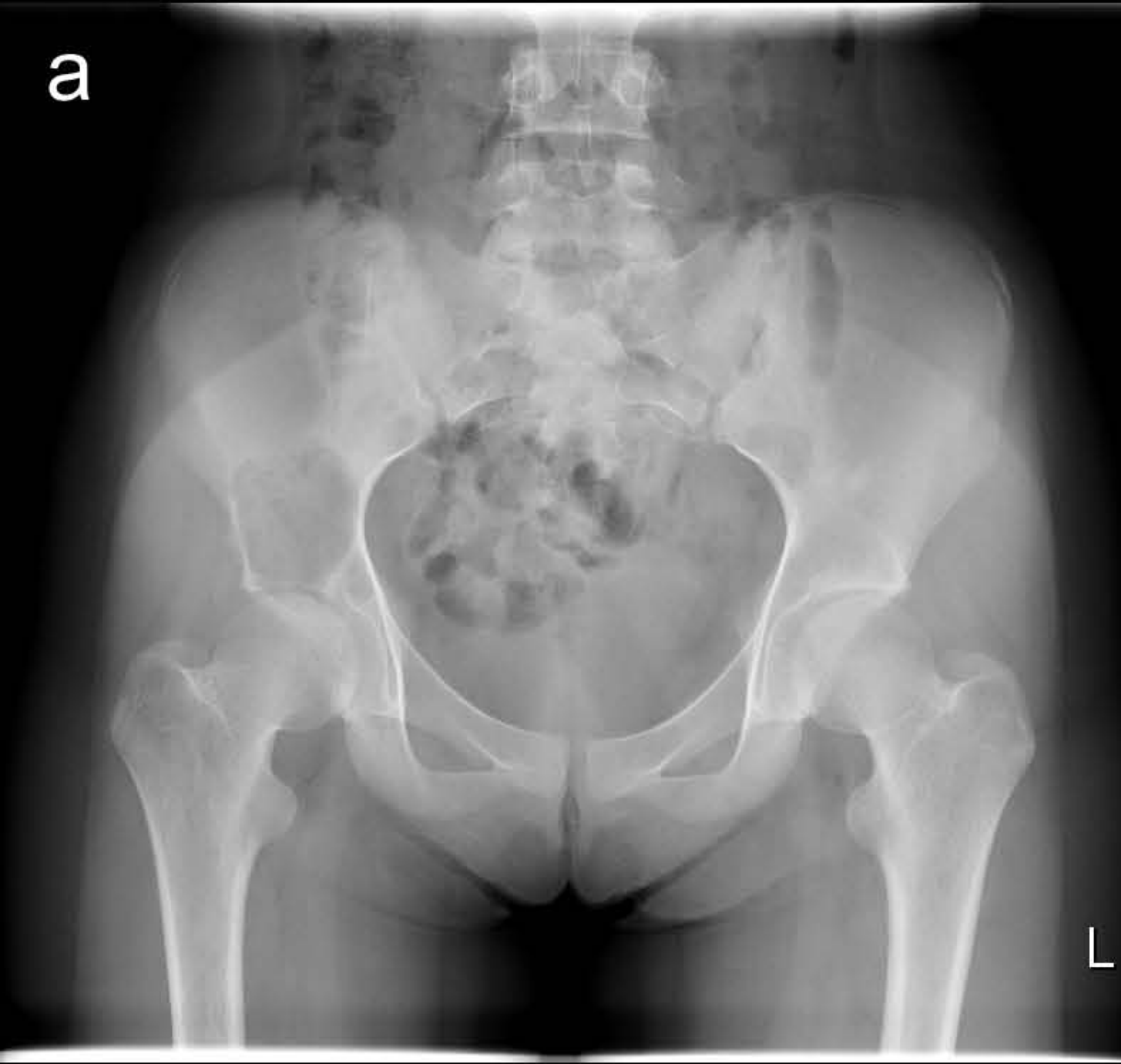
Fig. 2. a Computed tomography (CT) on admission of the patient revealed the lucent expansile lesion at the acetabulum and the thinning of the cortex. **b** CT after preoperative chemotherapy showed a sclerotic change in the cortex.

