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Granulocyte-Stimulating Factor-Induced Bone Marrow Reconversion Simulating Neuroblastoma Metastases on MRI: Case Report and Literature Review

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Granulocyte colony–stimulating factor (GCSF), often used as an adjunct to chemotherapy, can pose a dilemma in differentiating the associated bone marrow changes from metastatic disease on magnetic resonance imaging. The phenomenon has been previously reported in children undergoing treatment for primary musculoskeletal malignancies [1, 2]. We present a case of GCSF-induced marrow reconversion simulating neuroblastoma metastases on MR imaging. An interesting observation in our case was intense abnormal signal in a pattern of metaphyseal bands, which, to our knowledge, was not previously reported in the English literature to be associated with GCSF-induced marrow reconversion.

Case Report

A 5-year-old boy presented with a six month history of neuroblastoma, primary to the adrenal gland and metastatic to the distal femora with a positive bone marrow aspirate. He originally received multi-agent chemotherapy and underwent resection of the primary adrenal mass after achieving bone marrow remission.

At our institution, the patient received two courses of high-dose chemotherapy over two months. Neupogen, a granulocyte colony-stimulating factor, was administered with the myelosuppressive chemotherapy. The pre-treatment MR imaging of the lower extremities demonstrated two known, treated metastatic lesions located in the distal aspects of the left femoral diametaphysis and right femoral metaphysis (Fig. 1).

Three weeks following the initiation of chemotherapy, MRI of the lower extremities was repeated (Fig. 2). The two known, treated femoral lesions were essentially unchanged, although the patient developed diffuse, abnormal patchy signal within the bone marrow, especially within the femoral metaphyses. This abnormal signal was most pronounced in a pattern of metaphyseal bands. The abnormal marrow signal was hyperintense on fluid sensitive sequences, hypointense on T1W sequences, and showed mild enhancement on the post-contrast sequences. The findings were initially worrisome for disseminated metastatic disease, although marrow reconversion was the favored etiology given the patients recent Neupogen therapy and the dramatic increase in peripheral white blood cell count to 17,200/uL from the pretreatment level of 5,700/uL. Furthermore, the patient showed no clinical evidence of disseminated disease. Nonetheless, short term follow-up MRI was recommended.

MRI was repeated three weeks later, or six weeks post initiation of chemotherapy (Fig. 3). The abnormal marrow signal persisted, although the signal intensity dramatically decreased. The fact that the patient had not received additional chemotherapy lent further support for marrow reconversion. One week later, I131-MIBG scan showed no evidence of recurrent or active metastatic disease (Fig. 4).

