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REVIEW ARTICLE

The effects of granulocyte colony-stimulating factor on MR images of bone marrow

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Abstract

Granulocyte colony-stimulating factor (G-CSF) analogs such as filgrastim/pegfilgrastim are increasingly used to enhance neutrophilic recovery after chemotherapy. It is widely known that, physiologically, pegfilgrastim stimulates marrow mitotic activity and induces marrow reconversion from fatty to cellular. However, there is limited literature discussing the effects of pegfilgrastim on musculoskeletal magnetic resonance imaging, with the consensus that marrow reconversion secondary to pegfilgrastim therapy is easily confounded with a malignant process, especially in patients with a history of cancer. We attempt to discuss the expected changes and MRI findings after pegfilgrastim therapy through a summary of current literature. Additionally, we provide images from our own practice to support the previously established findings. G-CSF-stimulated reconversion can appear as patchy expansions of baseline hematopoietic marrow, but can also appear to be diffusely homogeneous, adding to its ambiguity. We conclude that using a baseline MRI, clinical information, and assessing sequential MRI changes in conjunction with pegfilgrastim therapy may aid the differentiation between benign and pathological change. We expand our discussion to include the effects of novel technologies, such as whole-body MRI, chemical shift imaging, and contrast agents in helping the distinction.

Keywords MRI · Pegfilgrastim · G-CSF · Marrow · Reconversion · Neulasta

Introduction

Granulocyte colony-stimulating factor (G-CSF) is a naturally occurring glycoprotein that stimulates the hematopoietic stem cells in bone marrow to produce and release granulocytes. Currently, pharmaceutical analogs of G-CSF such as filgrastim (Neupogen) are used as adjuncts to chemotherapy to enhance neutrophilic recovery and to provide prophylaxis against neutropenic fever [1]. Pegfilgrastim (Neulasta) is a PEGylated form of filgrastim that has been chemically modified to reduce immunogenicity and prolong circulation time. It is preferred by many patients due to a reduced dosing frequency, and has seen increasing usage in immune reconstitution post-chemotherapy. Currently, there is ample evidence suggesting that G-CSF enhances marrow mitotic potency and increases marrow maturation [2]. However, there is a limited amount of literature describing the effects of G-CSF on bone MR imaging. An increase in marrow cellularity in a cancer patient receiving pegfilgrastim therapy could indicate physiologic marrow response, but could also raise concerns for a malignant process. Therefore, the purpose of this article is to summarize the current uses of pegfilgrastim and to describe the common post-treatment MRI findings by consolidating existing literature.

As mentioned previously, pegfilgrastim has been chemically modified via the attachment of a polyethylene glycol group to reduce immunogenicity and renal clearance [3]. With a half-life of 15 to 80 h, pegfilgrastim functions by binding to surface receptors of hematopoietic stem cells to stimulate proliferation, differentiation, and release of granulocytes [4]. It was approved by the FDA in 2002 to decrease the incidence of febrile neutropenia, and is administered in doses of 6-mg injections [5]. It is given at least 24 h after each chemotherapy and not within 14 days of the next session, making it less disruptive to the patients' lives than filgrastim, which may need to be administered up to ten times a day [6]. Current guidelines recommend pegfilgrastim as primary prophylaxis

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after chemotherapy when the risk of febrile neutropenia is over 20% [7]. Pegfilgrastim is also used to treat hematopoietic radiation injury syndrome, and is administered after possible radiation exposure exceeding 2 Gys [8]. Furthermore, it has been shown in numerous studies to stimulate neutrophilic engraftment and cell survival after autologous stem cell transplantation [1]. The most commonly reported side-effect of therapy is mild-to-moderate bone pain, affecting 25–38% of patients, but it is also worth mentioning that in breast cancer patients treated with G-CSF, myelodysplastic syndrome or acute myeloid leukemia were more likely to develop (hazard ratio = 2.14) [7, 9]. Pegfilgrastim is eliminated mainly via neutrophil-mediated endocytosis and via renal clearance to a smaller degree [10]. Pegfilgrastm-jmdb is a bio-similar of pegfilgrastim that has been recently approved by the FDA for reducing risks of febrile neutropenia in patients with non-myloid cancer who are receiving myelosuppressive chemotherapy [11]. Due to both its structural and functional similarity to pegfilgrastim, it can be assumed that our discussion of G-CSF will pertain to pegfilgrastim-jmdb as well.

