Hyaline fibromatosis syndrome: A case report

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Hyaline fibromatosis syndrome (HFS) is a rare monogenic disease inherited in an autosomal recessive pattern and characterized by hyaline deposits on the skin, mucosa, and multiple organs; osteoporosis; and joint contractures. This progressive condition is caused by mutations in the gene encoding the anthrax toxin receptor 2 protein (*ANTXR2*). HFS is a disabling disease, and patients suffer from progressive pain and disfiguring symptoms. There are few published case reports detailing oral findings in patients with this condition. The present case report describes a 4-year-old female patient who showed severe manifestations of HFS, emphasizing the oral manifestations, the histopathologic aspects of HFS, the molecular pathogenesis, and the interdisciplinary management of patients affected by this condition. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e328−e335)

Hyaline fibromatosis syndrome (HFS; OMIM #228600) is a rare autosomal recessive condition, which evolves with the accumulation of hyaline material on the skin and in various organs. More severe cases have been reported under the denomination *infantile systemic hyalinosis* (ISH),[1] and the term *juvenile hyaline fibromatosis* (JHF) has been reserved for milder cases with more prolonged survival.[2] Both conditions represent different degrees of severity on the spectrum of diseases caused by mutations in Anthrax Toxin Receptor 2 (*ANTXR2*).[3] Therefore, Nofal et al. proposed the unifying term *HFS* and a grading system based on severity of the disease, classified as mild, moderate, and severe.[4]

The gene responsible for HFS, *ANTXR2*, was first associated with capillary formation, and it was initially named capillary morphogenesis gene 2 (*CMG2*).[5] More recently, Scobie et al. identified a receptor for the anthrax toxin encoded by this gene, changing its official name.[6] In an animal model, *ANTXR2* loss of function promotes collagen VI accumulation, similar to what happens in HFS.[7] To better characterize the mutational spectrum of HFS, genotype−phenotype correlation studies have demonstrated an association between the phenotypic variability and different types of mutation. A mutational hotspot in *ANTXR2* exon 13 was identified, and frameshift mutations that lead to a premature stop codon and splicing mutations were typically associated with a more severe form of the disease.[3,8] Despite this association between mutation type and the degree of phenotypic severity, the molecular consequences of the mutations remain to be evaluated at the messenger RNA (mRNA), protein, and functional levels.[9]

The abnormal accumulation of a hyaline substance in patients with HFS affects multiple organs, and prominent nodules are commonly present. Protein-losing enteropathy may result from the presence of nodules in the intestines and is characterized by diarrhea and weight loss.[10] Limitation of movement is frequently caused by joint stiffness and pain, evolving to deformities called contractures.[1] Gingival hypertrophy usually develops between ages 6 and 12 months, interfering with feeding and speaking.[11]

Patients with HFS suffer from progressive pain and disfigurement.[11] If treatment is ineffective, it is important to make decisions regarding possible palliative interventions. The recognition and acknowledgment that such a decision is required should be followed by the integration of available evidence with patients' values in the process of shared decision making.[12]

The present case report describes the genetic and clinical features of HFS, emphasizing its oral manifestations, histopathologic aspects and the interdisciplinary therapeutic approach in its treatment.

CASE REPORT

A 4-year-old female patient was the only child of healthy parents in a consanguineous marriage (being first cousins). The mother reported that she had a full-term pregnancy, and all examinations in the prenatal period showed no alterations. Fifty hours after delivery, the mother and the child were discharged, with no complications. However, the newborn cried whenever handled, causing the parents to become concerned.

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Received for publication Mar 12, 2020; returned for revision May 11, 2020; accepted for publication Jun 26, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.06.022

At age 6 months, the mother started to notice erythematous areas in the skin around the nose and eyes of the infant, hyperpigmentation at flexural areas, and restricted facial and body movements. The patient was referred for specialized medical attention. Clinically, small pearly papules appeared in the pressure areas, dorsum, neck, and face. Nodules with pink-reddish discoloration were present in the perianal region. Short stature, limited joint movement, and pain were important complaints at the time. Diffuse osteopenia and articular contractures of elbows, knees, and hands were radiographically observed. Cognitive development was not compromised. The patient was diagnosed with HFS at age 1 year and 5 months, on the basis of clinical and radiographic findings. The condition evolved, with significantly joint contractures, making locomotion impossible and fixing the limbs in a "frog-leg position". Larger subcutaneous nodules developed bilaterally on the scalp. The physical features are shown in Figure 1.