Fig. 3. a Coronal T1-weighted magnetic resonance imaging (MRI) (TR 500 ms, TE 5 ms) scan on admission revealed low intensity. **b** T2-weighted MRI (TR 3250 ms, TE 100 ms) images taken at the time of admission showed areas of mixed iso and high intensities. **c** T1-weighted gadolinium (Gd)-enhanced MRI (TR 180 ms, TE 1.4 ms) taken on admission of the patient showed strong enhancement at the tumor. **d** T1-weighted MRI (TR 500 ms, TE 5 ms) after preoperative chemotherapy showed areas of low intensity and the size of tumor was unchanged. **e** T2-weighted MRI (TR 3250 ms, TE 100 ms) showed regions of high intensity. **f** T1-weighted Gd-enhanced MRI

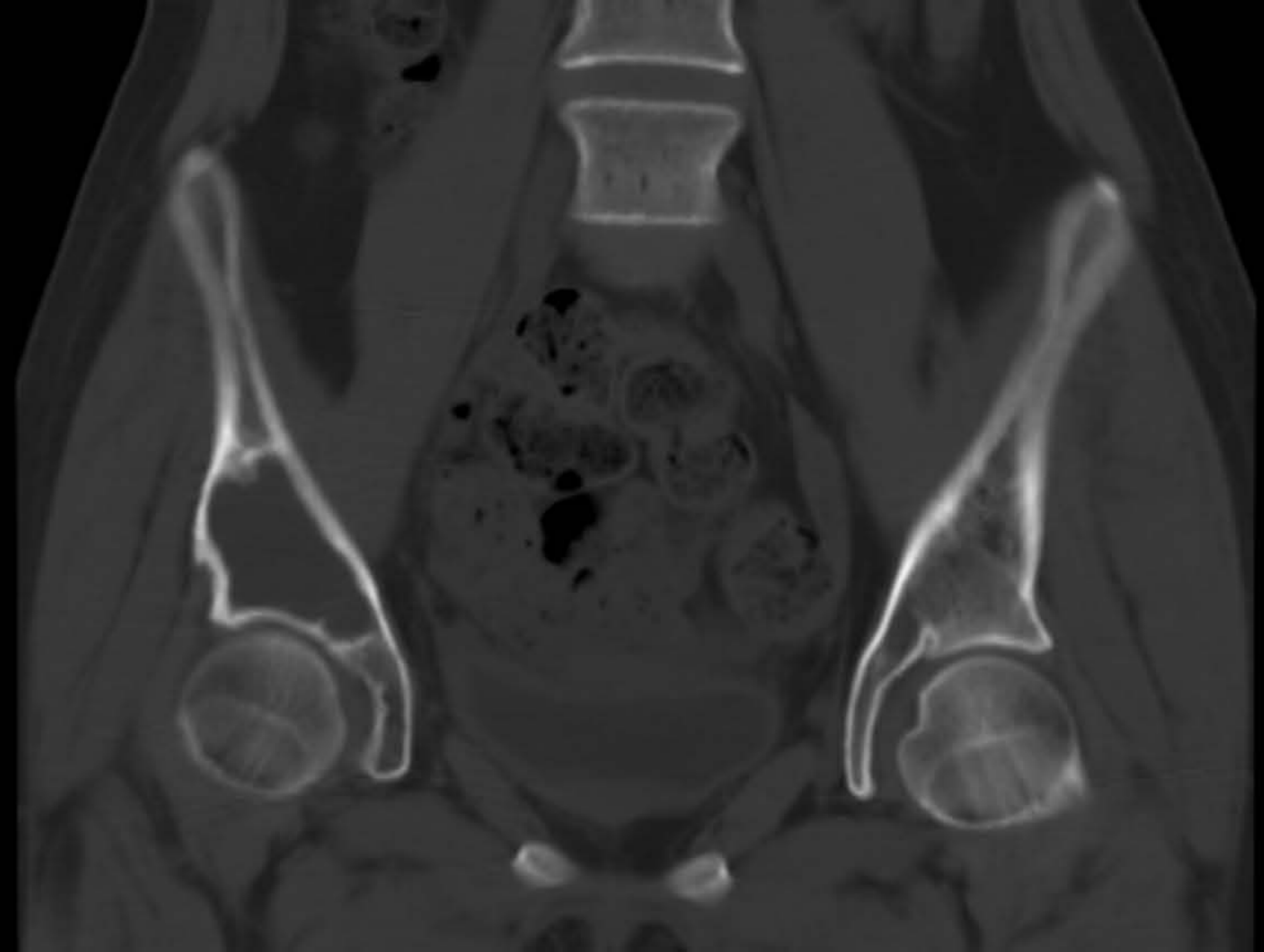
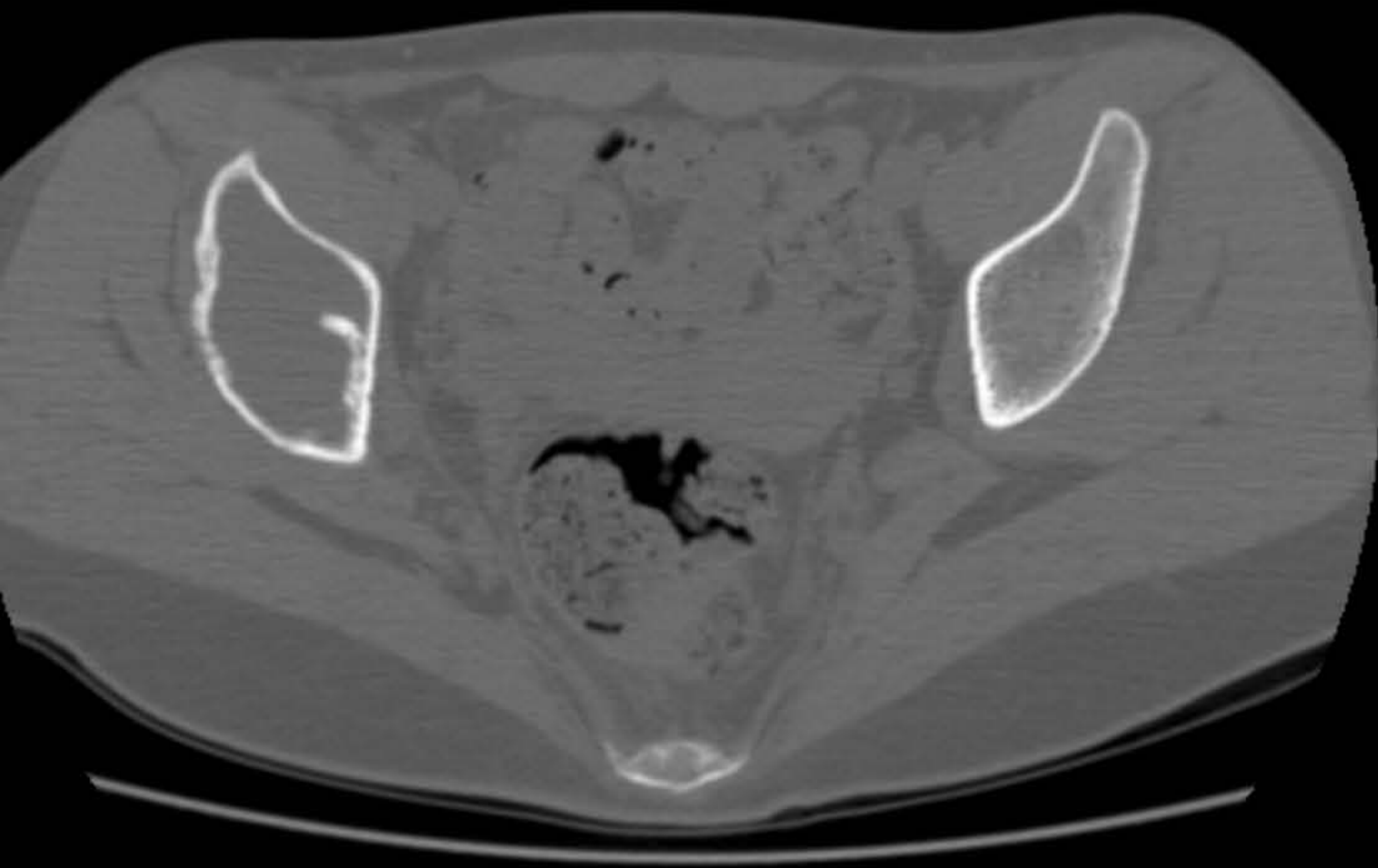
