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CASE REPORT

Hyaline fibromatosis syndrome (juvenile hyaline fibromatosis): whole-body MR findings in two siblings with different subcutaneous nodules distribution

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Abstract Hyaline fibromatosis syndrome (juvenile hyaline fibromatosis) is a rare, progressive, autosomal recessive disorder whose main hallmark is the deposition of amorphous hyaline material in soft tissues, with an evolutionary course and health impairment. It may present involvement of subcutaneous or periskeletal soft tissue, or may develop as a visceral infiltration entity with poor prognosis. Very few radiological data about this inherited condition have been reported, due to the extreme rarity of disease. We herein present a case of two siblings, affected by different severity of the disease, with different clinical features. They were examined by whole-body MR (WBMR) in order to assess different lesions localization, to rule out any visceral involvement and any other associated anomalies and to define patients' management.

Keywords Whole body MR · Fibromatosis · Hyaline · Juvenile

Introduction

"Hyaline fibromatosis syndrome" is the term proposed by Denadai to identify two different severity forms of the same disease, since juvenile hyaline fibromatosis (the most used term in literature) and hyaline systemic fibromatosis present overlapping features and common genetic disorders.

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HFS is a rare, progressive, autosomal recessive disorder characterised by deposition of amorphous hyaline material in soft tissues [1]. Clinical features include subcutaneous nodules with a tendency to enlarge and ulcerate, localised on the scalp, dorsum and joint regions. Gingival hyperplasia, pinkie pearly papules localised on the chin, neck and auricular pavilion are almost inevitably present; joint flexion contractures, associated to osteolytic lesions and osteoporosis have been frequently reported. Cognitive development is instead usually normal [2].

In literature, abnormalities have been reported to begin in the first few months after birth, with progressive flexor joint contractures, which cause a frog-like position preventing the patient to stand and walk [3]. Very few radiologic data are found in literature because of the rarity of the condition. We present two siblings affected by HFS studied by whole-body 1.5 T MR system (Achieva®, Philips Healthcare, The Nederlands).

Case report

Case 1

A 10-year-old girl, born at term after an apparently normal pregnancy and delivery, without any medical attendance in a rural area of Morocco, was referred to the paediatric surgery department because of the presence of large sub-cutaneous nodules. In 2015 she moved to Italy from Morocco with her relatives. No history of parental consanguinity was reported and the other family members were healthy, except for an older sister, presented as our second case. Clinical history was not well defined due to difficulties in acquiring clinical and radiological documents from the homeland.

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At 6 months of age, her parents noticed she experienced stiffness and difficulties in moving. Mental development was abnormal and milestones delayed. At the time of presentation she was in a wheel chair because of spastic quadriplegia, with severe dorsal-lumbar scoliosis, incontinence and intellectual disability. She reported recurrent episodes of bronchitis and diarrhoea. Cutaneous examination revealed soft nodules bilaterally on the auricular pavilion, the scalp and the dorsum (Figs. 1 and 2). The dorsum presented two big nodules, the smaller one approximately 10 cm long in diameter with a surface that appeared ulcerated and infected, and a larger one that measured 18 cm. Parents also described small pearly papules in the perianal region. Gingival hyperplasia with deformed mouth opening was revealed on oral examination. Flexion contracture was noted at left lower limb.

Hematologic and biochemical investigations were within normal limits, except for microcytic anaemia. First, brain MR was performed for assessing neurological impairment, and showed right encephalomalacia due to hypoxic-ischemic brain injury, which probably occurred in perinatal period (Fig. 3).

MR of the scalp displayed, in parietal and occipital area and in the periauricular region, multiple subcutaneous nodules with a heterogeneous iso-intense soft tissue-like signal in T1-weighted images (WI), iso-hyper intense signal in T2WI, and discreetly enhancing in the contrast phase of study. Histological specimens from ulcerated dorsum subcutaneous nodule biopsy reported hyaline deposition material (PAS positive) mixed with fibroblasts and vascular elements (Fig. 4).