Marrow physiology

Hematopoietic marrow can be up to 70% cellular at birth, and gradually changes to fatty marrow with age in a process known as physiologic conversion. Conversion begins in the distal skeleton and progresses from diaphysis to metaphysis [12]. A detailed schematic demonstration of physiological age-related change can be seen in Fig. 1. On T1-weighted MR images, as the ratio of fat to hematopoietic marrow increases, signal intensity increases as well. Reconversion describes a process in which fatty marrow reverts to cellular due to an increased drive for hematopoiesis. In stimulating granulocyte production from the hematopoietic niche, pegfilgrastim therapy functionally induces reconversion. Therefore, a subsequent decrease in marrow MRI signal post therapy could indicate an increase in cellularity secondary to marrow infiltration, metastasis, or pegfilgrastim-stimulated reconversion.

There are other bone-marrow activators currently on the market, such as erythropoietin (Epo). Erythropoietin is a hematopoietic hormone that has been shown to activate bone marrow stromal cells. It is secreted from the kidneys and liver in response to hypoxia, and functions through the JAK-STAT pathway to expand the production of erythrocytes [13]. It is widely known that Epo administration also affects marrow MRI signal via reconversion, particularly in the lumbar spine [14]. However, the specific imaging pattern and its effects on granulocyte proliferation is poorly understood [14].

Imaging findings

To our knowledge, there has not been any reported difference between filgrastim and pegfilgrastim in terms of MR imaging. Therefore, a review of previous literature will discuss the effects of G-CSF therapy in general. Approximately 16 days after starting G-CSF therapy, MRI of the marrow demonstrates nonspecific decreased T1w and increased T2w signals [15]. Confusingly, in infiltrative bone tumors and in metastasis,

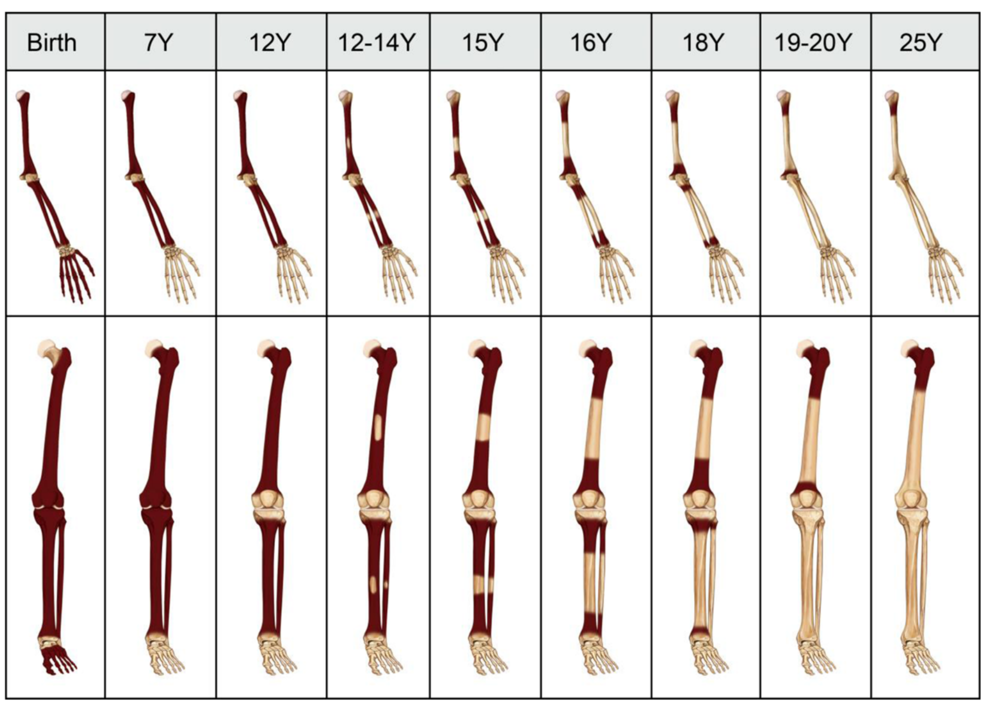


Fig. 1 Schematic demonstration of physiological age-related changes of the distal skeleton. At birth, red marrow predominates the distal skeletal system. Around puberty, physiologic marrow conversion can be observed starting in the distal skeleton as red hematopoietic marrow is replaced by fatty acellular marrow. Conversion initially begins in the diaphysis and proceeds towards the epiphysis. By the early 20s, only the metaphysis of long bones and parts of the central skeleton (vertebral bodies/sacrum, not shown) maintain active hematopoietic potential

MR imaging of bone marrow exhibits decreased T1w signal as well [16]. Furthermore, MR images of pegfilgrastim-induced reconversion exhibits non-specific patterns and may be homogeneously diffuse or patchy in appearance [17]. It is vital to differentiate between benign and malignant processes to plan subsequent testing and/or treatment, since reconversion misdiagnosed as cancer could lead to unnecessary and invasive biopsies, negatively impacting patient care.