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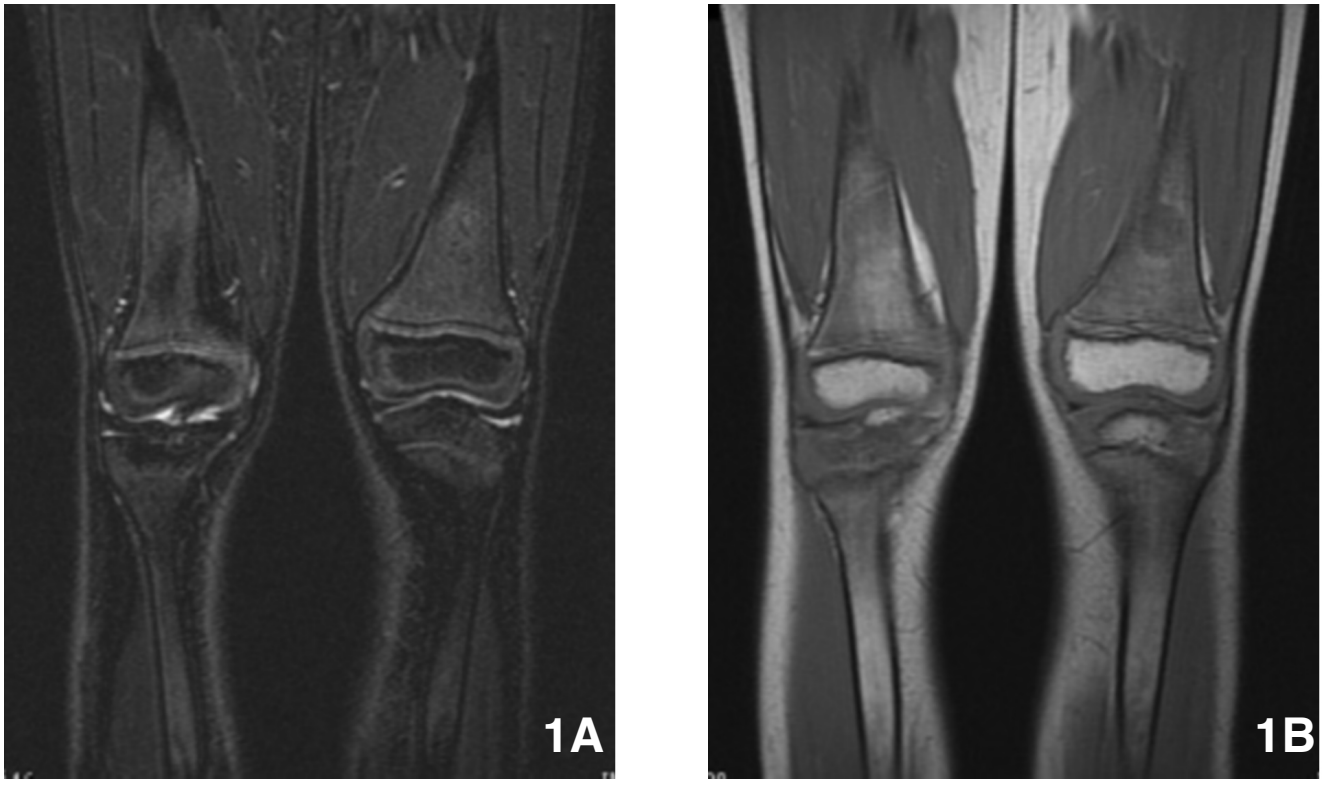


Figure 1. Initial study. **1A.** Coronal STIR (TR 2700, TE 73) MR image shows a focal lesion in the distal left femoral diametaphysis showing minimally increased signal, consistent with a treated neuroblastoma metastasis. **1B**. Coronal T1 (TR 600, TE 8) MR image better depicts the intermediate-low signal treated lesion, as well as an additional, barely conspicuous lesion in the distal right femoral metaphysis.

At outside institutions, eventual F18-FDG PET scan (not shown) and bone marrow aspiration demonstrated no evidence of active disease.

Discussion

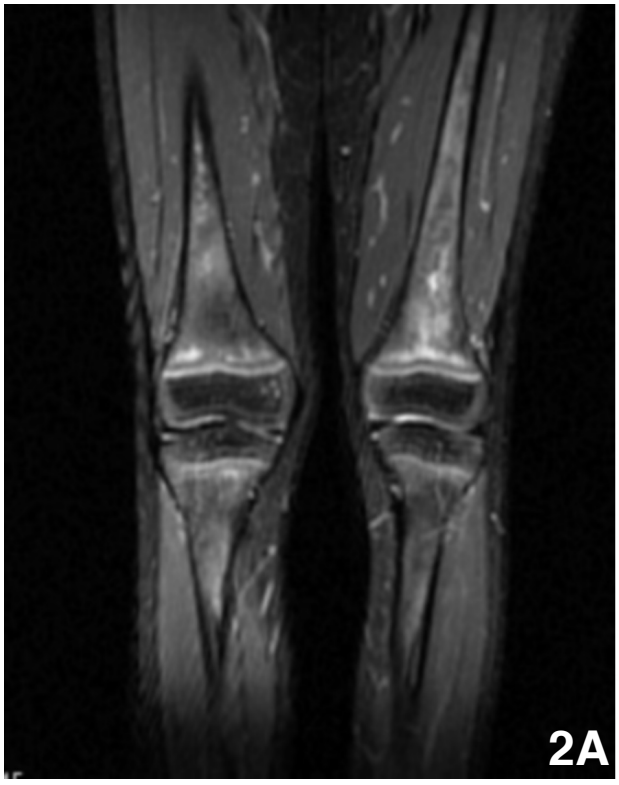
Hematopoietic growth factors are marrow regulators which support proliferation and differentiation of blood cells of different lineages [10-11]. Recombinant granulocyte colony-stimulating factor (GCSF) (Neupogen, Amgen) is frequently used as an adjunct to chemotherapy, especially when administered in high doses, in order to stimulate the marrow to produce more white blood cells, therefore counteracting the myelosuppressive effects [1-4].

