

JUVENILE HYALINE FIBROMATOSIS: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract

Juvenile hyaline fibromatosis (JHF) is a rare disease with autosomal recessive inheritance that occurs mainly in childhood and is characterized by the deposition of amorphous hyaline material in the skin and other organs. There are approximately 70 cases reported in the literature. Herein we describe the case of a 14-month-old boy with multiple cutaneous nodules around small and large joints, papulous skin lesions, hyperpigmented plaques and nodules in the perianal region, flexion contractures and stiffness of joints and diffuse osteoporosis. Symptoms were present since the second month of life. Histopathologic studies of joint nodulations demonstrated the presence of hyaline material, confirming the diagnosis of juvenile hyaline fibromatosis.

Keywords: Juvenile Hyaline Fibromatosis; Systemic Hyalinosis; Juvenile Idiopathic Arthritis.

Resumo

A Fibromatose Hialina Juvenil é uma doença rara, com herança autossômica recessiva ocorrendo principalmente na infância e caracterizada por depósito de substância hialina amorfa na pele e outros órgãos. Há aproximadamente 70 casos publicados na literatura. Os autores descrevem o caso de um menino de 14 meses de idade com múltiplos nódulos cutâneos em pequenas e grandes articu-

lações, placas hiperpigmentadas e nódulos perianais, contraturas articulares em flexão com dor e edema e osteoporose difusa. Os sintomas surgiram desde os dois meses de vida. O estudo histopatológico das nodulações articulares demonstrou a presença de material hialino, confirmando o diagnóstico de fibromatose hialina juvenil.

Palavras-chave: Fibromatose Hialina Juvenil; Hialinose Sistêmica; Artrite Idiopática Juvenil.

Introduction

Juvenile hyaline fibromatosis (JHF) was first described in 1873 by Murray as «molluscum fibrosum».¹ Other names such as *puretic syndrome*, *systemic hyalinosis*, *disseminated painful fibromatosis* and *hyalinic multiplex juvenile fibromatosis* have been used in the literature, as reported in 1976 by Kitano.² He coined the term juvenile hyaline fibromatosis, which has been adopted since then. JHF is a congenital autosomal recessive disease, with the same distribution between genders, most commonly diagnosed in early childhood, yet there are some reported diagnoses in adult life.³⁻⁶ It is characterized by papulonodular skin lesions, gingival hyperplasia, joint contractures and bone lesions.^{3,4}

We present a case of JHF and a review of the literature. This rare entity is a rather difficult diagnosis that must be recalled as a differential diagnosis for juvenile idiopathic arthritis and other diseases with subcutaneous nodules, pain, edema and joint contractures.

Case report

RAR, a 14-month-old boy, had a normal birth, without medical attendance, in a rural area of Ama-

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Figure 1. Papules and nodules in the auricular area, neck and thorax.



Figure 3. Nodulation and swelling on the wrist and proximal and distal interphalangeal joints.



Figure 2. Perianal granulomas.



Figure 4. Ankle nodule and edema.

zonas State. His mother did not have prenatal assistance. At 2 months of age, he began to develop stiffness of the joints with progressive limitation of motion and swellings in auricular pavilion, mentum, thorax and dorsum. He was the first-born child from a consanguineous marriage – the parents were cousins. The boy had recurrent episodes of pneumonia. On admission, he was febrile, tachypneic, presenting cranial asymmetry due to a prominence on the parietal region, hypertelorism, wide anterior fontanel (5x6cm). Skin findings included extensive infiltration with hyperemia, and gross papules and nodules on the ears, mentum, neck, tho-

rax, dorsum (Figure 1). He has also hyperpigmented plaques and nodules in the perianal region (Figure 2). Nodules with tenderness and local heat were seen over the proximal interphalangeal (PIP) and metacarpophalangeal joints (MCP), wrists, knees, ankles, anterior thorax and lumbar areas (Figures 3, 4). Knees and elbows showed flexion contractures (Figure 5). He had no visceral enlargement in the abdomen. Retard in neuro-psicomotor development was evident. Laboratorial results revealed hypochromic anemia and leucocytosis by the time of the occurrence of pneumonia and an elevated erythrocyte sedimentation rate;



Figure 5. Contracture flexion of the elbows.