Various patterns of reconversion secondary to G-CSF therapy have been recorded. In a study looking at 25 adult patients with soft tissue sarcomas or primary bone tumors who underwent chemotherapy with G-CSF administration, Hartman et al. found that approximately 40% of patients exhibited obvious signs of reconversion on MR imaging. Out of these patients, 90% exhibited increased T2-weighted signal intensity in proximal segments of long bones and pelvises [18]. Seventy percent of patients had a diffuse pattern of bone marrow hyperintensity in T1 and hypointensity in T2, and 30% exhibited focal changes [18]. In patients with primary bone malignancies that were contiguous with reconversion signal, the reconversion signal demonstrated characteristics (signal intensity, appearance) that were different from the primary malignancy and appeared discontinuous [18]. There were abnormal gadolinium enhancements on the images from the primary bone tumor, but none from reconversion [18].

In addition to the study conducted by Hartman et al., two case series and several case reports summarize the effects of G-CSF on the appearance of marrow MR imaging. Fletcher et al. looked at 15 pediatric patients undergoing chemotherapy, 11 of whom were receiving G-CSF treatment concurrently. All patients who had fatty marrow before G-CSF treatment exhibited MR changes consistent with reconversion, most prominent in the femur and pelvis, that correlated temporally with an increase in absolute neutrophil count [19]. Reconversion in younger children with prominent amounts of red marrow were more difficult to assess [19]. In a case series of 13 adults, Layer et al. discovered that G-CSF administration induced increased marrow signal in the lumbar and femoral area, with most of the changes having a nonspecific diffuse appearance. The authors drew the conclusion that assessment based on single MRI alone was not possible without pretherapeutic images [20]. In a case report (Fig. 2), Vanel et al. showed that G-CSF therapy mimicked a growth of primary neuroectodermal tumor of the bone during preoperative chemotherapy. The authors suggested that a comparison of the contralateral limb may be beneficial as benign changes tend to be symmetrical [21]. In another case (Fig. 3), Kouba et al. found that G-CSF administration in a patient with severe aplastic anemia and neutropenic sepsis induced multiple focal lesions in the vertebral body highly similar to the appearance of neoplasms [22]. The authors recommended utilizing PET imaging prior to G-CSF administration if malignancy is suspected [22]. Finally, Naples et al. found that in a 5-year-old boy who underwent marrow repletion with G-CSF after chemotherapy for neuroblastoma presented with MRI marrow lesions that falsely simulated neuroblastoma metastasis (Fig. 4) [15].

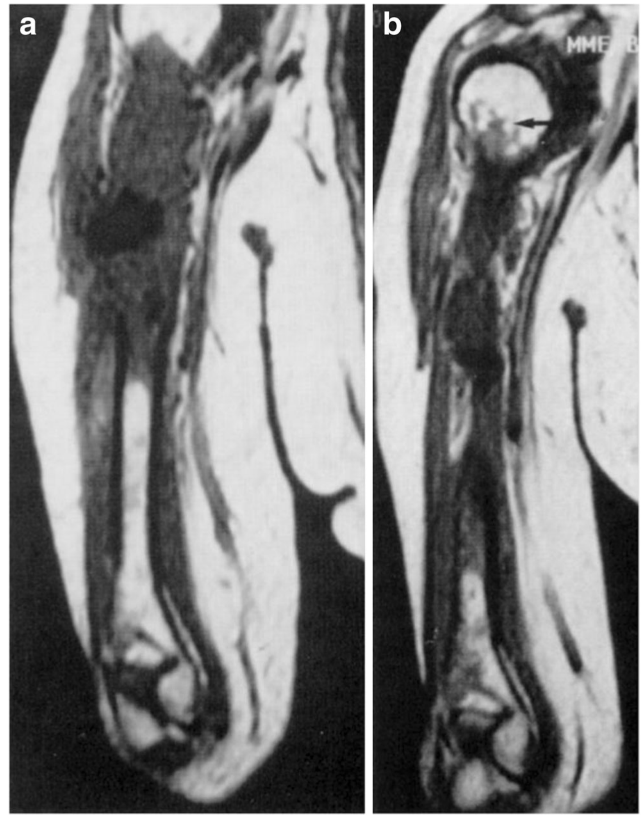


Fig. 2 MR images of a 52-year-old woman with biopsy-proven primary neuroectodermal tumor of the bone. Initial imaging (**a**) showed 13 cm of the distal humerus to be free of disease. However, after preoperative chemotherapy in conjunction with G-CSF, there was an apparent increase in the volume of the lesion with only 8 cm free of disease (**b**). After amputation and histological analysis, the apparent growth of pathologic-appearing marrow was determined to be marrow reconversion secondary to G-CSF therapy [21]

