Pediatr Radiol (2012) 42:1218–1222
DOI 10.1007/s00247-012-2440-0

ORIGINAL ARTICLE

Marrow signal changes observed in follow-up whole-body MRI studies in children and young adults with neurofibromatosis type 1 treated with imatinib mesylate (Gleevec) for plexiform neurofibromas

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Received: 8 March 2012 / Revised: 8 May 2012 / Accepted: 16 May 2012 / Published online: 22 June 2012

Abstract
Background We observed bone marrow signal changes (BMSC) in patients with plexiform neurofibromas after treatment with imatinib mesylate (Gleevec).
Objective To evaluate the pattern and natural history of BMSC.
Materials and methods The data were obtained from a pilot study of imatinib mesylate in patients with plexiform neurofibromas. All patients underwent baseline and sequential whole-body STIR 1.5-T MRI after treatment. The bone marrow signal on MRI was evaluated for abnormalities, location and pattern, and any change on follow-up studies.
Results The study group included 16 patients (8 males) with a median age of 14 years (range 4 to 25 years). The mean whole-body MRI follow-up duration was 1.9 years. Of the 16 patients, 14 (88%) developed BMSC. The signal change was asymmetrical in 9 of the 14 patients (64%). The appendicular skeleton was involved in all 14 patients and the axial skeleton in 3 patients (21%). BMSC was followed in 13 patients and decreased signal was seen in 9 patients (69%) after a mean duration of 1.3 years of treatment (range 0.6 to 2.9 years); no complications were observed.
Conclusion BMSC appeared in most patients with neurofibromatosis type 1 following treatment with imatinib mesylate. BMSC was unusually asymmetrical and involved the lower extremities. On follow-up, BMSC often showed a decrease without complications.

Keywords Plexiform neurofibromatosis · MRI · Bone marrow

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Introduction

Imatinib mesylate (Gleevec; Novartis, East Hanover, NJ) represents a new generation of chemotherapy-specific drugs that were developed for the treatment of chronic myeloid leukemia (CML) [1]. Imatinib mesylate selectively inhibits tyrosine kinase and was later found to inhibit other targets. It was tried for the treatment of various tumors and found useful in advanced gastrointestinal stromal tumors because of its action in inhibiting of *c*-kit proto-oncogene [2].

Plexiform neurofibroma (PNF) is one of the major features of neurofibromatosis type 1 (NF1) [3]. It can cause substantial morbidity, disfigurement and functional impairment, and can transform into a malignant peripheral nerve sheath tumor, a complication that is refractory to treatment [4, 5]. Studies in a mouse model have demonstrated that imatinib mesylate can decrease the size of PNF by a direct effect on the neurofibroma cells by inhibiting platelet-derived growth factor receptors (PDGFR) α and β [6] and indirectly by inhibiting *c*-kit in mast cells that promote tumor production of Schwann cells [7]. Based on the results in the mouse model, imatinib mesylate was administrated to a critically ill 3-year-old child with

PNF compressing her airway and resulted in a marked decrease in tumor size [7].

To evaluate the efficacy of imatinib mesylate in patients with NF1 and PNF, we participated in a pilot study of imatinib mesylate therapy. Patients in our pilot study underwent whole-body MRI. We noted abnormal signal in the bone marrow of our patients after the start of treatment with imatinib mesylate. Fluid retention is a common side effect of imatinib mesylate [8–12]. We believe our finding of abnormal marrow signal is due to localized bone marrow edema. This is a unique finding.

The purpose of our study was to investigate the frequency, distribution and time relationship of the MR appearance of bone marrow signal changes (BMSC) in relation to imatinib mesylate administration in patients with NF1.