(TR 180 ms, TE 1.4 ms) showed only weak marginal enhancement around the tumor.

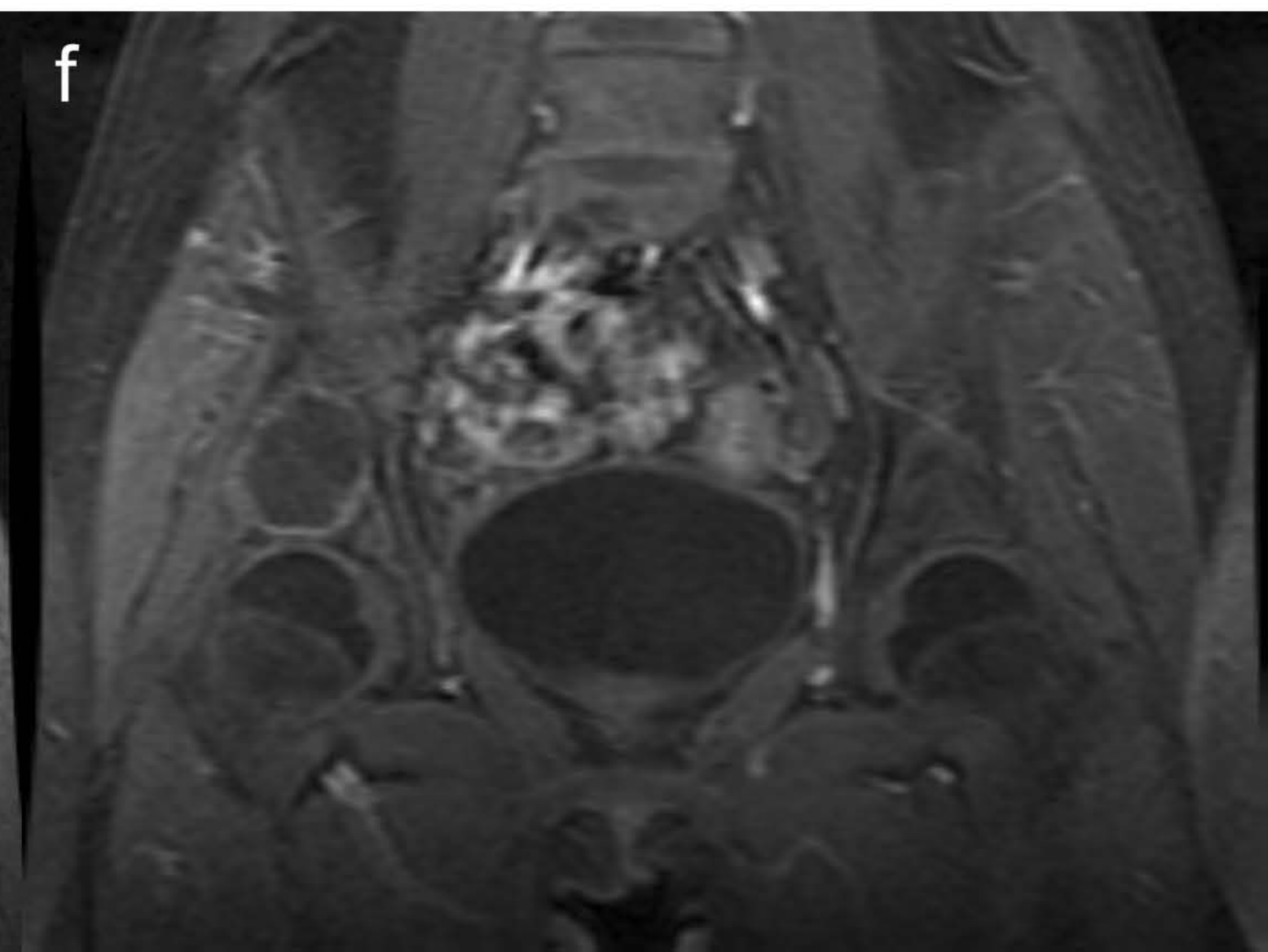
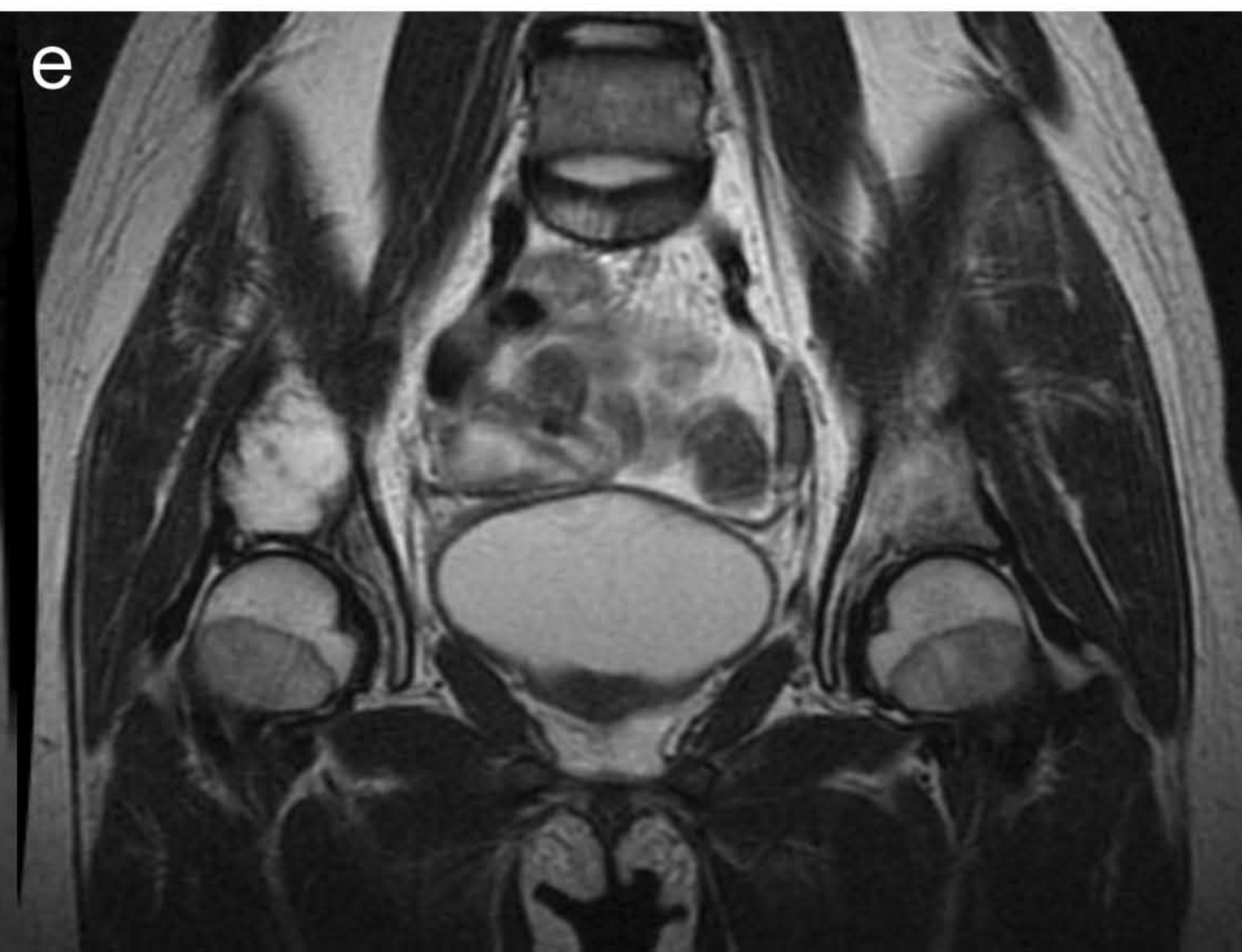
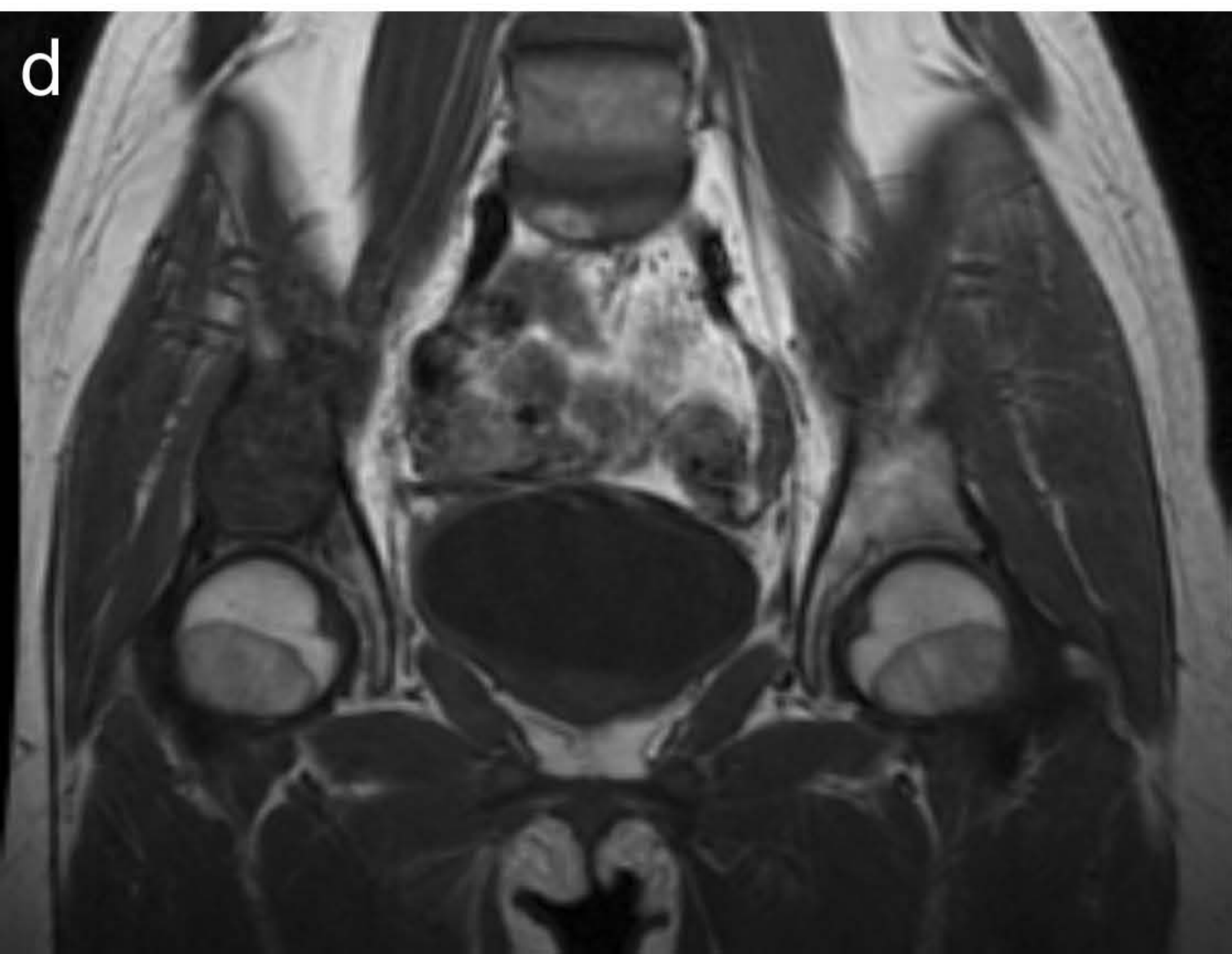
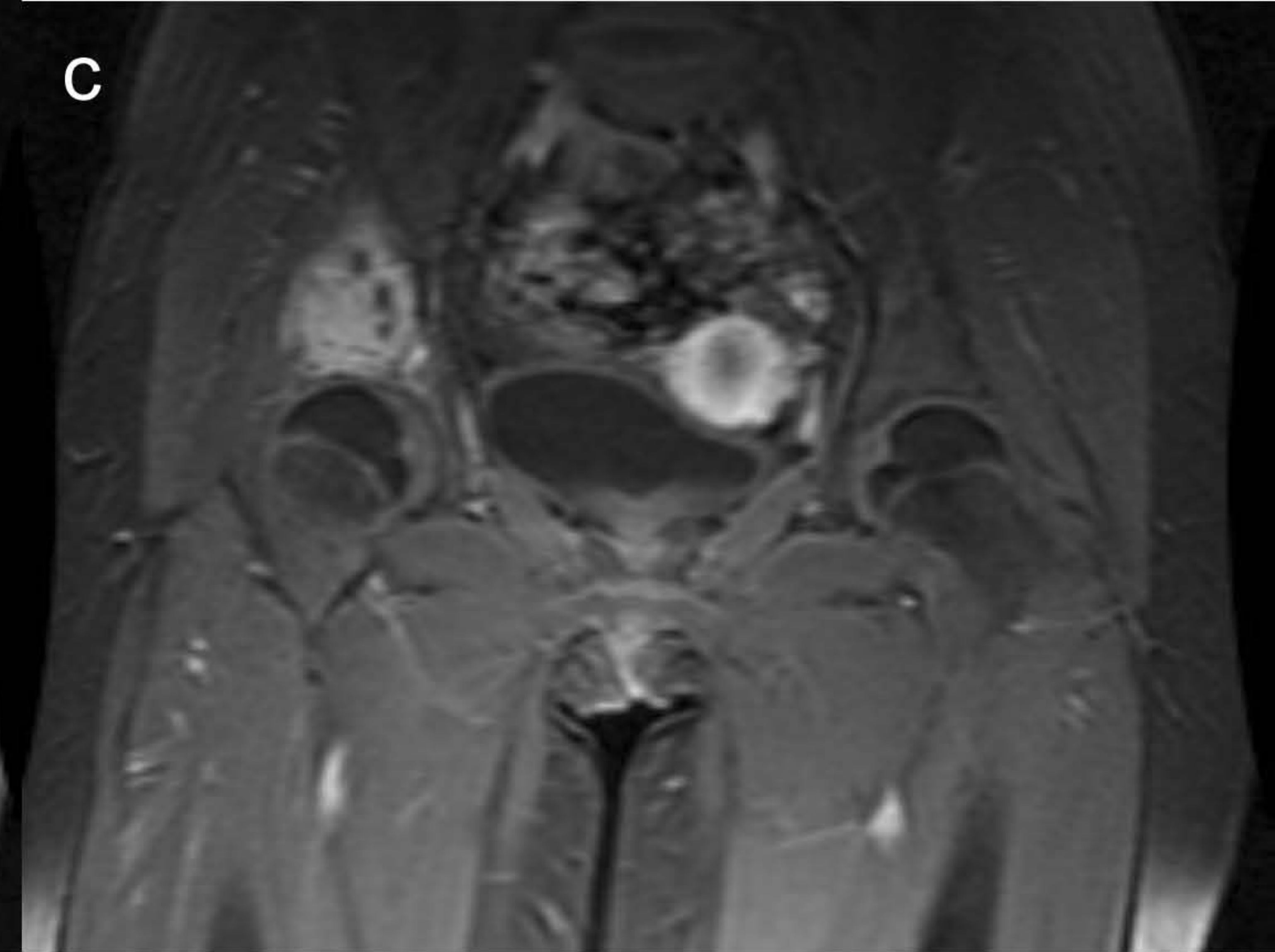
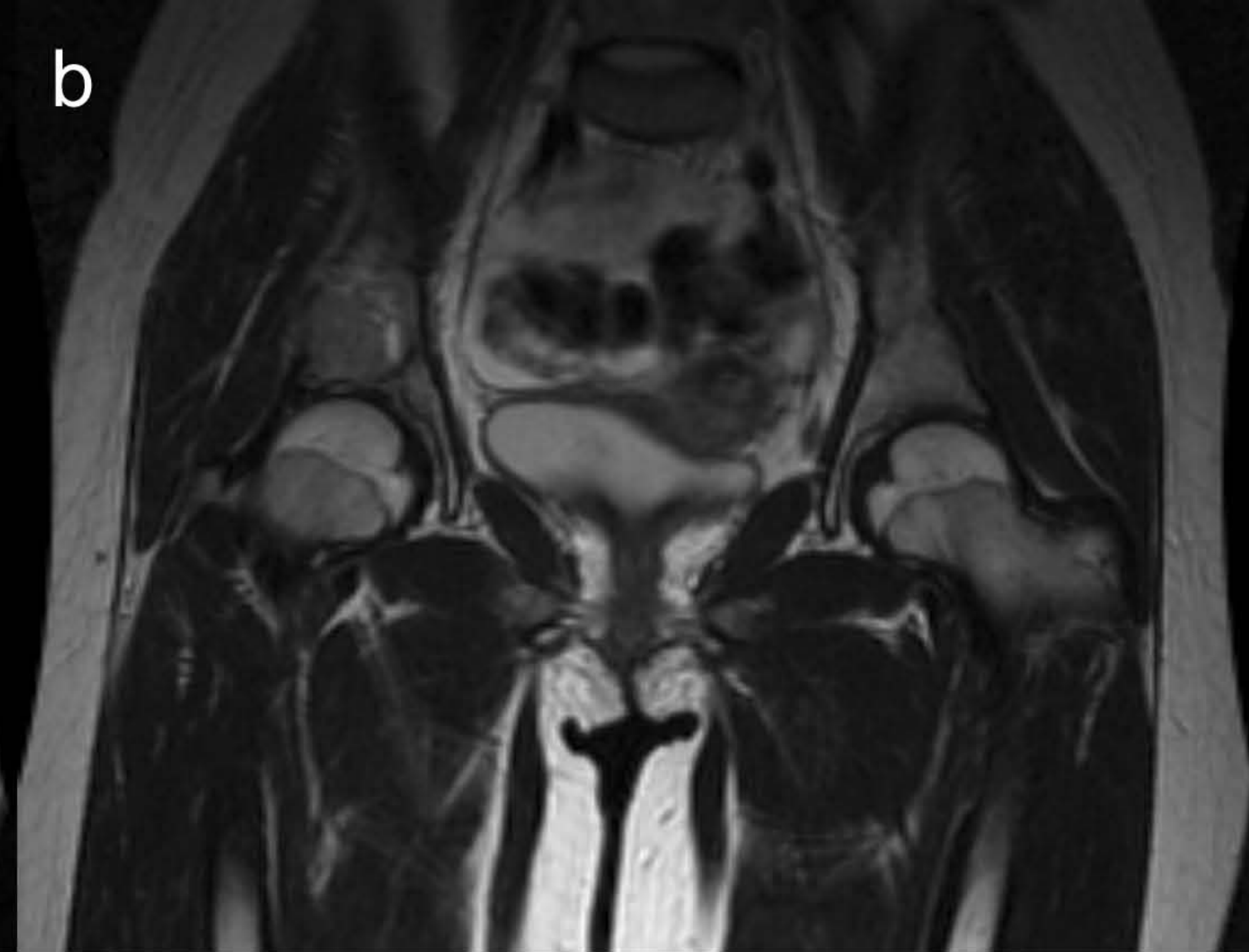