The patient's dental history included acute pain and abscesses, extensive gingival hyperplasia covering the surfaces of deciduous teeth, and compromised nutrition and oral hygiene. The oral findings were associated with moderate fever, and the patient was treated with antibiotics and anti-inflammatory drugs. The patient's parents also reported that she suffered frequent episodes of diarrhea and weight loss. The patient was then referred to the dental service of the Clinics Hospital of the Universidade Federal de Minas Gerais (Minas Gerais, Brazil) when she was 3 years old. The main complaint at the first appointment was difficulty in oral feeding caused by the presence of extensive gingival hyperplasia and the poor condition of teeth. Physical examination revealed small papules with a smooth, pink surface that were scattered on the skin around the lips and eyelids; enlarged lips with reduced elasticity; and limited mouth opening. Submucosal nodules were diffusely distributed on the lips and buccal mucosa bilaterally. On intraoral examination, extensive and massive gingival hyperplasia was observed covering the dental surfaces. The gingival mucosa was erythematous and bled at the slightest manipulation. Oral hygiene was poor, and bacterial biofilm was observed in all teeth. The upper incisors were decayed and showed pulp exposure. The patient's oral condition affected her speech development as well. Panoramic radiography revealed a congenitally absent left lateral incisor and multiple cavities (Figure 2).

Considering the damage caused by gingival hyperplasia to the patient's oral and systemic health, a surgical approach involving gingivectomy and excision of intraoral nodules was proposed. The patient was placed under general anesthesia and nasotracheal intubation. A fragment of the anterior mandibular gingiva, measuring 1.5 cm in the largest diameter, was removed by using an electric scalpel. However, during the procedure, significant bleeding occurred. Local hemostatic measures were insufficient to control the bleeding, and the patient lost 120 mL of blood, resulting in hypotension. As the patient's coagulogram values were within