To demonstrate the chronology of imaging findings in association with the course of pegfilgrastim therapy, we show MR images of a patient receiving chemotherapy and pegfilgrastim injections for the treatment of a metastatic myxoid liposarcoma nodule of the left lateral thigh (Fig. 5). Baseline MRI before chemotherapy and pegfilgrastim therapy show a lesion lateral to the left greater trochanter that is hypointense on T1/hyperintense on T2. The epiphysis and metaphysis demonstrates age-appropriate hyperintense signal on T1 and hypointense signal on T2 (Fig. 5a, b, c, d). One year into pegfilgrastim therapy, the patient's bone marrow shows increased areas of patchy reconversion following the same pattern along previous areas of marrow activity, with an expected reduction of the adjacent soft tissue mass (Fig. 5g, h, i). Finally, at the 1.5-year mark, axial T1 and T2 demonstrate an even larger presence of hematopoietic marrow with almost

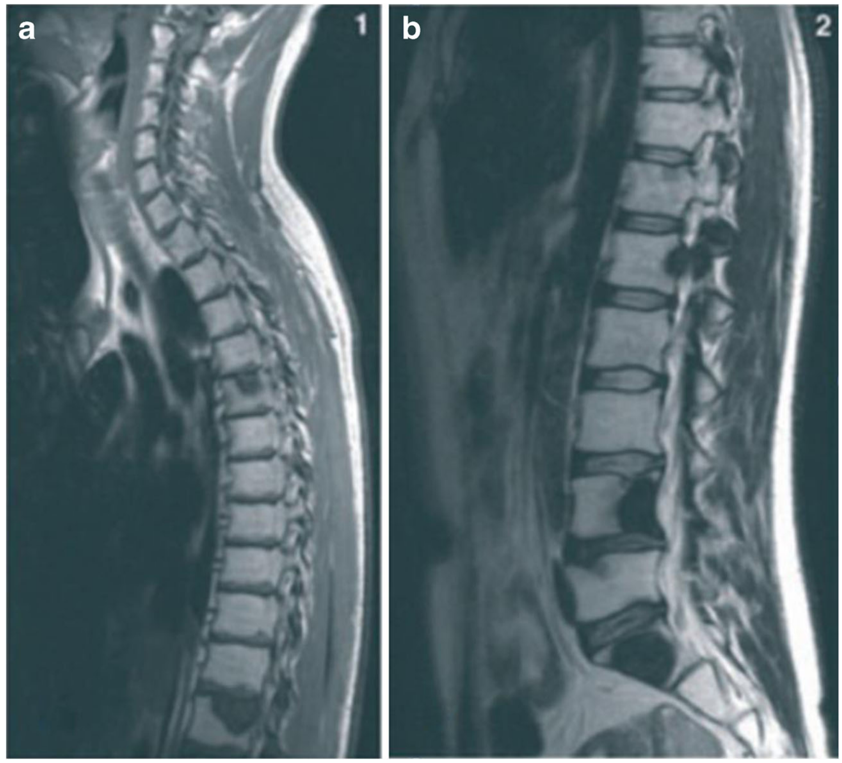


Fig. 3 MR images of a 25 year old man with biopsy-proven aplastic marrow who developed neutropenic sepsis and treated with G-CSF. Subsequent MRI scans showed multifocal lesions highly representative of neoplasm in both the thoracic (**a**) and lumbar (**b**) spine, but PET-CT-directed surgical biopsy from S1 vertebral body showed no malignant cells [22]

complete resolution of the adjacent sarcoma (Fig. 5j, k). Our images correspond to the patchy, focal pattern of reconversion secondary to pegfilgrastim therapy previously described in the literature.

We show another patient who received chemotherapy in conjunction with pegfilgrastim for the treatment of Ewing sarcoma of the right femur to demonstrate diffuse changes on MRI (Fig. 6). The pathological infiltration of the right femur as well as the baseline marrow signal can be observed in Fig. 6a and b. Four months after initiating chemotherapy and pegfilgrastim injections, areas of hypointensity on T1 and hyperintensity on T2 can be observed, corresponding to reconversion. Compared with the previous case in Fig. 5, the area of reconversion is relatively homogenous. Furthermore, it is worth noting that reconversion may affect any bone with hematopoietic potential. T1 and T2 axial images demonstrate homogenously cellular marrow in the iliac wing, which would be unexpected in a post-pubertal patient without G-CSF therapy (Fig. 6e, f).

Clinical findings

Additional clues such as chronology and clinical findings may aid the differentiation between G-CSF response and pathological processes. For example, if the pattern of signal intensity corresponded temporally with the course of pegfilgrastim therapy, then it may be suggestive of hematopoietic recovery. As mentioned before, bone pain is the most common reported side effect with pegfilgrastim therapy. Patients who report bone pain onset after injection, especially at the ends of long bones and in the back, are more likely to be experiencing it due to therapy resulting from marrow reconversion. Furthermore, pegfilgrastim-stimulated reconversion will follow areas with previous marrow activity, whereas a pathological infiltrative process can deposit anywhere in the bone. Establishing a baseline MRI before pegfilgrastim therapy is useful in assessing the anatomical position of signal abnormality.