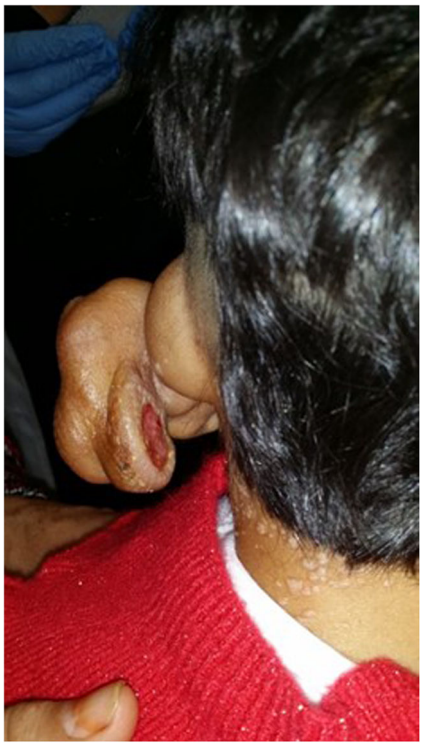

Fig. 1 Patient 1, 10-year-old girl. Partially ulcerated subcutaneous nodule involving auricular pavilion and pearly papules behind the neck

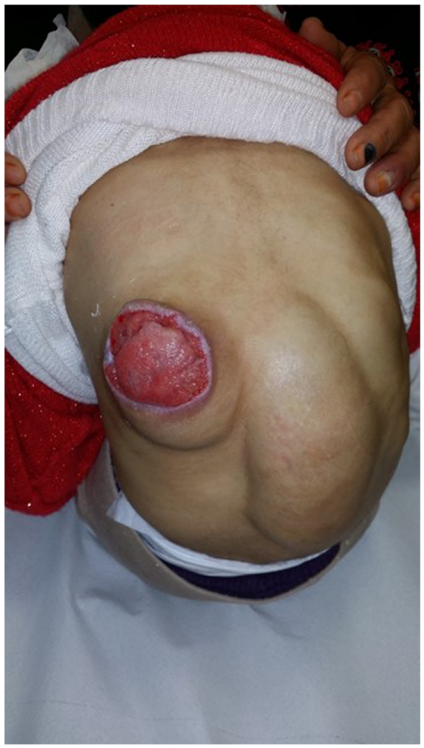

Fig. 2 Patient 1, 10-year-old girl. Ulcerated nodules on the dorsum

In order to rule out any visceral involvement, WBMR was planned. In WBMR multiple nodules were detected in the dorsum, scalp and periauricular area, the bigger one of 18 cm in diameter, iso-intense in T1WI, low hyper intense in T2WI. No deposition of hyaline material was detected in joints or in abdomen wall, but an important gaseous dilatation of distal large bowel and rectum and mild pericardial effusion was displayed (Fig. 5).

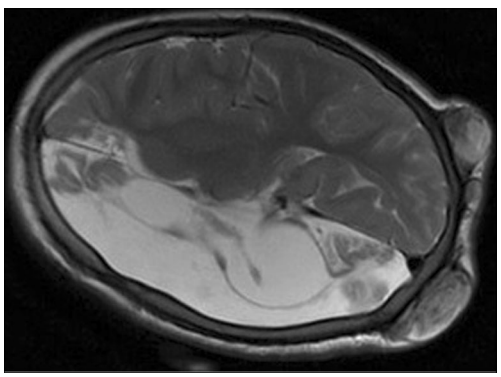

Fig. 3 Patient 1, 10-year-old girl. T2-weighted axial MR scan shows heterogeneous hyperintense signal of the subcutaneous nodules on the scalp. Encephalomalacia and atrophy