Materials and methods

This review was approved by the Institutional Review Board of our institution. As part of a pilot study to evaluate the use of imatinib mesylate to treat patients with NF1 and PNF, patients underwent repeated MRI examinations. As some patients with NF1 have multiple sites of PNF, whole-body MRI was performed. A baseline examination was performed before the start of the treatment. Additional studies were done after 2, 6 and 12 months, and then annually while on therapy. All patients met clinical diagnostic criteria for NF1. Only patients with a biopsy-proven PNF that was potentially life-threatening or with significantly impaired quality of life were included. All patients had at least one follow-up study. All MRI examinations were performed with a 1.5-T MAGNETOM Avanto (Siemens Medical Solutions, Erlangen, Germany) using only a STIR sequence in the coronal, sagittal and axial planes (159×512, time to recover 3,000 ms, time to echo 17 ms, time to inversion 150 ms).

Using a Synapse workstation (Fujifilm, Stamford, CT), two fellowship-trained pediatric radiologists with 14 years and 31 years of experience retrospectively reviewed in consensus the examinations for each patient in order of acquisition. All the examinations obtained after starting treatment were compared to the pretreatment baseline studies for the presence of any new posttreatment bone marrow bright signal. The affected bone was recorded. The BMSC was classified as either focal (if it was well-defined) or diffuse (if it was widespread in the bone marrow). For each patient, the location of BMSC was classified as symmetrical or asymmetrical, and the amount of BMSC between studies was categorized as stable, decreased, increased or variable (some BMSC decreased and some increased).

Medical records were reviewed for change in treatment with imatinib mesylate and the presence of cutaneous edema was identified on physical examination.

Table 1 BMSC in 16 patients (age ≤25 years) after treatment with imatinib mesylate

Patient number	Age (years)	Gender	MRI follow-up (years)[a]		Pattern of signal change		Distribution of the signal changes					Interval change
			Start of treatment	End of treatment	Focal	Diffuse	Epiphysis	Symmetrical	Upper extremity	Lower extremity	Axial skeleton	
1	7.5	Male	2.9	1.0	No	Yes	No	Yes	No	Yes	No	Decreased
2	9.1	Male	1.9	No	Yes	Yes	No	No	Yes	Yes	No	Variable[b]
3	4.1	Female	2.6	1.1	No	Yes	No	Yes	Yes	Yes	No	Decreased
4	22.3	Female	1.5	No	No	No	No	–	No	No	No	No abnormality
5	14.3	Female	2.0	No	Yes	Yes	No	No	Yes	Yes	Yes	Increased
6	4.0	Female	3.2	No	No	Yes	No	Yes	Yes	Yes	Yes	Stable
7	11.0	Male	1.5	No	Yes	No	Yes	No	Yes	Yes	No	Variable[b]
8	15.2	Female	1.1	No	Yes	No	No	No	No	Yes	No	Resolved
9	11.9	Male	0.9	No	Yes	Yes	No	No	Yes	Yes	No	Variable[b]
10	10.5	Male	1.9	No	Yes	No	Yes	No	No	Yes	No	Resolved
11	13.6	Male	3.0	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Resolved
12	16.9	Female	2.5	1.1	Yes	Yes	No	No	No	Yes	No	Resolved
13	25.0	Male	1.0	No	No	Yes	No	No	No	Yes	No	No follow-up
14	20.0	Male	2.1	No	No	Yes	No	Yes	Yes	Yes	No	Decreased
15	22.1	Female	2.3	0.2	Yes	Yes	No	No	Yes	Yes	No	Resolved
16	20.8	Female	0.4	No	No	No	No	–	No	No	No	No abnormality

[a] Time between the last follow-up MRI scan and the start of treatment and end of treatment with imatinib mesylate.

[b] The signal showed an increase in some areas but a decrease in other areas.

Results

We identified 16 patients (8 males) with a median age of 14 years (range 4 to 25 years). Treatment with imatinib mesylate was completed in 15 patients with an average treatment period of 1.7 years (range 0.6 to 3.0 years). One patient (patient 6) was still receiving treatment when the imaging findings were reviewed. The average length of whole-body MRI follow-up was 1.9 years (range 0.4 to 3.2 years). Only four patients (patients 1, 3, 12 and 15) had follow-up (average 0.9 years, range 0.2 to 1.1 years) MRI studies after completion of treatment.