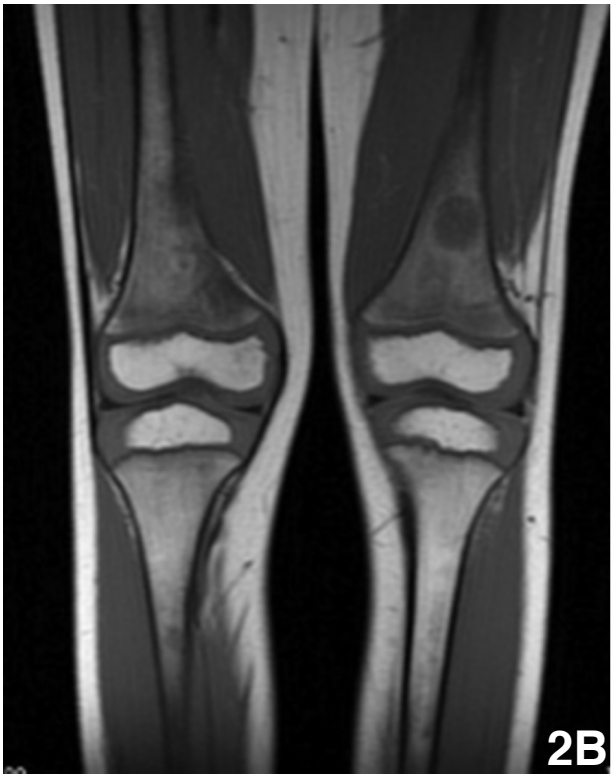
Magnetic resonance (MR) imaging has been shown to demonstrate bone marrow signal changes related to the reconversion from fatty to hematopoietic marrow induced by GCSF. In children, marrow reconversion is usually limited to the extremities due to the normal progression of conversion of red to fatty marrow starting in the epiphyses and extending into the metaphyses and then diaphyses over approximately two decades. GCSF-induced marrow signal changes are nonspecific, characterized by decreased signal on T1W and increased signal on fluid-sensitive sequences in regions with previously demonstrated normal yellow marrow [4-9]. MR is typically used to follow the response to chemotherapy for many musculoskeletal tumors, and such bone marrow signal changes may be difficult to differentiate from recurrent or metastatic disease [5, 9, 12-13]. Nonetheless, certain observations may aid in this differentiation.

Alterations in marrow signal on MR imaging related to GCSF therapy have been shown to coincide with elevations in the peripheral white blood cell count [1-3]. This was demonstrated in our case, with the initial MR marrow signal changes appearing with a substantial increased in the peripheral leukocyte count. Subsequent imaging revealed decreased marrow signal abnormalities coinciding with normalization of the leukocyte count. There is paucity of information in the literature regarding the persistence of abnormal marrow signal related to GCSF therapy.

Noting the time interval between initiation of therapy and onset of MR marrow signal changes may lend support for GCSF effects. Fletcher et al demonstrated a median of 16 days between initiation of GCSF therapy and development of MRI marrow signal alterations [1]. In our case, such MRI findings were observed three weeks after the initiation of therapy.

Bone marrow reconversion often exhibits the typical pattern of diffusely increased skeletal radiotracer uptake on Tc99m-MAA and FDG-PET scanning [3]. Furthermore, lower standard uptake values (SUV) favor red marrow reconversion over tumor. Seven weeks after initiation of