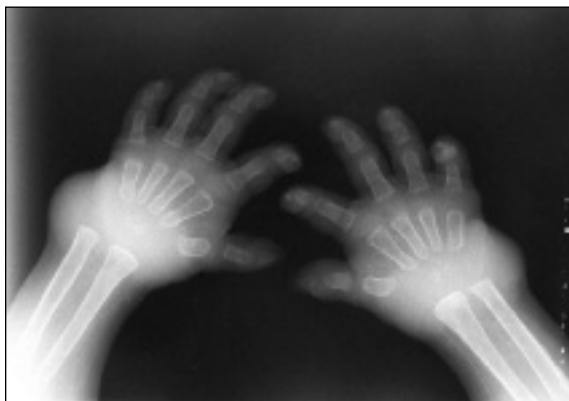


Figure 6. Diffuse porosis and soft tissue swelling.

rheumatoid factor was negative, as well as toxoplasma, rubella, cytomegalovirus and herpes serologies. Serum electrolytes and renal and liver function tests were normal. Doppler echocardiography showed mesocardia without hemodynamic repercussion. X-rays revealed areas of bone reabsorption in the proximal tibia, enlargement of



Figure 7. Diffuse porosis and periarticular soft tissue enlargement.

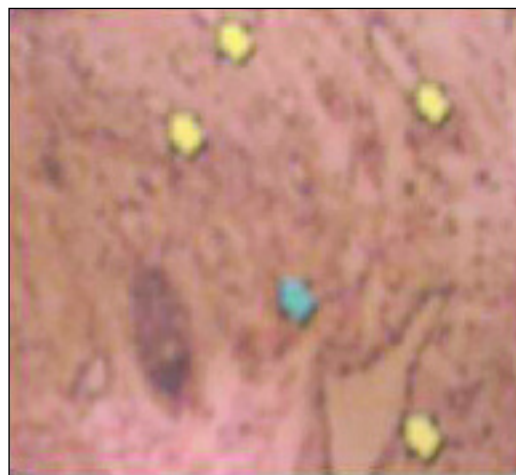


Figure 8. Biopsy of joint nodule showed tissue with fibrotic areas and infiltration of hyaline material.

metaphysis of long bones and costal arches (10th to 12th), diffuse porosis, subcutaneous nodules, articular stiffness (Figures 6, 7) and calcifications in the right ear. Bone age was equivalent to 9-12 months. Magnetic resonance image (MRI) of the right elbow showed an expansible lesion with soft-tissue intensity and enhanced signal in contrasted phase, without evidence of infiltration of bone structures and without evidence of joint fluid. Ultrasound (US) of the wrists, PIPs, elbows, knees

and nearby soft tissues demonstrated multiple solid hypoechogenic subcutaneous nodules. Abdominal organs were normal by US and computerized tomography (CT) screening. Skin biopsies revealed epidermis with hyperkeratosis and atrophic zones and dermis with several enlarged new formed capillaries, disposed in groups, characterizing capillary hemangioma. Biopsies of joint nodules showed tissue with fibrosis areas with infiltration of hyaline material (Figure 8). The two nodules removed for biopsy (elbow and ankle) recurred after 30 days. The diagnostic hypothesis of FHJ based on clinical, laboratory and image findings was confirmed by histopathologic study. Antibiotics were initiated for pneumonia. Nonsteroidal anti-inflammatory drug (NSAIDs) and physical therapy lead to some improvement of the joint (pain, edema and contractures) complaints. The parents were guided to the medical accompaniment and physiotherapy, however as family inhabits a very distant rural area of Amazonas State, this did not occur, and the patient died one year after discharge.

Discussion

FHJ is a heritable disorder that maps to the long arm of chromosome 4, at 4q21.⁷ Detrimental mutations in the capillary morphogenesis gene 2 (CMG2) located on 4q21 were found.^{8,9} The occurrence in siblings with the antecedent of parental consanguinity in some cases suggests autosomal recessive inheritance.¹⁰ Investigations suggests that FHJ represent an error in the synthesis of glycosaminoglycan by fibroblasts¹¹⁻¹⁴ or abnormal collagen metabolism with an increased synthesis and degradation of collagen type I and a reduced overall metabolism of collagen type III.^{15,16}

Main clinical features include skin lesions, gingival hypertrophy, joint contractures, osteolysis and osteoporosis.⁴ Skin lesions can be polymorphous papules, small, rosy, clustered and located in the face and neck, particularly around of the nostrils and ears, paranasal folds and the chin.^{5,13,17} Nodular lesions or plaques on perianal regions may occur^{18,19} as in our patient. De Rosa et al postulated the existence of two forms of FHJ: a localized form with very slow growth and a diffuse form with large and rapidly growing tumors.²⁰ Great subcutaneous tumors can also occur and are frequently located on the scalp, and less commonly on the trunk and limbs.¹³ The tumors may be either

hard or soft, mobile or bound to the underlying fascia, and may ulcerate.² Cutaneous and gingival lesions, painful when located in flexion contractures of the joints, appear in the first year of the child.^{3,17,21-23} Extensive gingival hyperplasia makes suction and mastication difficult, which can lead to malnutrition,⁵ recurrent infections and death in childhood.^{12,24} In the present case we did not observed gingival hypertrophy, as already was described.²⁵ It is believed that mesenchymal cells overproduces the hyaline amorphous substance, resulting in tumor formation. Repeated mechanical stress enhances the proliferation of mesenchymal cells and the production of more amorphous substance.^{17,26} Movements stimulate the joints of the extremities, and capsules become infiltrated with amorphous tumoral tissue, resulting in flexion contractures.¹⁷