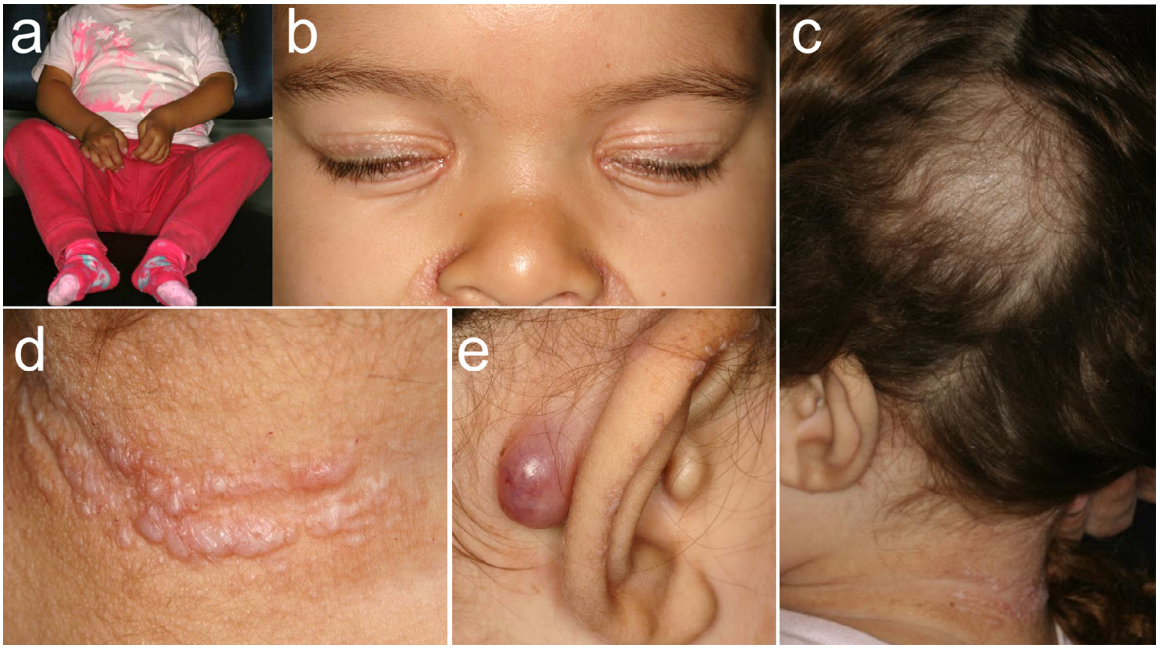

Fig. 1. Physical appearance of a 4 year-old patient with hyaline fibromatosis syndrome (HFS). **A,** The limbs fixed in a "frog-leg position." **B,** Multiple small pearly papules on the skin near the nose and eyelids. **C,** Subcutaneous large nodules on the scalp bilaterally. **D,** Pearly papules observed in flexural areas, such as the nuchal skin. **E,** Nodules present on external ears.

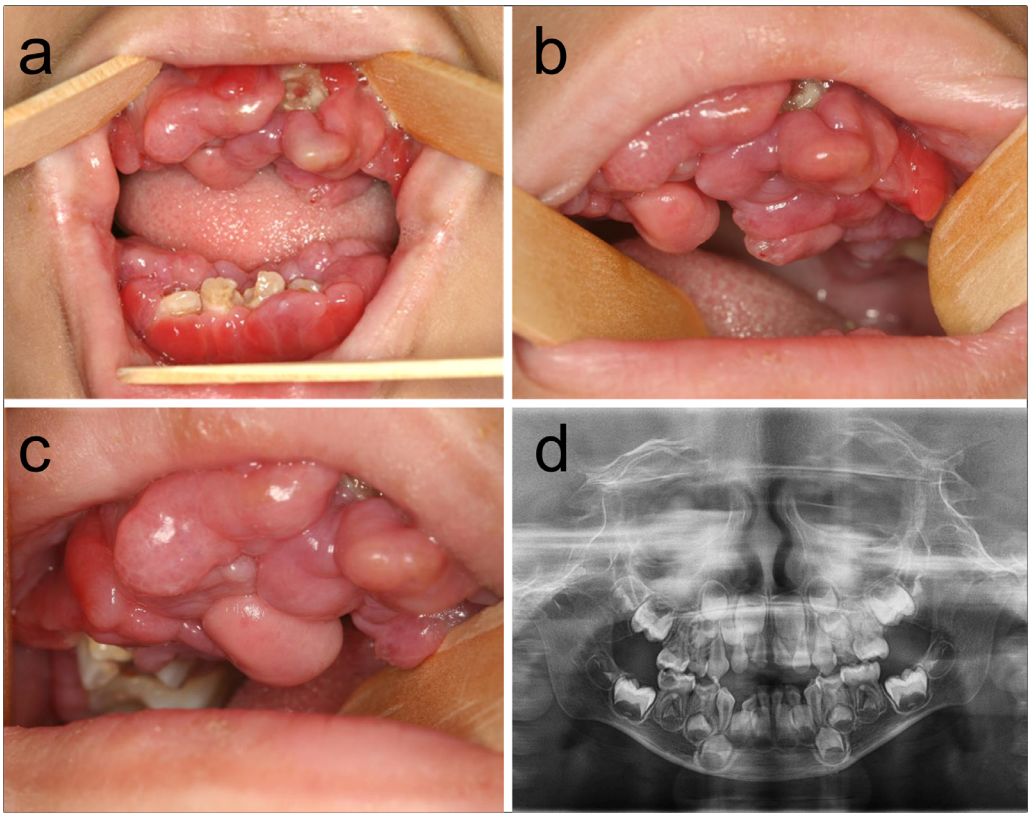

Fig. 2. Clinical and radiographic images of the oral condition of patient with hyaline fibromatosis syndrome (HFS). Massive gingival hyperplasia affected the maxilla and mandible **(A)**, bilaterally **(B and C)**. Panoramic radiography shows the deciduous dentition affected by multiple cavities **(D)**.

the normal range, the excessive bleeding was attributed to the inflammatory gingival condition. The surgical procedure was stopped, and the excised tissue was submitted for histopathologic examination.