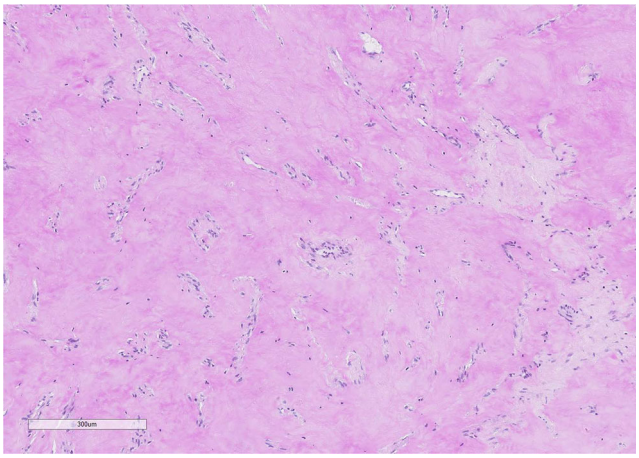

Fig. 4 Patient 1, 10-year-old girl. High power histopathological image show hyaline material deposition from the dorsum nodule, Ematoxylin-eosin stain

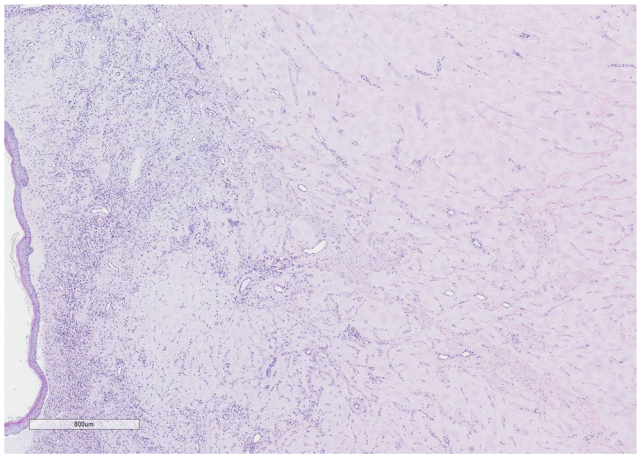

Fig. 6 Patient 2, 23-year-old woman. High power histopatological image show hyaline material deposition from the periauricular region, Ematoxylin-eosin stain

Case 2

The older sister of 23-years-old, presented slightly different clinical features. Parents reported that at the age of 5 the patient had begun to develop multiple soft subcutaneous nodules, especially on the scalp and dorsum, that enlarged gradually. Auricular pavilion presented bilateral deformities (histological specimen, Fig. 6). She started suffering movement impairment and pain at lower limbs, hips and shoulders. In a short period, multiple nodules involving the distal interphalangeal hands joints with clubbing and extension deformities appeared. Clinical investigation revealed mild gingival hyperplasia, multiple nodules in the scalp, hands, periorbital and dorsal region (Figs. 7 and 8). Hematologic and biochemical investigations were normal. X-ray evaluation of the hands revealed both erosive and sclerotic lesions with soft tissue swelling (Figs. 9 and 10).

WBMR was performed, revealing only subcutaneous lesions with no visceral involvement. MR study reported multiple nodules (heterogeneous hyperintense on STIR, and hypo-isointense on T1WI, showing high diffusion water restriction signal) localised in periarticular regions of knees, hips and elbows (Figs. 11, 12 and 13). Intra-articular joint effusion was also noted at left knee. Others nodules were detected bilaterally at gluteus, dorsum (the largest of 19 × 9 × 8 cm), and scalp. One of the left periorbital nodule showed compression to the left eyeball (Fig. 14).

Brain MR revealed no abnormalities except for little hyperintense spots on FLAIR sequences reported at insula/corona radiata suggestive of little spot of ischemic injuries. Histological specimens of an excised nodule, revealed amorphous hyaline material, cords of spindle-shaped cells embedded in a homogeneous eosinophilic PAS positive matrix. For both patients periodical clinical

