

Skeletal radiology following hematopoietic stem cell transplantation in infantile osteopetrosis: an overlooked assessment tool

Radiología esquelética posterior al trasplante de células madre hematopoyéticas en la osteopetrosis infantil: una herramienta de evaluación desestimada

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Respected editor,

We read with considerable interest the latest article published in your journal by Gaytán-Morales et al¹. The genetic-skeletal diagnosis and management of a child with malignant infantile osteopetrosis were presented in a systematic and comprehensive manner¹. The authors' reported outcome was satisfactory regarding the prevention of development of disease-related complications, the unremarkable course of allogeneic hematopoietic stem cell transplantation (HSCT), and the resolution of radiological skeletal abnormalities¹. This study underscores the importance of both early diagnosis and multidisciplinary approach for management, which is especially relevant for rare diseases like malignant infantile osteopetrosis that usually has a fatal course in case of no or delayed treatment. HSCT has been successfully used to treat various genetic skeletal dysplasias as mucopolysaccharidosis, especially type IH, and malignant infantile osteopetrosis². However, treatment's success depends on several factors, age being the most important, and disease severity at the time of diagnosis, as well as the treatment². The presence of other bone therapeutic modalities to

treat genetic skeletal dysplasia further highlights the importance of early diagnosis of rare diseases^{2,3}; the potential health economic burden of managing the disease-related complications of osteopetrosis as repeated infections and hospitalizations and occurrence of pathological fractures prompts early diagnosis and referral to a specialized center⁴. Noteworthy, the surgical management of pathological fractures in osteopetrosis is problematic concerning extended healing time and higher risk of infection regardless of osteopetrosis subtype⁴.

Unsurprisingly, most physicians tend to be unaware of the specific diagnostic features of rare diseases, including malignant infantile osteopetrosis. This unawareness can increase the incidence of misdiagnosis and the subsequent disease morbidity and mortality with delayed referral to a tertiary or disease specialized center. The fact that a considerable percentage of genetic skeletal dysplasias, including infantile forms of osteopetrosis, are not readily recognizable at birth compounds the diagnostic challenges. Additionally, patients with malignant infantile osteopetrosis may present with non-specific infections like

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Date of reception: 20-03-2021

Date of acceptance: 09-04-2021

DOI: 10.24875/BMHIM.21000048

Available online: 27-07-2021

Bol Med Hosp Infant Mex. 2021;78(5):495-496

www.bmhim.com

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community-acquired pneumonia, among others¹. Despite the advances of genetic testing and imaging modalities, attention to basic clinical and plain radiographic correlations remains the cornerstone of diagnosis of genetic skeletal dysplasias⁵.

The reporting of rare cases¹ in the literature is important because it expands the disease phenotype-genotype correlations, further elaborates on the clinical and pathological responsiveness to HSCT in the various subtypes of malignant infantile osteopetrosis, and thus provides information for decision making. Although the article demonstrated the positive radiographic skeletal response of the skull following HSCT, the axial and appendicular skeleton response was not reported. This point may be worthy to be investigated by the authors¹ in an upcoming study, especially when their patient has been followed up for roughly three years. Most of the literature on HSCT use in malignant infantile osteopetrosis has focused on the amelioration of non-skeletal manifestations. Literature on radiologic responsiveness of skeletal abnormalities to HSCT in malignant infantile osteopetrosis included descriptive (categorical) assessment of plain radiographic assessment^{6,7}. Two recent reports used analytical methods like bone morphological analysis by densitometry⁸ and nuclear magnetic resonance imaging (MRI)⁹ to quantify the skeletal responsiveness to HSCT. Generally, the short and intermediate-term outcomes were satisfactory^{8,9}; herein, the skeletal radiologic responsiveness itself served as an outcome tool. Further studies are needed to show reliable correlations between skeletal radiologic responses to HSCT and the preoperative, genetic and transplant characteristics of the patient. For example, the studies by Shapiro et al.⁸ and Gaytán-Morales

et al.¹ both included patients with osteopetrosis secondary to mutations in *CLCN7*. It would be interesting to know how these patients with the same underlying gene involvement correlate with respect to skeletal radiologic response following HSCT and how patients with the same mutation respond. In conclusion, the hematologic—non-skeletal responses—and skeletal responses to HSCT should be researched conjointly to draw a comprehensive and accurate picture of the treatment response.

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