Microscopically, the fragment of gingival tissue was observed to be covered by stratified, parakeratinized squamous epithelium. The connective tissue was highly collagenized, showing accumulation of extracellular matrix and a sparse population of stromal cells. The connective tissue cells showed intracellular vacuoles. Chronic inflammatory infiltrate was focally observed (Figure 3). Periodic acid-Schiff positively stained the hyaline deposits, and Congo Red staining was negative.

After the surgical intervention, outpatient dental care was instituted to promote the patient's oral health and to remedy the inflammatory gingival condition. The parents were instructed to use a cotton swab soaked in 0.12% chlorhexidine solution to clean the gingival grooves and the dental surfaces 3 times a day and to apply 0.2% chlorhexidine gel left in place overnight. The importance of oral hygiene procedures in comprehensive care was emphasized, and nutritional guidance was provided as well.

During a year of follow-up, progressive improvement was seen in the patient's mouth opening, speech, and oral food intake capacity. However, the gingival inflammatory condition persisted, although to a lesser extent. Despite these notable improvements, the patient's oral health remains suboptimal because of the gingival hyperplasia and oral nodules, which continue to cause significant functional limitations. We also observed recurrence of gingival hyperplasia in the anterior region of the mandible 9 months after biopsy (see Figure 2).

To better elucidate the syndrome's etiopathogenesis and to provide genetic counseling, direct sequencing of exon 13 of *ANTXR2*, a hotspot region recognized in HFS, was performed. Briefly, genomic DNA was isolated from the formalin-fixed paraffin-embedded hyperplastic gingival tissue by using the Deparaffinization Solution (Qiagen, Germany) and the DNA FFPE Tissue Kit (Qiagen, Germany), according to the manufacturer's instructions. Buccal swabs were collected from the patient and both parents after obtaining free and informed consent. Genomic DNA was isolated from the swabs by using DNeasy Blood & Tissue Kit (Qiagen, Germany). Spectrophotometer (Nano−Drop 2000 instrument; ThermoFisher Scientific, Waltham, MA) was used for assessing the quantity and purity of DNA.

Exon 13 of *ANTXR2* was amplified by using standard polymerase chain reaction (PCR) with primers