The imaging findings are summarized in Table 1. Of the 16 patients, 14 (88%) developed BMSC. BMSC was asymmetrical in 9 of the 14 patients (64%) and symmetrical in the other 5 (36%). The appendicular skeleton was involved in all 14 patients, while the axial skeleton was involved in only three patients (21%). The pattern of BMSC was diffuse in six patients (Fig. 1), focal in three (Fig. 2) and mixed in five. In three patients, BMSC involved the epiphysis (Fig. 3).

BMSC was first demonstrated, on average, after 0.5 years (range 0.2 to 1.4 years). Follow-up MRI studies were performed in 13 patients after the first appearance of BMSC. It decreased in 9 of the 13 patients (69%) after a mean period of 1.3 years (range 0.6 to 2.9 years) without any observed complications. BMSC decreased first after completion of treatment in only one patient (patient 1). In all other eight patients, BMSC decreased during treatment. In five patients (patients 8, 10, 11, 12 and 15), BMSC resolved completely. In one patient (patient 1), resolution of BMSC in the bilateral femurs was observed on a follow-up study 1.0 years after completion of treatment. The tibiae were not imaged in that study. In one patient (patient 14), BMSC resolved

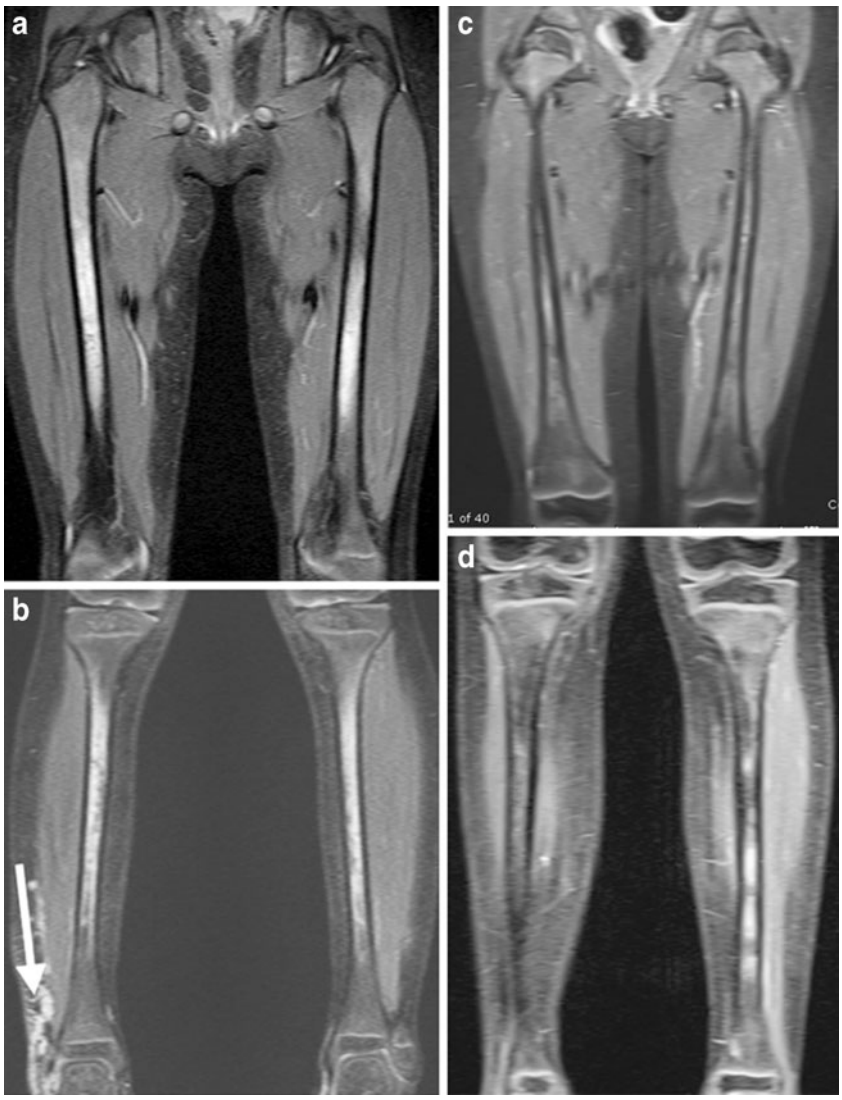

Fig. 1 A 4-year-old girl (patient 3) with NF1 and PNF who developed diffuse BMSC after treatment with imatinib mesylate. BMSC resolved after discontinuation of treatment. Coronal STIR images of the legs 2 months after treatment with imatinib mesylate demonstrate diffuse bone marrow edema in the femurs (**a**) and tibias (**b**). There is a right distal leg PNF (**b**, *arrow*). The BMSC had resolved in the femurs (**c**) and markedly decreased in the tibias (**d**) 1 year later