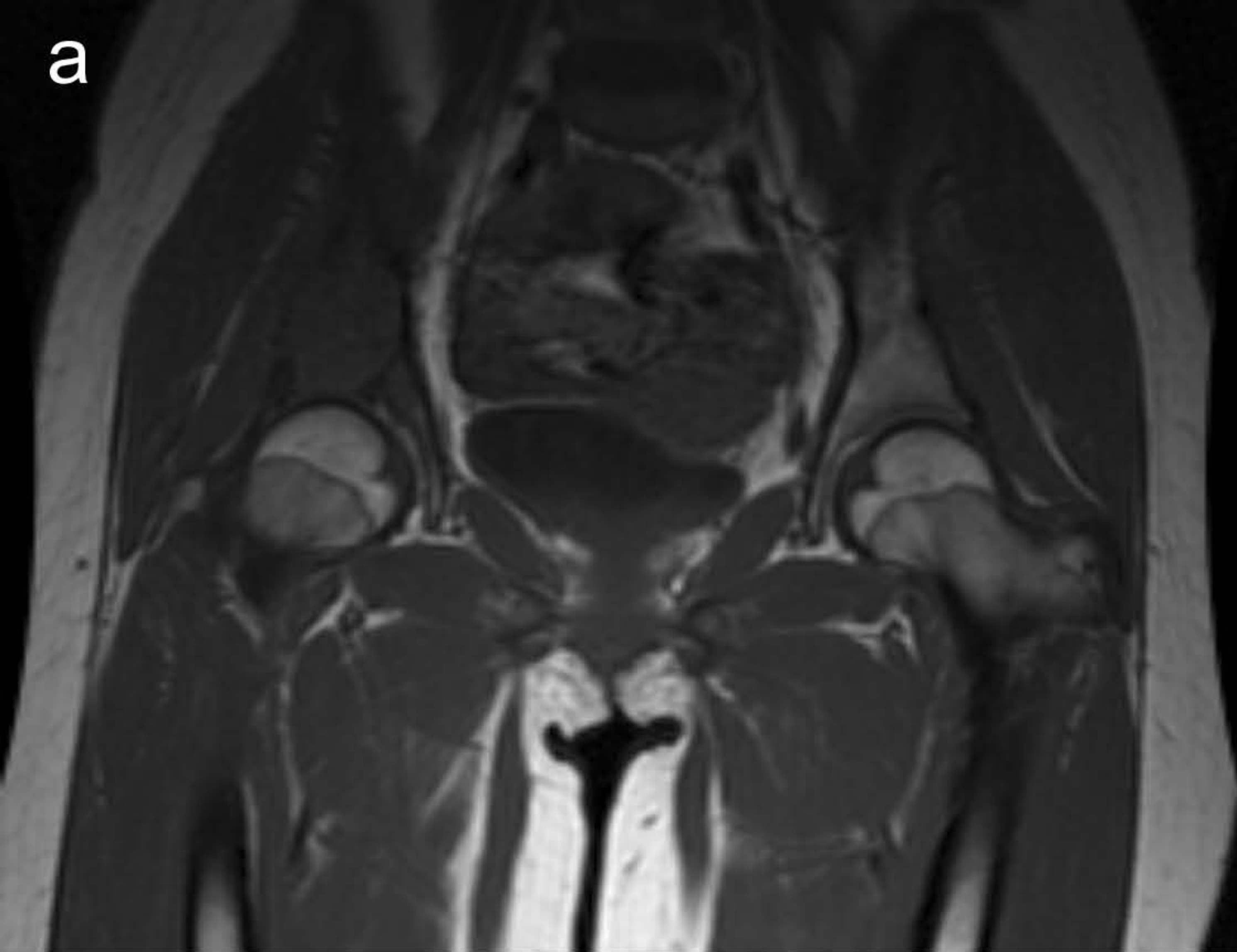
Fig. 4. a Thallium-201 scintigrams at the time of patient admission showed areas of high-accumulation at the right acetabulum (black arrow). **b** Thallium-201 scintigrams after preoperative chemotherapy showed no accumulation at the right acetabulum.