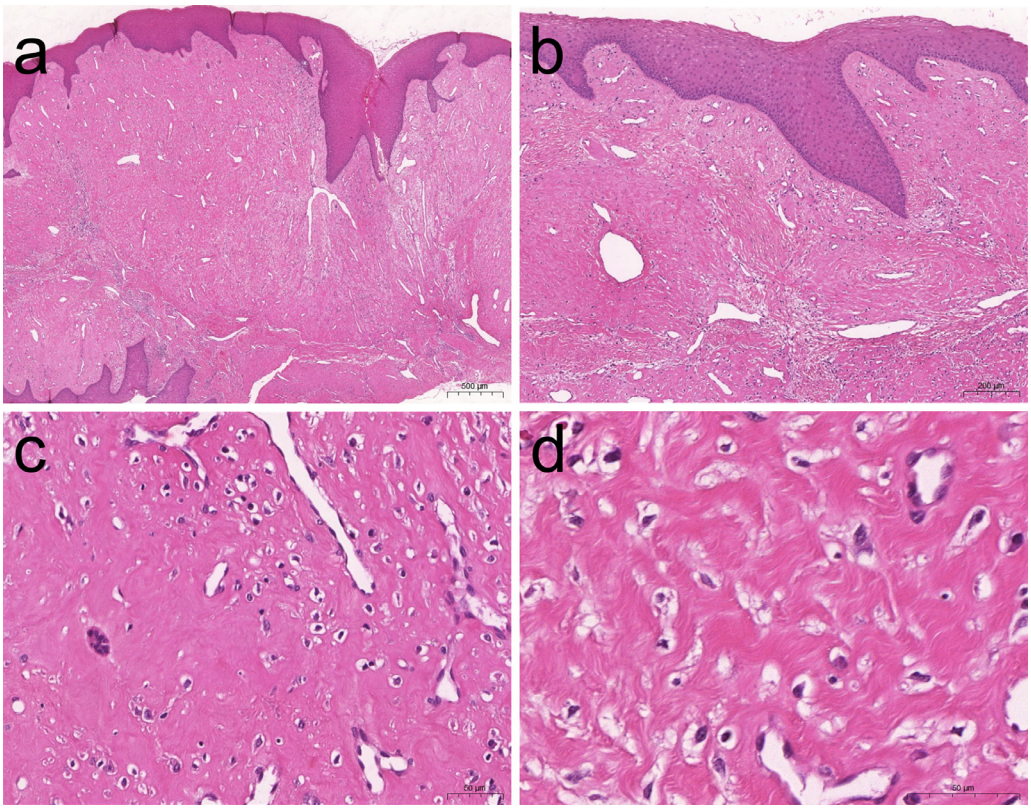

Fig. 3. Histopathologic features of the biopsy specimen of the gingival lesions. **A,** The gingival specimens were covered by stratified parakeratinized squamous epithelium (Hematoxylin and eosin [H&E]; original magnification: × 20). **B** and **C**, The connective tissue was highly collagenized, with hypocellular areas showing eosinophilic and amorphous material (H&E, original magnification × 50 and × 200). **D,** Clear spaces give the spindle cells a vacuolar aspect (H&E, original magnification × 400).

designed with the use of Primer−BLAST (http://www.ncbi.nlm.nih.gov/tools/primer-blast)[13]: forward primer (5'-TACACATCCTTACTATCTCCTCTCT-3') and reverse primer (5'-TTTGGGCATGGTATCTGCATT-3'). ExoSAP−IT PCR Product Cleanup Reagent (Life Technologies, Carlsbad, CA) was used for purification of PCR products. DNA sequencing reactions were carried out by using Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Waltham, MA) and then sequenced on an ABI 3730 DNA Analyzer (Applied Biosystems, Waltham, MA). The sequences were visualized in the software SnapGene Viewer, and the chromatograms were manually inspected in comparison with the reference sequence.

Sequencing of the patient's DNA revealed a homozygous frameshift mutation (c.1074 del; *P*.Ala359 Hisfs*50) characterized by deletion of T (thymine), which causes the substitution of alanine by histidine and a frameshift. The patient's father and mother carried the same heterozygous deletion. A homozygous single nucleotide polymorphism (SNP rs12647691) was also detected in the DNA sequence of the proband and the mother, whereas this SNP was heterozygous in the father. Additionally, the mother had the heterozygous synonymous SNP rs72653288. The molecular features detected in the patient and the parents are further characterized in Figure 4.

DISCUSSION

HFS was previously referred to as *ISH* and *JHF* in the literature. ISH was described as a more severe condition compared with JHF and associated with early-onset and lower survival.[14] However, both conditions share important similarities, and overlapping features occur in some borderline cases.[15,16] Although the clinical features of the present case were consistent with ISH, we adopted the unifying term *HFS*, following the concept of clinical overlap previously highlighted by Nofal et al.[4]

In the present case, the patient showed the initial signs of the condition in the first 6 months of life, revealing early onset of the disease. The parents reported that the child cried constantly, and this was later associated with pain and restricted joint movements. Decreased limbs movement and crying when manipulated were the earliest findings in this condition, as reported by Felix et al. Because of the presence of restriction of movement, imaging examinations were conducted, and they