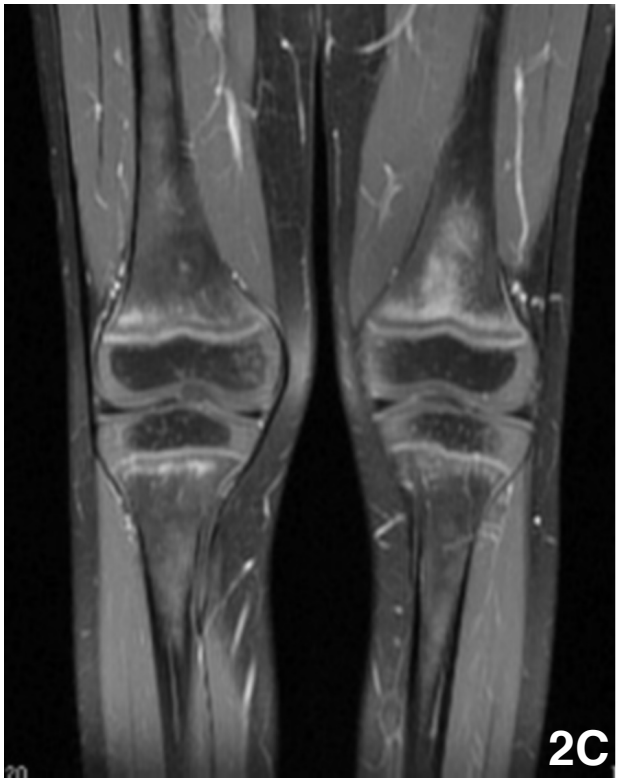
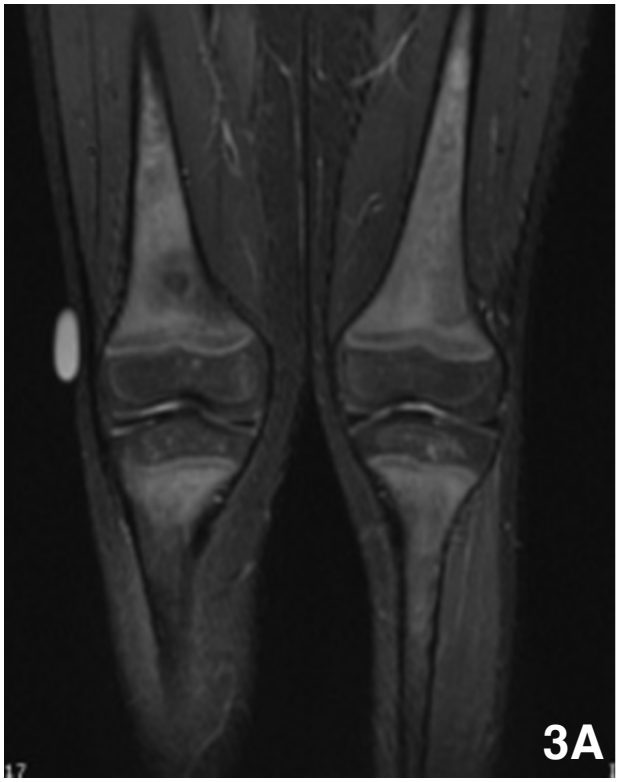
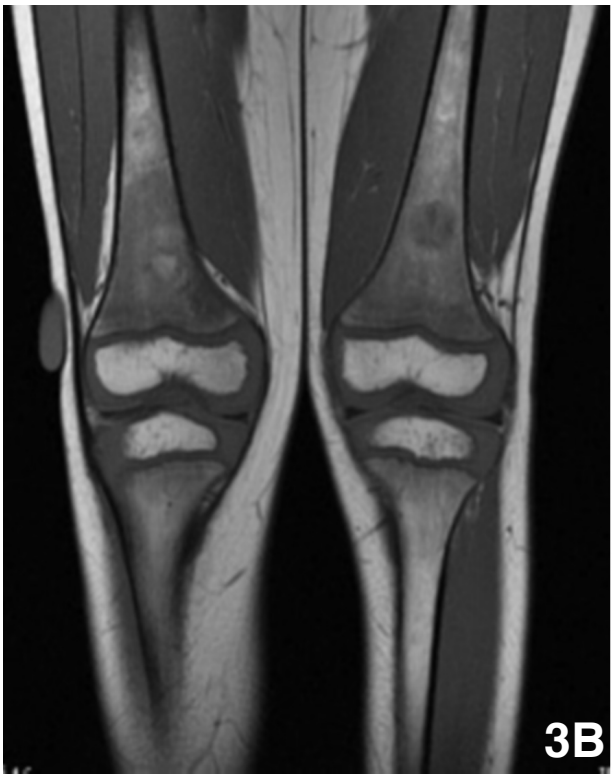


Figure 2A. Coronal STIR (TR 3900, TE 44) MR image demonstrates the known, treated femoral lesions as well as new abnormal patchy hyperintense signal within the distal femora and proximal tibiae, especially along the physes.
2B. Coronal T1 (TR 550, TE 11) MR image shows corresponding patchy decreased marrow signal.
2C. Coronal T1 with fat saturation (TR 717, TE 11) post contrast MR image demonstrates corresponding mild patchy marrow enhancement.