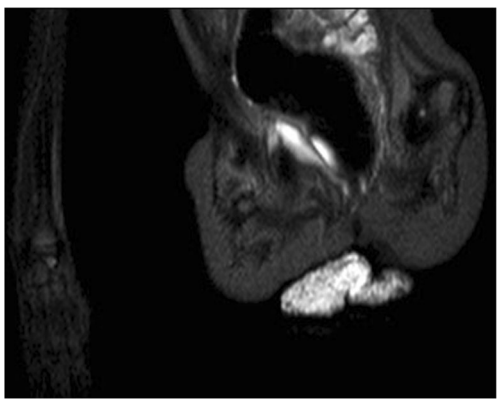

Fig. 5 Patient 1, 10-year-old girl. Fat Sat T2-weighted image: gaseous dilatation of distal large bowel and rectum

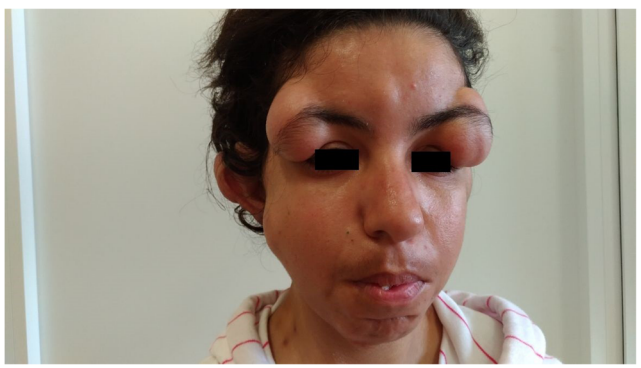

Fig. 7 Patient 2, 23-year-old woman. Bilateral nodules involving periorbital region with initial bulging effect on eyeballs

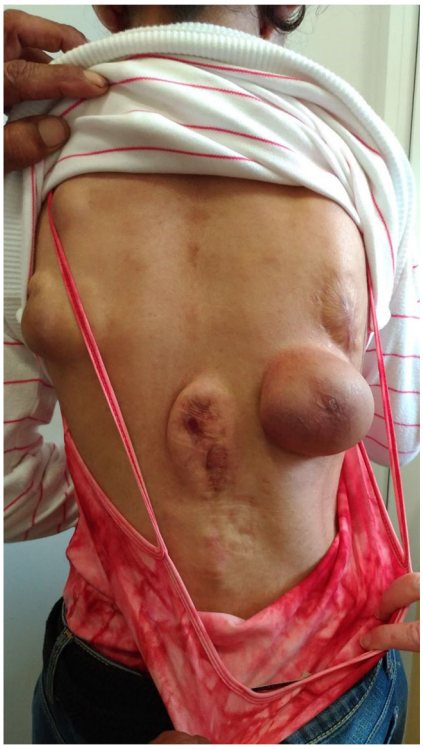

Fig. 8 Patient 2, 23-year-old woman. Nodules and scars due to surgical excision on the dorsum

and diagnostic follow up was planned, along with eventual surgical excision of large and/or symptomatic nodules.

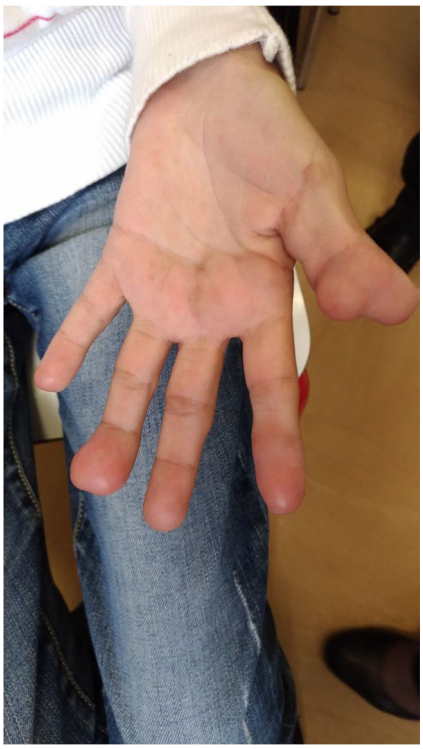

Fig. 9 Patient 2, 23-year-old woman. Multiple nodules involving distal interphalangeal joints