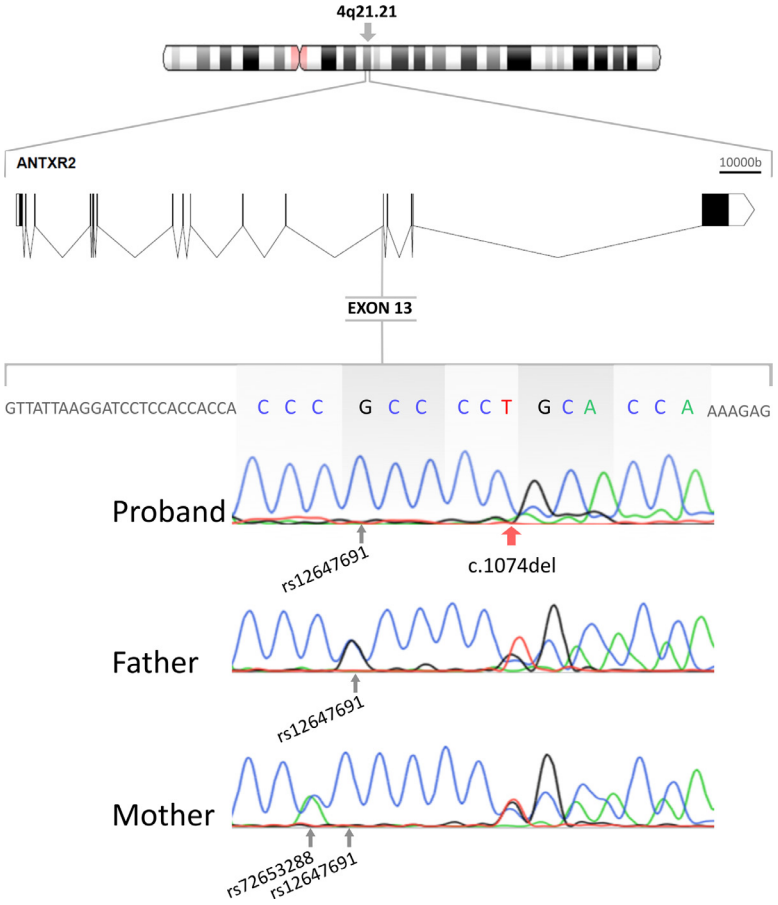

Fig. 4. Molecular study of patient with hyaline fibromatosis syndrome (HFS) and parents. *ANTXR2* is located on chromosome 4q21.21. Exon 13 is a hotspot of mutations implicated in HFS pathogenesis and was sequenced in the present case. The chromatogram of the patient's DNA sequencing exhibits the frameshift mutation c.1074 del in homozygosis state (indicated by a red arrow), in addition to the single nucleotide polymorphism (SNP) rs12647691. The sequencing chromatogram of the father shows the same frameshift mutation c.1074 del in heterozygosis state, as well as the SNP rs12647691. The mother is also heterozygous for the frameshift mutation c.1074 del and shows the SNPs rs12647691 and rs72653288. The SNPs are indicated by gray arrows.

revealed diffuse osteoporosis.[14] Diffuse osteopenia and articular contractures were radiographically observed in our patient on the initial diagnostic tests, and progression of these conditions caused severe physical disability. Osteolytic lesions associated with cortical erosions, mainly in the long bones, have also been reported in a subset of JHF cases, but skeletal involvement is often milder compared with that in ISH.[16,17] Articular contractures and osteoporosis associated with osteolytic lesions are also components of Winchester syndrome, caused by mutations in the membrane-bound matrix metalloprotease 14 gene (*MMP14*).[18]

The skin lesions in our patient initially appeared as an erythematous rash and progressed to pearly papules and nodules in various parts of the body. Cutaneous involvement is an important hallmark of this condition and frequently described as a papuloerythematous rash, polypoid lesions, and nodular pearly lesions.[14,19] In the present case, these lesions were located on the perianal skin and the nuchal skin surrounding the nose and the eyes; on the external ears; and on other areas subjected to pressure. The high frequency of lesions in areas associated with repeated movement or pressure suggests that mechanical stress may be the trigger for deposition of the perivascular hyaline matrix, resulting in the cutaneous lesions.[11,15]