Skeletal manifestations include osteolysis of the distal phalanges and cortical defects of the long bones. Widespread osteoporosis, scoliosis, and reduced height and weight have been described.²⁷ Cranial abnormalities, as found in our patient, were reported previously.^{18, 28}

Biochemical and laboratorial abnormalities, excluding those associated with infectious process, were not observed in our patient, and in accordance with published reports.^{3,5,27-29} Hypochromic and microcytic anemia has been attributed to iron deficiency consequence of under nutrition^{5,28} and elevated ESR has been reported.⁵

On radiologic evaluation, most authors mention the presence of lytic lesions, with erosions of long bones,^{5,28} phalanges¹³ and pubic symphysis.⁵ Osteoclastic lesions in the cortical layer of long bones and diffuse osteoporosis have been also reported.²⁷ The same authors observed joint contractures and absence of osteolytic lesions.^{3,27} In the present case, radiographic studies did not found osteolytic lesions, evidencing just diffuse osteoporosis, resorption areas in the proximal and medial faces of the tibias with metaphysis enlargement and enlargement of costal arches (10th to 12th), as reported elsewhere. These lesions are found in older patients. The US may evidence an increased echogenicity on surface of abdominal organs, probably due fat infiltration,²⁹ but in our case the US was normal. MRI of the right elbow revealed an expansive lesion with soft tissue sign intensity and intensive enhancement at the contrasted phase, as described in the literature⁵ without evidences of infiltration of bone structures or joint fluid.

The histopathology examination of the nodules revealed an abundance of amorphous hyaline material (fibroblasts embedded in an abundant homogeneous eosinophilic hyalinized matrix),^{28,30} positive on PAS (periodic acid-Schiff).^{3,5,27} Some theories have been proposed to unravel the origin and nature of the hyaline material, suggesting aberrant synthesis of glycosaminoglycans by fibroblasts¹¹⁻¹⁴ or abnormal collagen metabolism.¹⁵ An immunohistochemical study on several organs of a child with JHF found that pro- $\alpha 2$ (I) chain and collagen type III chain were absent in skin.²⁴

Differential diagnosis of JHF must be performed with congenital generalized fibromatosis, Winchester syndrome,^{3,5} infantile systemic hyalinosis (ISH),^{29,31} Farber lipogranulomatosis (FLG),²⁹ and juvenile idiopathic arthritis (JIA). Congenital generalized fibromatosis is characterized by multiple nodules on the dermis and subcutaneous tissues since birth, as well as involvement of the gastrointestinal tract, kidneys, lungs and death within a few days of life.³² Winchester syndrome is characterized by low stature, flexion contractures of the small joints, generalized osteoporosis and opacity of the cornea. Cutaneous lesions are uncommon and when present consist of hyperpigmentation and hypertrichosis.^{6,32} In FLG we found laryngeal abnormalities, delayed mental development (moderate/severe), low stature, chronic pulmonary inflammatory disease, cutaneous and subcutaneous nodules, osteoporosis and opacity of the cornea. JIA has functional limitation and flexion contractures, likely to be confounded with FHJ. The diagnosis of JIA is clinical, based on arthritis found in more than one joint with duration longer than six weeks.

Nowadays there is no specific therapy for FHJ. Surgical resections of the tumors and of the gingival hyperplasia are possibilities^{23,33} with improvement for short periods of time, due the high frequency of recurrences.^{5,13,23} Injections of proteolytic enzymes are being tested in gingival hypertrophy, as well as topical steroidal hormones on the skin nodulations.^{2,4} Orthopaedic surgery followed by local radiotherapy and physiotherapy may be tried for intraosseous lesions. However, because of osteolytic lesions, functional prognosis seems to be poor.⁵

Oral D-penicillamine has been used in some patients^{16,29} with improvement in joint contractures and flexibility, even though subcutaneous tumors continued to grow.²⁹

In children with recurrent or untreatable disease chemotherapy, radiotherapy and endocrine therapy (antioestrogens and progestational agents) have been used.³⁴ In the current case, nonsteroidal anti-inflammatory drug and physiotherapy were important for functional improvement and control of pain, but with no improvement in final outcome occurred.

Conclusion

FHJ is a progressive disease with a dim prognosis. Diagnosis must be made as early as possible for applying rehabilitative measures in an attempt to improve quality of life in patients affected by this rare disease.

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