Additionally, marrow response due to G-CSF on MRI can correlate with elevations in peripheral leukocyte count, and a close monitoring of the complete blood count may be helpful in making the diagnosis [15]. As previously mentioned, Fletcher et al. found significant elevations in absolute neutrophil count in seven out of seven pediatric patients that had positive MRI findings. However, Hartman et al. reported white blood cell elevations in only ten out of 25 patients (40%) receiving G-CSF therapy. This may suggest that peripheral blood count is not a reliable indicator of G-CSF marrow reconversion, but the second study had several caveats. First, the white blood count was compared to physiologic levels, but patients receiving chemotherapy would be

Fig. 4 MR images of a 5-year-old boy with a history of primary adrenal neuroblastoma metastatic to the distal femora receiving chemotherapy in conjunction with G-CSF. Coronal STIR (**a**) image showed a focal lesion in left diametaphysis with increased signal consistent with neuroblastoma metastasis, and T1 (**b**) showed the reduced signal intensity coming from the same lesion. MRI of the lower extremities 3 weeks later (**c**, **d**) showed abnormal patchy signal within the femoral metaphysis without dramatic change to the known metastatic lesions. The lesions were worrisome for further disseminated disease, which was ruled out by short-term follow-up MRI and I131-MIBG scan [15]

expected to be neutropenic, so a "normal" level in white blood count could be secondary to G-CSF stimulation [18]. Second, the temporality of white blood count and G-CSF therapy was not discussed in detail, as the blood work was drawn anywhere from 0 to 42 days post-treatment [18]. White blood cell levels may rise and fall due to concurrent chemotherapy regimen, and a more systematic study closely monitoring white blood counts may be warranted.

Novel technology

Chemical shift imaging is a technique that relies on signal loss from microscopic fat and is used widely in adrenal imaging to aid the differentiation between benign and malignant processes [23]. In a retrospective study looking at 55 patients with indeterminate skeletal lesions of the spine, chemical shift imaging correctly diagnosed 33 of 45 benign and 11 out of 12 malignant lesions, yielding a sensitivity of 91.7% and a specificity of 73.3% [23]. Specific to our discussion, out of five cases of hematopoietic marrow, one was misdiagnosed as malignant, possibly due to a low microscopic fat content in the reconverted marrow [23]. Chemical shift imaging may aid the differential if initial MR imaging is unclear, but may not be sufficient in becoming the mainstay in delineating hypercellular benign marrow from malignant processes [23].

Whole-body imaging has recently gained popularity in the diagnosis of various diseases such as lymphomas, myelomas, and systemic musculoskeletal pathologies. Studies show that whole-body imaging is superior to radiographic skeletal survey when diagnosing plasma cell neoplasms (74 vs. 61% accuracy) [24]. There has been one case discussing the use of whole-body imaging to assess marrow response following G-CSF therapy prior to peripheral blood stem cell harvest. Imaging demonstrated an increase in T2 signal intensity in the posterior iliac crest that corresponded with elevations in white blood cell count, consistent with known physiologic