Fig. 5. a, b Histological biopsy analysis revealed an atypical and pleomorphic morphology, and large, bizarre nuclei. (hematoxylin and eosin stain, magnification a:100×, b:40×), **c** Immunohistochemical analysis of α SMA was focally positive (magnification 100 \times). **d** Specimen of surgery revealed complete necrosis (hematoxylin and eosin stain, magnification 100 \times).

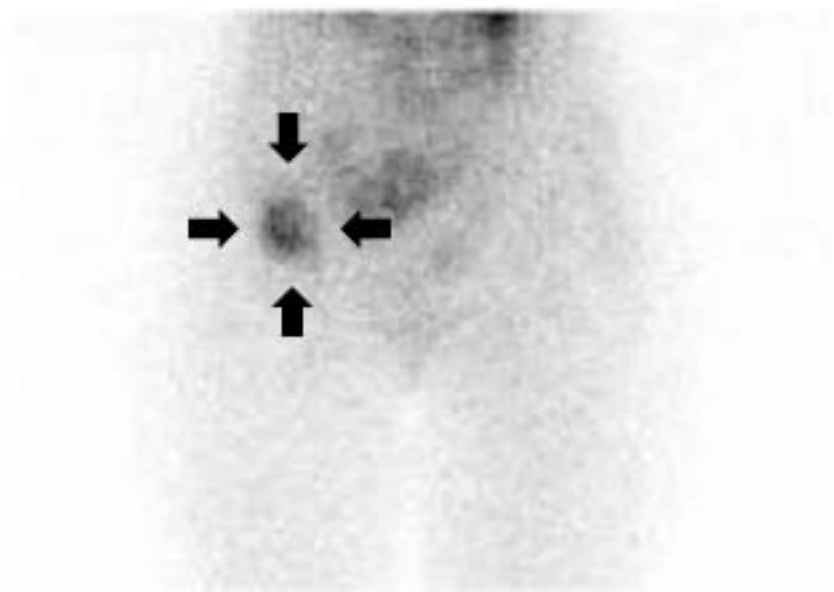








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