Destructive Juvenile Idiopathic Arthritis: don’t overlook rare genetic skeletal disorders

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We read with interest the report by Miyamae and colleagues describing severe joint damage, loss of carpal bones and foreshortened fingers in a patient diagnosed with long-standing juvenile idiopathic arthritis (JIA).[1] We would like to bring to the reader's attention that a ~~the observed~~highly similar -clinical and radiographic phenotype ~~in this patient~~ may ~~be the~~ result ~~of a~~from rare skeletal disorders characterized by osteolysis. JIA is a group of heterogenous diseases characterized by chronic arthritis leading to severe joint damage in some individuals. Diagnosis of JIA mainly relies on clinical, radiological, and laboratory findings ~~examination~~ and requires exclusion of resembling diseases. Differential diagnosis is very broad and includes well-known and common conditions (such as infections, neoplasms, systemic rheumatic diseases, inflammatory bowel diseases, vasculitides, chronic recurrent multifocal osteomyelitis, …) but also very rare genetic diseases involving the immune system (monogenic immune-mediated disorders), metabolic pathways (storage disorders),[2] or the skeleton (skeletal dysplasias).[3] Extensive osteolysis is uncommon, even in long standing JIA and should prompt the consideration of rare osteolysis syndromes in the differential diagnosis (Table 1).[2–4] These genetic disorders cause severe osteolysis (some bones literally vanish over time) that can mimic inflammation-associated changes occurring in destructive JIA. Affected individuals typically present in childhood or early adulthood with multiple joints involvement (pain, contractures and/or deformations) in association or not with other symptoms (Table 1) and display poor response ~~to~~if usual JIA therapies are attempted~~treatments~~ (although very few data on outcomes are available). Notably, osteoporosis is frequently associated and inflammatory features (such as fever) cannot alone distinguish from JIA.[2]

Although very rare, these conditions deserve to remain in the pediatric rheumatologist's mind at every step of the JIA patient's care. Indeed, failure to recognize them leads to unnecessary immune-suppressive drugs exposure, lack of specific treatment and/or monitoring, altered prognosis evaluation and missed opportunities for genetic counselling. We respectfully thank the authors for reporting this interesting case which gave us the opportunity to alert the reader for the existence of these rare osteolytic disorders. We would be interested to know whether additional (genetic) tests were performed to exclude these conditions in this patient, in particular the possibility of Farber disease given the striking clinical and radiographic resemblance to the family reported by Bonafé et al.[2]

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Disease	Gene	MOI	Pattern of osteolysis	Possible additional suggestive findings
Farber disease (Type 2-3), Acid ceramidase deficiency (OMIM #22800)	*ASAH1*	AR	Preferential involvement of carpal and tarsal bones, radius, ulna and phalanges	-Subcutaneous nodules (over pressure points) -Voice hoarseness -Pulmonary, cardiac and neurological defects
Multicentric carpotarsal osteolysis (OMIM #166300)	*MAFB*	AD	Preferential involvement of carpal and tarsal bones, relative sparing of metacarpals and phalanges	-Progressive nephropathy starting in childhood -Corneal clouding or opacities
Multicentric osteolysis, nodulosis and arthropathy, Torg-Winchester syndrome (OMIM #259600 and #277950)	*MMP2, MMP14*	AR	Preferential involvement of carpal and tarsal bones, long bones can have widened diaphyses and thin cortices	-Subcutaneous nodules (palms and soles) and pigmented lesions -Coarse facial features -Gingival hypertrophy -Cardiac defects -Corneal opacities

Table 1. Rare osteolysis syndromes affecting the carpal and tarsal bones

AD: autosomal dominant; AR: autosomal recessive; MOI: Mode of inheritance. Note that other genetic disorders with osteolysis (Familial expansile osteolysis, Progeria, Hajdu-Cheney osteolysis, mandibuloacral dysplasia, Gorham-Stout disease) are not listed in this Table since their clinical and radiographic features differ from the patient reported.

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Author's contributions

Clément Triaille: literature search, writing (original draft). Filip Vanhoenacker and Geert Mortier: supervision, validation, writing (review and editing). All authors agreed on the final version of the article.

Conflict of interest

Authors declare no competing interest.

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