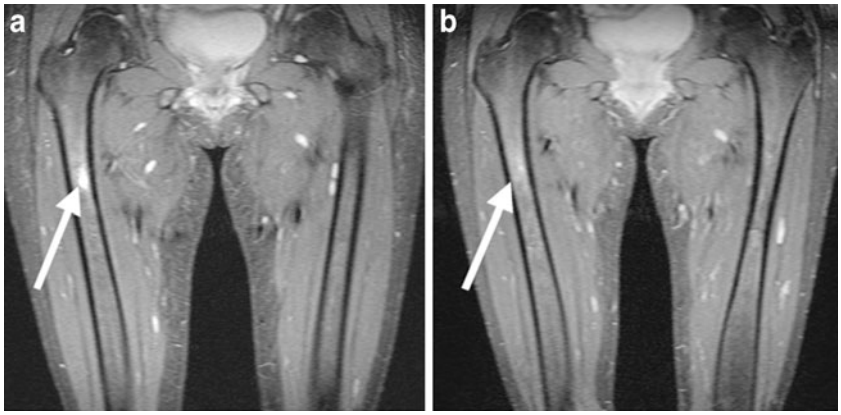

Fig. 2 A 17-year-old girl (patient 12) with NF1 and PNF who developed focal BMSC after treatment with imatinib mesylate. Coronal STIR MR images of the femurs demonstrate focal bright signal in the proximal right femur (**a**, *arrow*) 2 months after treatment, which had nearly resolved 1 year later (**b**, *arrow*)

completely in the upper extremities with residual bright signal in the lower extremities. During treatment, one patient (patient 5) had increased BMSC and two others (patients 2 and 9) had variable changes in BMSC. These three patients had a mean follow-up of 1.6 years (range 0.9 to 2 years). Five of the 14 patients who developed BMSC (36%) had edema at other sites, including the face (three patients), soft tissue of the lower extremities (one patient), and both the face and lower extremities (one patient). The dose of imatinib mesylate was decreased prior to the 2-month follow-up MRI scan in each of these five patients.

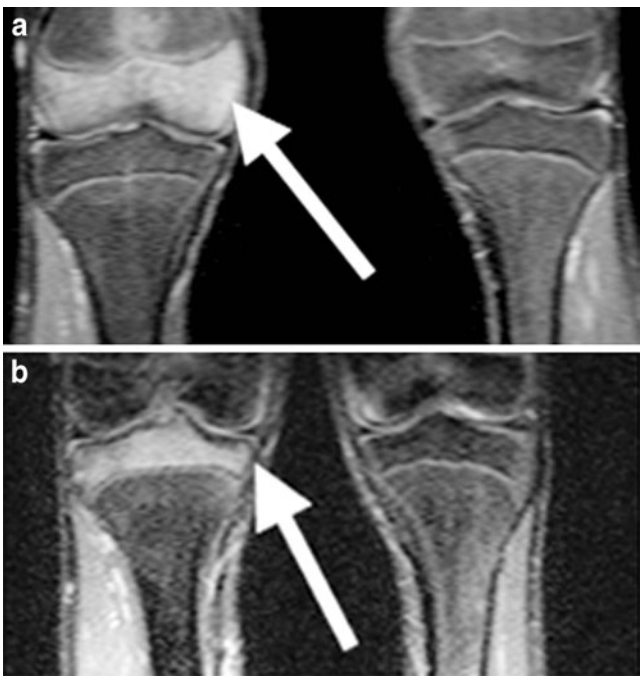

Fig. 3 An 11-year-old boy (patient 7) with NF1 and PNF treated with imatinib mesylate who developed migratory epiphyseal edema. Coronal STIR MR image of the legs 8 months after treatment demonstrates distal right femoral diffuse epiphyseal BMSC (**a**, *arrow*). The BMSC had resolved and new epiphyseal BMSC had developed in the proximal right tibia 4 months later (**b**, *arrow*)