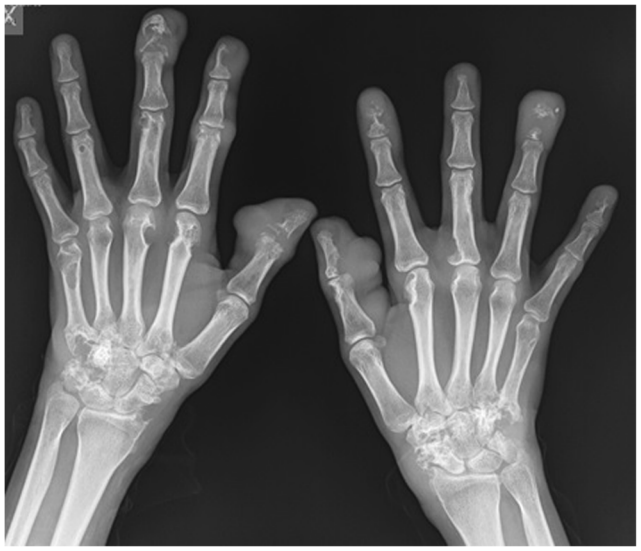

Fig. 10 Patient 2, 23-year-old woman. Conventional X-ray of the hands depicts erosive and sclerotic lesions of distal interphalangeal joints and tissue swelling

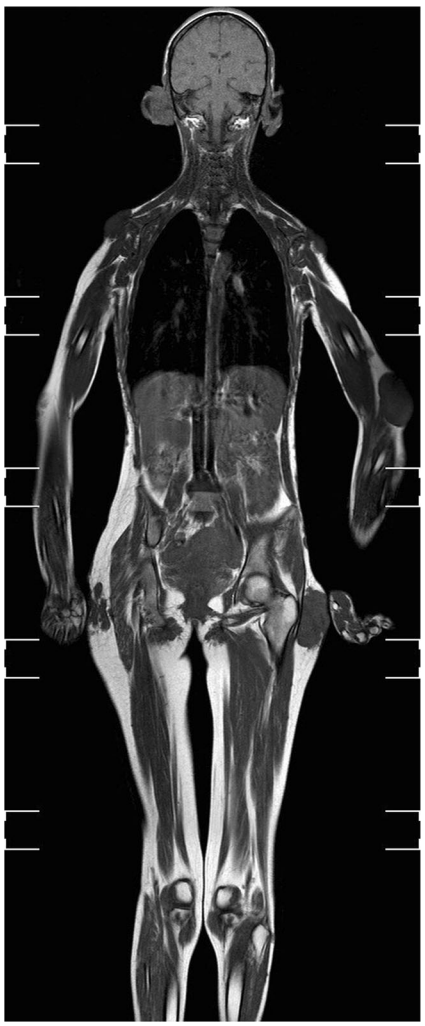

Fig. 11 Patient 2, 23-year-old woman. Coronal WBMR T1 W images. Multiple nodules hypo-isointense on T1WI, localised in periarticular regions of knees, hips and elbows