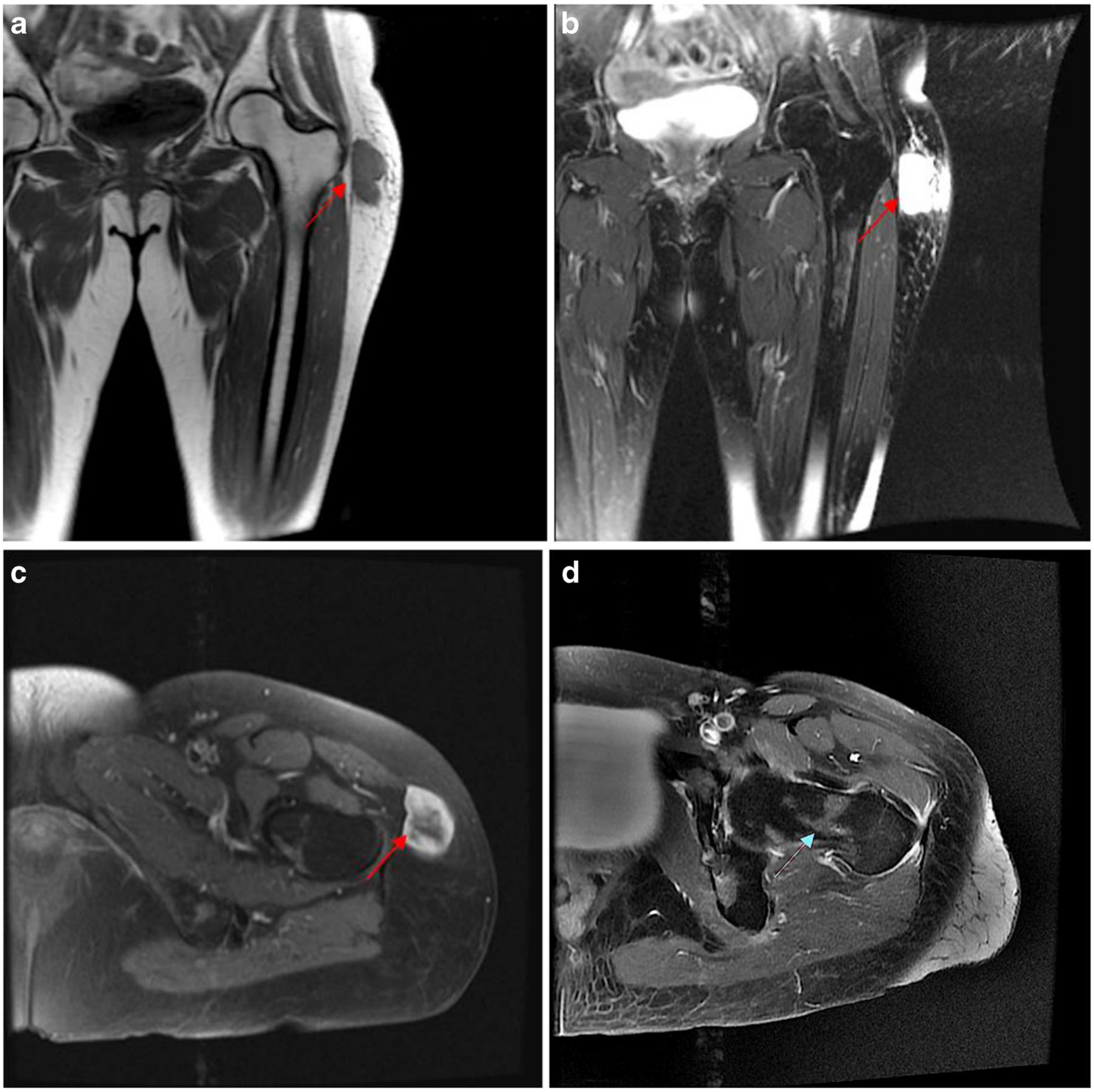


Fig. 5 T1 (**a**) and T2 (**b**) images of a 60-year-old female with biopsy-proven subcutaneous metastatic myxoid liposarcoma nodule of the lateral aspect of the left hip region (*red arrow*) of the left lateral thigh before pegfilgrastim therapy. The mass was not resected due to history of recurrence and systemic metastasis, and she has received multiple doses of radiation therapy for her disease. T2 post-contrast (**c**) of the same patient before pegfilgrastim therapy. T2 at a slightly superior level (**d**) from the lesion shows baseline residual hematopoietic marrow that appears hyperintense to adjacent bone (*blue arrow*). T1 (**e**), T2 coronal (**f**), and T2 axial (**g**) images of the same patient 1 year after initiating chemotherapy with pegfilgrastim therapy. Bone marrow shows increased areas of reconversion along with reduction of the soft tissue mass. As demonstrated in both the coronal T1 and T2 sequences, the reconversion signal (*blue arrow*) is patchy in appearance. T1 axial (**h**) and T2 axial (**i**) images of the same patient 1.5 years after initiating chemotherapy with pegfilgrastim therapy. Area of reconversion signal (*blue arrow*) in the femoral neck has widened compared to the previous figure

effects of G-CSF [25]. To our knowledge, there has been no discussion in using whole-body MRI to discriminate between reconversion and malignant infiltration.

As mentioned previously, Hartman et al. reported that gadolinium enhancement was demonstrated in malignant processes of the marrow but not in reconversion. However, contrast enhancement is largely variable, with obvious signal in patients with intermediate- and high-grade diffuse bone malignancies, but less efficacious in low-grade malignancies [26]. To our knowledge, there have been no discussions on using gadolinium enhancement to study the effects of G-CSF.

Lastly, the use of ultrasmall superparamagnetic iron oxide nanoparticles (USPIO) as a recent and novel