Hyaline deposits also result in papules in the eyelids and in skin lesions in frictional areas in a condition referred to as *Urbach-Wiethe disease* (lipoid proteinosis). Microvascular alteration is caused by mutations in the extracellular matrix gene 1 (*ECM1*) in this condition.[20] The deposits correspond to basal membrane−laminin (in skin laminin-10); type IV collagen; nidogen; and perlecan.[21] *Hyaline* is a widely used term that includes different biochemical compositions. In amyloidosis, deposits of amorphous, hyaline, acellular material may occur locally or involve multiple organs, showing apple-green polarization on Congo red

staining.[22] Hyaline deposits are also observed in biopsy specimens of erythropoietic protoporphyria, a condition associated with painful photosensitivity.[23] Some other diseases, such as ligneous periodontitis,[24] juvenile colloid milium,[25] lichen sclerosus,[26] and localized scleroderma,[27] also exhibit hyaline material; therefore, clinicopathologic correlation is essential for the differential diagnosis.

Previous reports of cases of HFS have described features involving multiple sites, with different degrees of severity and extent. In brief, the dermatologic findings most commonly reported include pearly papules on the skin,[10,15,17,19,28-35] macular lesions over bony prominences,[10,15,19,28,32-34,36] perianal coalescent nodular lesions,[10,15,17,19,28,29,32,33,35,36] generalized skin thickening,[10,33,35] and large subcutaneous nodules.[15,28,35] Skeletal findings of significant orthopedic limitations include joint contractures, restricted movement of joints, osteoporosis/osteopenia, osteolysis, and fractures.[4,10,11,14,15,28] Severe cases are associated with such complications as failure to thrive, recurrent infections, and early death in infancy.[4,35,36]

The results of a genome-wide linkage search in 4 affected individuals suggested that the gene for JHF is located on chromosome 4q21.21.[37] On the basis of the locus identification, the disease-causing mutations in *ANTXR2* in both conditions, JHF and ISH, were later characterized, defining them as part of the same spectrum of diseases.[35] *ANTXR2* encodes a single-pass type I transmembrane protein that includes an extracellular von Willebrand factor A domain with a metal ion-dependent adhesion site motif.[38] Bell et al.'s investigation of differential gene expressions in human capillary morphogenesis revealed a potential role of *ATXR2* in basement membrane matrix synthesis. *ANTR2* is upregulated during the morphogenesis of endothelial cells.[5] The encoded protein is primarily targeted to the endoplasmic reticulum and shows strong binding to collagen type IV and laminin.[5]

HFS is inherited in an autosomal recessive pattern, so this condition is frequently reported in offspring of consanguineous couples, as in the present case.[10,39,40] The geographic prevalence of HFS is suggested to be influenced by the degree of consanguinity.[40,41] Cases in offspring of nonconsanguineous parents have also been reported.[14,29] The parents in the present case were heterozygous for a pathogenic *ANTXR2* mutation (c.1074delT), and the proband was found to be homozygous for the same genetic mutation. Knowledge about the genetic bases of this condition may contribute to appropriate genetic counseling of these families.

HFS is a monogenic disease caused by different types of mutations spread throughout the *ANTXR2* gene. Molecular analysis showed that point mutations in gene sequences encoding the ectodomain and the transmembrane region resulted in the retention of the protein in the endoplasmic reticulum as a result of a folding-and-assembly defect.[42] Our patient was homozygous for a single nucleotide deletion in exon 13, a frameshift mutation that affects the cytosolic tail of the protein and leads to a premature stop. Analysis of the molecular effect of frameshift mutations in exon 13 revealed that these genotypes result in a decrease in ANTXR2 at the mRNA and protein levels, suggesting that mRNAs may be recognized by the nonsense-mediated mRNA decay pathway and degraded.[43] Functional studies indicated that the mutation c.1074delT also leads to defects at a protein-folding level.[9]