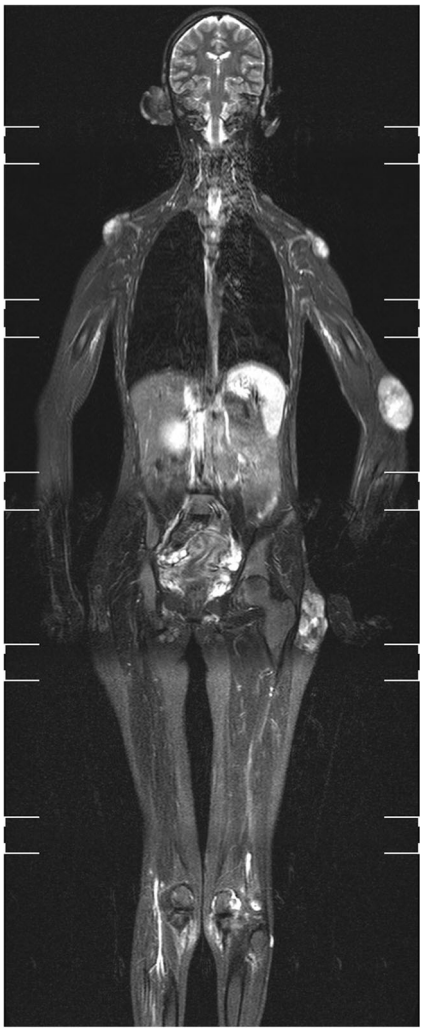

Fig. 12 Patient 2, 23-year-old woman. Coronal WBMR STIR. Multiple nodules heterogeneous hyperintense, localised in periarticular regions of knees, hips and elbows

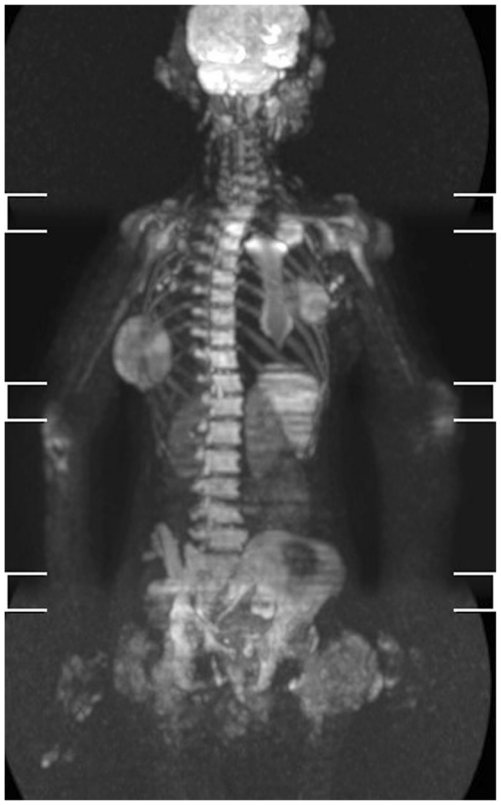

Fig. 13 Patient 2, 23-year-old woman. DWIBS images: disseminated multiple nodules in joints and dorsal region

Discussion

In 1873, Murray was the first to describe a condition he termed "molluscum fibrosum", later renamed by Kitano et al. in 1972 as juvenile hyaline fibromatosis [4, 5]. More recently, Denadai proposed to merge juvenile hyaline fibromatosis (OMIM 228600) and infantile systemic hyalinosis (OMIM 236490) into a single name, hyaline fibromatosis syndrome (HFS), because of the identification of genetic alterations in the same gene (CMG2 or ANTXR2) on chromosome 4q21 and because of the overlapping features of the two conditions [1, 6, 7]. The pathogenesis is not yet fully understood, but many theories propose a key role for aberrant synthesis of GAG's by fibroblasts and for abnormal collagen metabolism [8].

The main features of this syndrome include subcutaneous nodules with a preferential localization on the scalp, dorsum, limbs, periarticular regions, hyperpigmented plaques and papules in perianal region, skin tumours in the periauricular region, gingival hyperplasia, joint flexion contractures, osteolysis and osteoporosis [9, 10]. These nodules are histologically

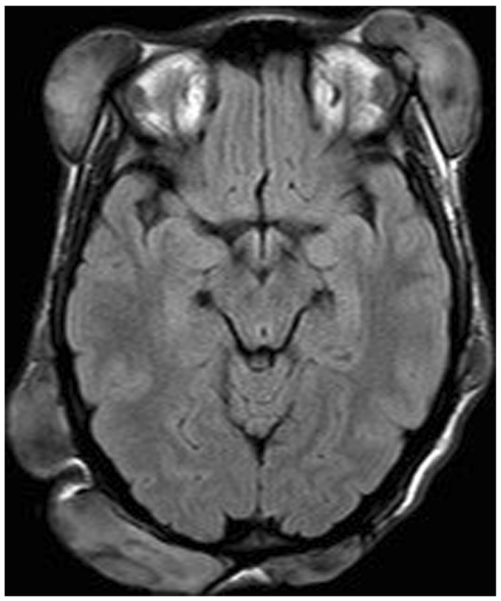

Fig. 14 Patient 2, 23-year-old woman. T1-weighted axial MR scan shows multiple nodules in the scalp