Discussion

The purpose of this study was to summarize the MRI findings in patients with NF1 and PNF who developed bone marrow edema during treatment with imatinib mesylate. Bone marrow changes have been reported in two other patients treated with imatinib for gastrointestinal stromal tumors [13]. We therefore believe that this marrow change is probably not unique to patients with NF1. The reason that it has been reported previously in only two patients is that whole-body MRI studies are not typically performed in patients with CML or gastrointestinal stromal tumor, which are the most common indications for treatment with imatinib mesylate. In patients with CML, BMSC may mimic recurrence of disease.

We found BMSC in almost all patients (88%) treated with imatinib mesylate. Follow-up MRI studies demonstrated a decrease in BMSC in most patients (69%). The decrease in BMSC was observed from 0.6 to 2.9 years after treatment and it is possible that, in patients who had persistent BMSC, a longer follow-up period may have shown a decrease in BMSC. It was usually (in 64% of patients) asymmetrical and involved the appendicular skeleton in all patients. BMSC was diffuse or focal and mainly involved the diaphysis and metaphysis of the long bones, but seldom involved the epiphysis.

The pathogenesis of BMSC is not known. Biopsy of BMSC has been reported in a patient treated with imatinib mesylate for gastrointestinal stromal tumor. Pathology demonstrated cell necrosis [13]. There is also a case report of massive bone marrow necrosis in a patient treated with imatinib mesylate for CML [14]. Bone marrow changes on MRI were not reported in that patient. Our study has the advantage of follow-up studies. None of the patients in our study developed typical MRI features of bone infarct. Imatinib mesylate can change bone mineralization metabolism [15]. Osteoporosis resulting from these changes can be associated with BMSC. Another possibility is that BMSC represents bone marrow edema. The signal characteristics,

time-course of the BMSC, lack of local bone symptoms and lack of long-term complications are highly suggestive that the abnormal MRI signal is due to edema. In addition, fluid retention is a common complication of treatment with imatinib mesylate [8–12].

Cutaneous edema is one of the most common side effects of treatment with imatinib mesylate and has been reported in up to 65% of patients [8–11]. Other forms of fluid retention included ascites, pleural effusion and pericardial effusion [12]. The development of edema is dose-related [11], but the pathophysiology of edema is unclear. As this is a dose-related effect, it may be related to a pharmacological effect of imatinib mesylate rather than hypersensitivity. One possible mechanism is related to the drug's inhibition of PDGFR, which has been shown to increase interstitial fluid pressure in the dermis of rodents [16]. The inhibition of PDGFR by imatinib mesylate may result in increased capillary permeability and extravasation of fluid [11, 16].

After its initial appearance, we noted a decrease in BMSC on further follow-up MRI studies in 69% of our patients, without any observed complications. One-third of our patients also had cutaneous edema, most commonly involving the face. We did not note an association between location and severity of cutaneous edema and BMSC.

There are several limitations to the study. One of the major limitations is the lack of pathological confirmation of BMSC. This was not needed, as patients did not have any symptoms or complications from the abnormal marrow signal. In addition, the study was reviewed in consensus and therefore there are no result of interobserver variability. However, this is justified as our study was a pilot study and a report of a new observation [17].

Conclusion

We found that BMSC commonly occurs in patients with NF1 treated with imatinib mesylate. The pathogenesis of BMSC is not clear. BMSC is usually asymmetrical, involves the appendicular skeleton and is often decreased or disappears without complications during treatment. Recognition of the frequent asymptomatic occurrence of BMSC should prevent erroneous diagnoses such as infection or tumor infiltration of the marrow.

Conflicts of interest We have no conflicts of interest to declare.

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