HFS is caused by homozygous or compound heterozygous mutation in the *ANTXR2* gene (608041) on chromosome 4q21.21. The variety of possible disease-causing mutations in HFS could explain the different levels of phenotypic severity. Thus, in a study that evaluated the genotype−phenotype correlation, missense and in-frame mutations in the cytoplasmic domain were associated with milder cases. However, patients with the infantile form of the condition showed an insertion/deletion mutation that altered the open reading frame. Severe cases also showed missense and truncating mutations affecting the extracellular von Willebrand factor A domain.[3] However, the multiplicity of possible allelic combinations makes this correlation increasingly complex. The mutation found in our patient has been previously described in a homozygous state as well as a compound heterozygote.[29,44] Interestingly, a significant variation in severity can be seen in individuals harboring this mutation. Homozygosis has been reported in severe cases, including 2 affected individuals in a Kuwaiti family and 1 in an Egyptian family.[3,44] An 8-year-old Moroccan patient also showed the homozygous state, but the manifestation of the disease was moderate in that case.[41] In affected individuals, compound heterozygosis ranged from moderate to lethal grades. This range of clinical severity may be, at least in part, a consequence of the different mutations in the second allele.[29,34,44]

The nature and location of the *ANTXR2* mutation influences not only the phenotype but also the possibilities for molecular treatment. Mutations that map the extracellular domain were previously demonstrated to affect folding, leading to degradation.[42] Nevertheless, the functional protein could be partially rescued by treatment with proteasome inhibitors.[43] Further studies analyzing the specific c.1074delT mutation demonstrated that it affects both the mRNA and protein folding levels, leaving gene replacement as the only future alternative in molecular treatment.[9]

To date, there is no definitive treatment for this condition. The few possibilities include interventions to minimize symptoms and prevent complications. Surgical excision of skin and oral lesions was considered in some

cases to prevent ulceration, pain, and infection.[15,16,45] However, the benefits of such a treatment choice must be carefully weighed against its risks. In the present case, the patient had severe complications during excision of oral lesions, and the procedure had to be aborted. Excessive bleeding during surgical removal of gingival hyperplasia was also reported by Stucki et al.[11] Local recurrence is often reported, showing that this approach may represent only a short-term benefit in some cases.[29,30] In the present case, recurrence in the region of biopsy was observed after 9 months. Therefore, some authors suggest that surgical interventions should be reserved only for ulcerated, infected lesions or those that cause significant functional impairment in the patient.[29,31] In line with this recommendation, in the present case, a less invasive approach was instituted after the unsuccessful surgical procedure. The patient has been followed up every 3 months for over a year and has no acute foci of infection. The guided oral hygiene program was well accepted by the parents and tolerated by the patient.

Joint contractures are a persistent and progressive feature of the disease and seem to be refractory to treatments described so far. Some options, such as physiotherapy, capsulotomy, cortisone, or D-penicillamine, have been reported to have benefited some patients, improving joint mobility and the symptoms.[15,31,33,45-47] However, there is no evidence that these treatments prevent the progression of joint deformities, and their effects appear to be only temporary.

Little is known about the influence of clinical manifestations on the prognosis of HFS. Systemic involvement seems to be associated with a worse prognosis because of early complications, more commonly associated with infiltration of the intestines leading to protein-losing enteropathy and diarrhea. Most patients have a fatal outcome before age 2 years in these cases.[4,36]

CONCLUSIONS

HSF is a disabling condition, for which there are no viable treatment alternatives as yet. Growing knowledge of the genetic bases of this disease has enabled identification of potential therapies; however, further studies are needed for the development of individualized treatment protocols. Molecular investigation is helpful in confirming the diagnosis and providing appropriate genetic counseling. In the present case, an interprofessional team, including dentists, nutritionists, pharmacists, dermatologists, palliative care specialists, and pediatricians, provided care to the patient, demonstrating the importance of an early multiprofessional approach to improve the survival and quality of life of individuals affected by the disease.

FUNDING

This work was supported the National Council for Scientific and Technological Development (CNPq)/Brazil and Coordination for the Improvement of Higher Education Personnel (CAPES, Finance Code 001).

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