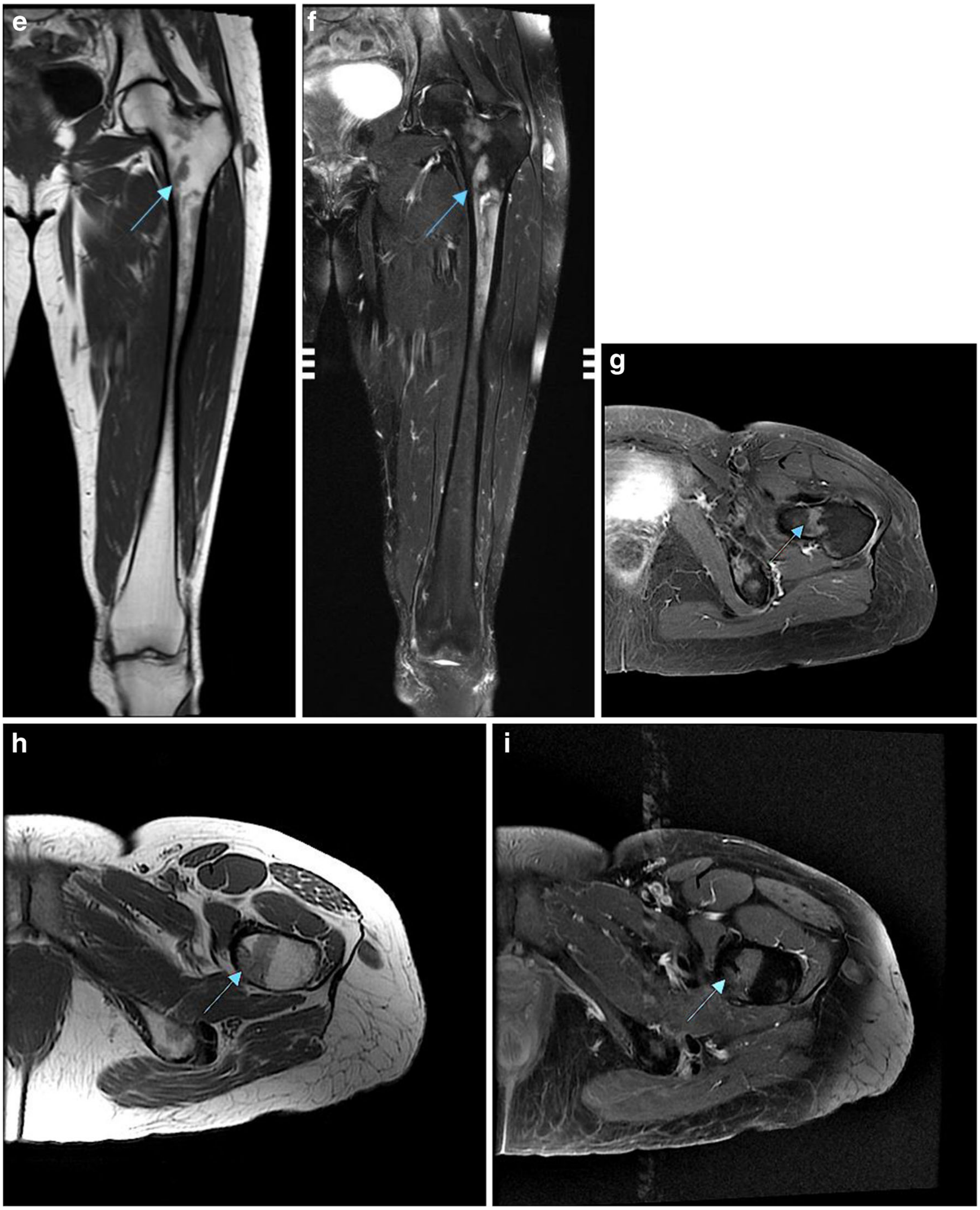
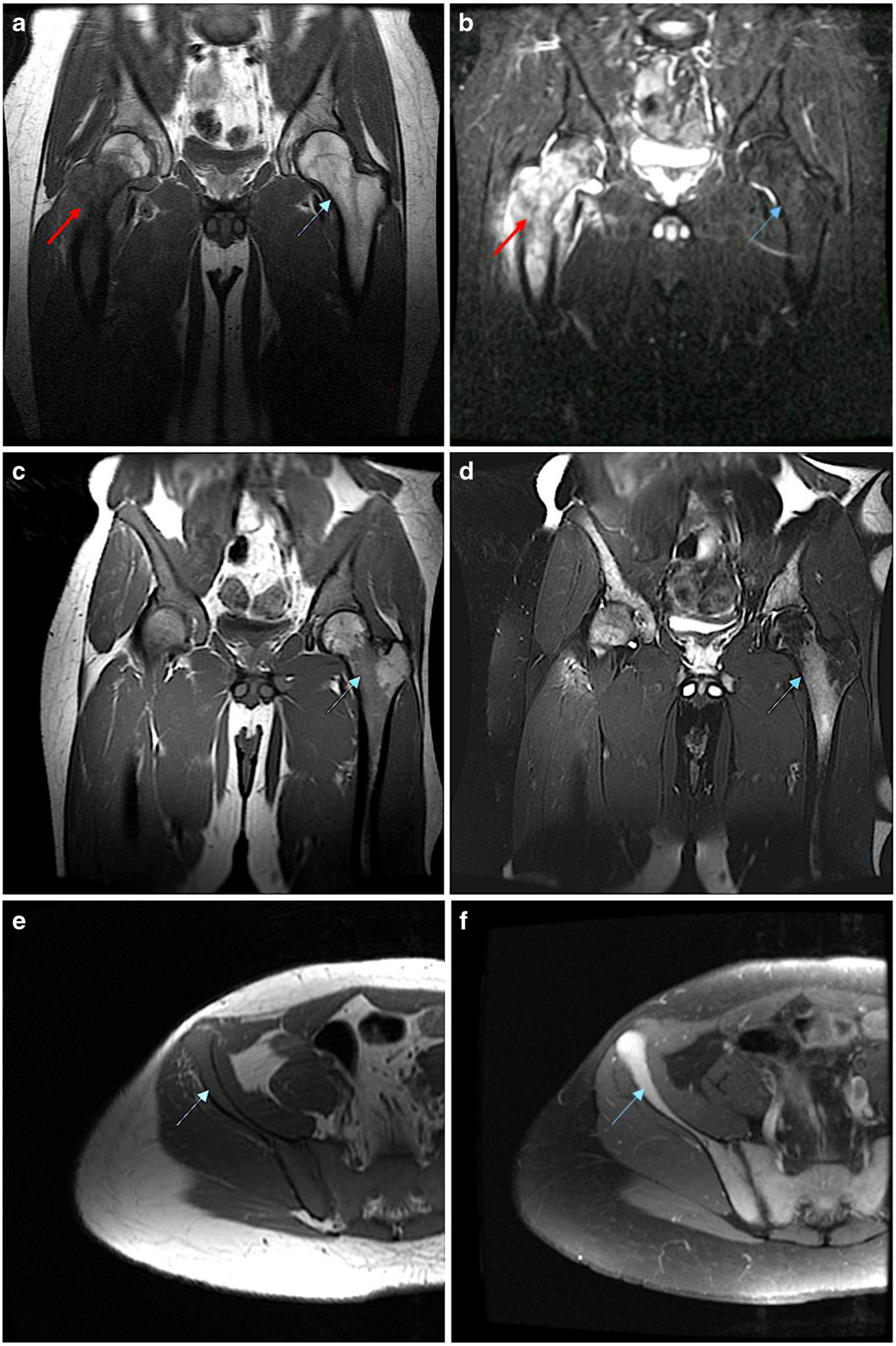


