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Case Report

Reversal of skeletal radiographic pathology in a case of malignant infantile osteopetrosis following hematopoietic stem cell transplantation

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ABSTRACT

Malignant infantile autosomal recessive osteopetrosis (ARO) is rare hereditable skeletal dysplasia characterized by a generalized osteosclerosis. ARO usually runs a fatal course in early childhood if untreated. Serious complications can arise from bone marrow suppression and pancytopenia. Hematopoietic stem cell transplantation (HSCT) is the only available treatment option that has been demonstrated to prolong life expectancy. Few publications with limited study participants have explored the employment of skeletal radiography to evaluate success of HSCT. We assessed the role of skeletal radiography as a tool to evaluate responsiveness to HSCT in a case of ARO with favorable short-term results.

1. Introduction

Malignant infantile autosomal recessive osteopetrosis (ARO) is a rare type of skeletal dysplasia characterized by a distinct radiographic pattern of generalized increase in bone density [1]. The reported incidence of ARO is 1 in 250,000 births [2]. Autosomal recessive osteopetrosis typically manifests in infancy. In general the prognosis is poor. It usually proves fatal in early childhood if untreated [2]. The most significant complications are related to the bone marrow suppression and bone expansion with subsequent cranial nerve compression [2]. Experimental and clinical research on stem cells has provided insights into regenerative medicine in general [3–7]. It has also suggested future avenues of research for the clinical applications of musculoskeletal tissue engineering. Such clinical applications may ameliorate the adverse impact of some skeletal disorders and offer a potential cure [8–11]. Hematopoietic stem cell transplantation (HSCT) offers a satisfactory treatment modality for a considerable percentage of ARO. Hematopoietic stem cell transplantation may affect disease outcome positively. It may arrest visual impairment and reverse hematopoietic and bone manifestations, especially if instituted in the first few months of life [2,12,13]. Studies that report skeletal radiographic response to HSCT in ARO are few with limited number of participants [13–15]. Amelioration of radiographic bone lesions after HSCT in ARO have been proposed to be important indicators of success of HSCT [13–15]. Nevertheless the detailing of these bony abnormalities and their precise response to HSCT in ARO has been reported only once [13]. The purpose of this study is to monitor the responsiveness of skeletal radiographic pathology to HSCT in a case of ARO on the short-term.

2. Case

An 18-months-old boy was brought to our outpatient clinic with complains of delayed milestones. He was first in order to a first cousin parents. Birth and family history were unremarkable. Clinical

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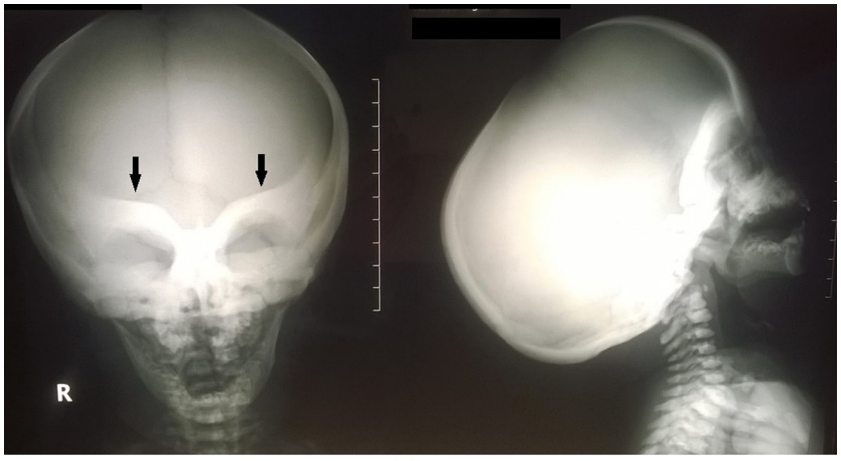
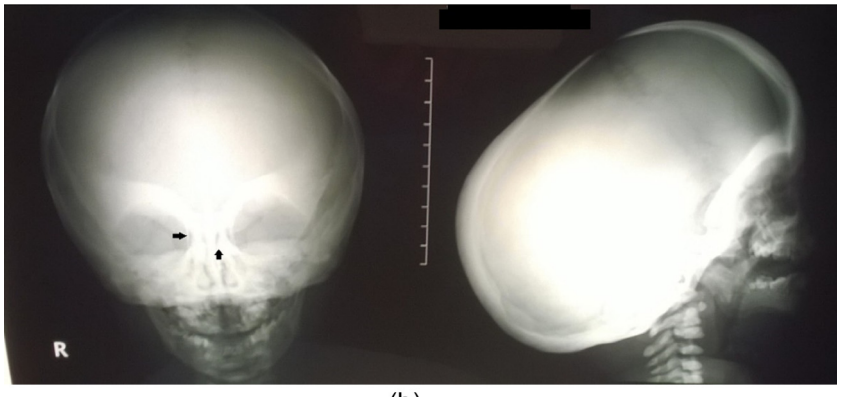
examination revealed macrocephaly with opened anterior fontanel, frontal bossing, nystagmus of left eye and retromicrognathia, near normal stature and proportions and abnormal dentition. He had small chest cavity with ptosed liver and mildly enlarged spleen with no focal lesions on ultrasonography. The blood picture revealed moderate anemia. The whole-body skeletal radiographic survey revealed the characteristic pattern of generalized increase in bone density associated with ARO. The patient was labelled as having ARO based on the classic history, clinical examination, and skeletal radiographic findings. Molecular analysis was not performed due to constrained resources.

The patient received HSCT at two years of age. The graft was prepared by deriving stem cells from the bone marrow of the healthy HLA identical mother. He received Busulfan and long courses of cyclophosphamide conditioning regimen. He received his stem cells through a Hikman central line. He received cyclosporine A and methotrexate for graft-versus-host disease prophylaxis. He had an uneventful post-transplant period with prompt engraftment after 27 days. To assess the hematopoietic performance the patient was evaluated clinically and biochemically at regular follow-up intervals. At one-year follow- up the patient's motor milestones normalized but he developed a proportionate short stature with remarkable dolichocephaly. Dentition abnormalities and anemia persisted. No functional limitations or recurrent infections were encountered. To characterize the radiologic response to HSCT we conducted a radiographic examination of the skull, spine, pelvis and whole appendicular skeleton at one-year follow-up. We analyzed the following features; bone-within-bone appearance and homogeneity of the medullary bone, corticomedullary differentiation, diaphyseal metaphyseal modelling of the metaphyseal ends of long bones especially distal femora, proximal tibias and humeri, increased density of skull base and periorbital bones and pathologic fractures (Figs. 1–5). All radiographic bone abnormalities showed complete resolution with few exceptions. The bone-within-bone appearance of the pelvis showed partial resolution while it persisted in the spine. The skull base and periorbital sclerosis persisted. The resolution of bone changes was highly bilateral and symmetrical. We detected a greenstick fracture of the distal right radius that healed following HSCT. We encountered no rachitic-like changes or signs suggestive of osteomyelitis. The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki



(a)



(b)

Fig. 1. Skull radiographs. **a**. Pre HSCT demonstrating an overall increased density of the bones of skull base and periorbital bones *(arrows)* with fundamental involvement of the medullary portion. **b**. One-year post HSCT radiographs demonstrating increased anteroposterior diameter of skull and macrocephaly. Note persistence of diffuse bone sclerosis except for small streaks of hypodense bone *(arrows)*.