Table 1 Proposed grading system by Denadai et al., G3 grade was proposed for the first patient (10 year old sister), G2 for the second patient (23-year-old sister)

GRADE	Skin and/or gingival involvement	Joint and/or bone involvement	Visceral involvement with or without clinical manifestations	Severe clinical impairment (organ failure or septicaemia)
1 (mild)	+	–	–	–
2 (moderate)	+	+	–	–
3 (severe)	+	±	+	–
4 (lethal)	+	±	±	+

Proposed grading system by Denadai et al. [1]

characterised by amorphous hyaline material, tangle of spindle-shaped cells in an eosinophilic PAS positive matrix [11, 12].

Hyaline material apposition is progressive and causes enlargement of subcutaneous lesions that evolve from papules to nodules and tumours that may ulcerate and become infected [3, 13, 14]. The most common locations are the scalp and the joints, but if systemic involvement is present, hyaline deposition may affect cardiac muscle, gastrointestinal tract, lymph nodes, spleen, thyroid, and adrenal glands, leading to a life-threatening condition [15].

Albeit there is not a therapy for these patients, the main treatment approach consists of palliative care, in excision of muco-cutaneous lesions, considering technical possibilities and aesthetic and functional repercussions, and in physical and nutritional care, which may minimise osteoarticular, muscular and nutritional consequences [3].

Our first patient presented the typical features of HSF, including nodules on the scalp and on the dorsum, pearly papules in perianal region, gingival hyperplasia, joint flexion contracture in left lower limb; nevertheless, systemic involvement, with intestinal infiltration was also supposed by WBMR assessment, and corroborated by clinical feature of persistent diarrhoea [14].

On the other hand, the second patient has instead no visceral involvement. The other main difference between the two siblings was the presence of periarticular nodules, which were detected only in the older sibling. This feature corroborates the hypothesis, reported in literature, that HSF hyaline deposition in joints may be caused by movement-dependent fibroblasts activation with hyaline production, resulting both in flexion contractures and pain and periarticular nodules [5, 16]. Our first patient, due to spastic tetraplegia, had severe limitation in movement and this condition could have probably influenced hyaline material deposition in articular and periarticular tissues.

Nofal et al. developed a disease score updated by Denadai et al., in order to classify patients on the basis of disease severity (Table 1) [1, 17]. According to this classification, our first patient may belong to G3 severe HFS class, whilst the second one to G2 moderate HFS class.

Osteolysis and osteoporosis at X-ray exams are widely reported. Osteolytic lesions commonly occur in the long bones, skull and distal phalanges, associated or not with soft tissue swelling [18–20]. Diffuse demineralization was reported in long bones and reabsorption in the medial aspect of the proximal tibiae seems to be a distinctive feature of the disorder [21]. X-ray exam of the hands of our second patient revealed multiple areas of erosion involving the distal phalanges associated with tissue swelling as typical signs of the disease. Only a few cross sectional imaging features have been reported in literature due to the extreme rarity of the disease [18, 20, 21].

These two cases in siblings demonstrate the pivotal role WBMR, in assessment of visceral involvement of the disease, defining patients' prognosis and management. WBMR due to its high soft tissue resolution, its multiplanarity and the lack of ionising radiation exposure, should be considered the imaging modality of choice in these classes of patients, since it provides a safe assessment of the typical features of HFS, the localization of nodules, and affords to rule out or detect visceral involvement. WBMR should be preferred in paediatric patients follow up due to the possible frequent evaluation of disease activity during therapy or after surgical resection, in these cases a radiation free technique becomes mandatory [22–24].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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