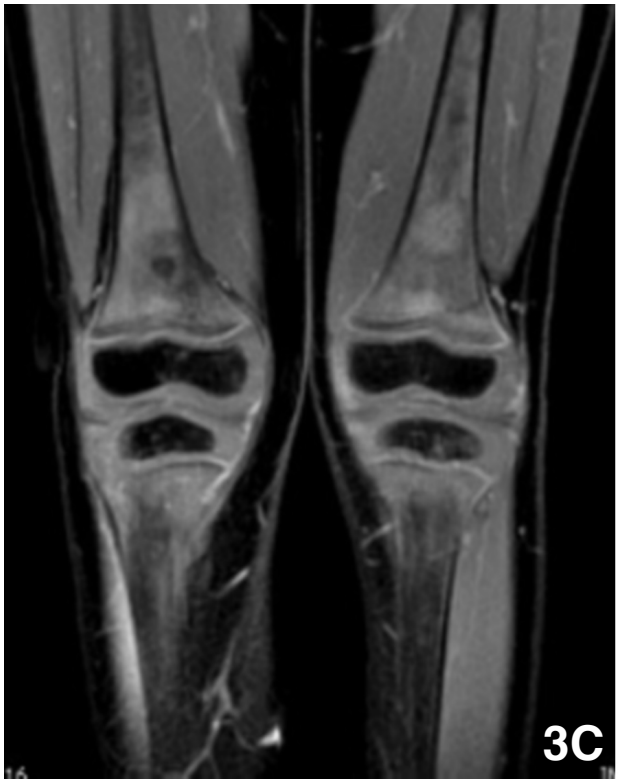


Figure 3A. Coronal STIR (TR 4500, TE 40) MR image shows decreased patchy abnormal marrow signal in the distal femora and proximal tibiae.
B. Coronal T1 (TR 550, 8TE) demonstrates corresponding interval decrease in patchy low marrow signal.
C. Coronal T1 with fat saturation (TR 145, TE 3) post contrast reveals the corresponding, very mild enhancement.

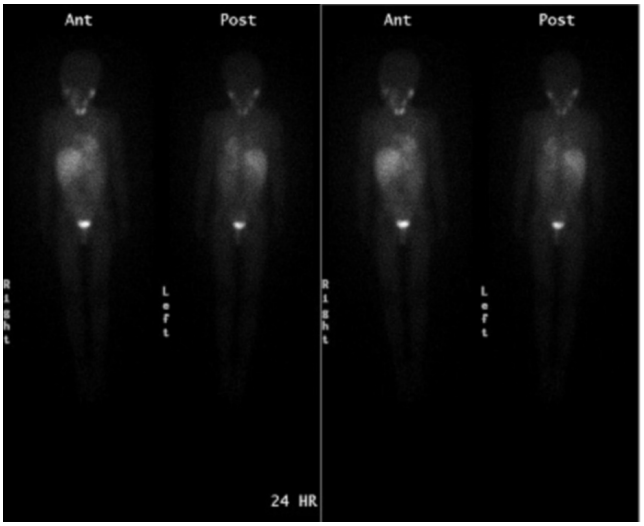


Figure 4. I131-mIBG scan shows no abnormal radiotracer uptake to suggest metastatic disease.

GCSF therapy, our patient underwent I131-mIBG scan which showed no evidence of metastatic neuroblastoma. The subsequent F18-FDG PET scan also showed no active metastases.

Although disseminated osseous metastatic disease may demonstrate diffuse marrow signal changes on MRI and increased radiotracer uptake on scintigraphic studies, clinical signs of such progressive disease would also be expected. Clinical observations coincided with imaging findings, as our patient continued to show no signs of disseminated disease

Histologic confirmation is usually not necessary if typical imaging and clinical findings argue against the presence of metastatic disease. Despite strong supporting evidence, our patient eventually underwent bone marrow aspiration, which was negative and affirmed our conclusion.

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