Fig. 5 (continued)

MRI contrast agent may have a role in differentiating between infiltration and reconstitution in patients with hypercellular marrow [27]. Reticuloendothelial (RES) cells are phagocytic cells located in the reticular connective tissue in bones. Infiltrative processes of the marrow deplete the RES cells, while G-CSF induces growth of all cell lines, including RES cells [28]. USPIO particles are electively phagocytosed by the RES cells in normal marrow. Thus, normal marrow reconversion demonstrates a USPIO-induced signal loss best visualized via T2w and STIR sequences, while neoplastic infiltrates will stay as hyperintense lesions [27].


a
b
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d
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◀ **Fig. 6** T1 coronal (**a**) and T2 (**b**) images of a 30-year-old male with Ewing sarcoma of the right femur before initiating chemotherapy and pegfilgrastim therapy. The right femur exhibits pathological infiltration of the marrow with decreased signal on T1 and increased on T2 consistent with patients known Ewing sarcoma (*red arrow*). The left femur exhibits baseline signal (*blue arrow*). T1 coronal (**c**) and T2 (**d**) images of the same patient 4 months after initiating chemotherapy and pegfilgrastim therapy. Areas of decreased signal on T1 and increased signal (*blue arrow*) on T2 of the femur, which corresponds to reconversion, can be observed. Compared with the previous patient, the reconversion signal is homogenous in appearance. T1 axial (**e**) and T2 axial (**f**) images of the same patient 4 months after initiating chemotherapy and pegfilgrastim therapy. The iliac wing is diffusely hypointense on T1 and hyperintense on T2 (*blue arrow*), corresponding to reconversion. Again, the reconversion signal is homogenous in appearance

Conclusions

The line between benign reconversion secondary to pegfilgrastim therapy and pathological marrow lesions can be easily blurred. Furthermore, most clinicians and/or radiology requisitions do not provide information as to specific therapy or drug exposure, which may hinder accurate interpretation. However, having access to the patient's baseline marrow MRI and correlating it with the course of pegfilgrastim therapy may clarify the diagnosis. Moreover, assessing for the location and pattern of bone pain and/or peripheral white blood cell elevations may provide additional insight. The distinction between marrow pathology and marrow reconversion secondary to pegfilgrastim is crucial to treatment planning. MRI alone proves difficult to make the distinction, but this article also highlights the importance of using other imaging modalities, clinical information, and novel MRI contrast agents and/or parameters to aid the radiologist's differential.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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