

An overlap of infantile systemic hyalinosis and Juvenile hyaline fibromatosis: A report of two sisters affected. (and review of the literature)

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Abstract :

We present an overlap of juvenile hyaline fibromatosis and infantile systemic hyalinosis in two sisters born to second-degree related parents and presented to us at the ages of eight years and six years suffering from chronic diarrhea, recurrent colicky abdominal pain, multiple skin nodules of variable sizes and sites, multiple joint stiffness, gum hypertrophy and multiple dental caries. Comprehensive investigation, including electron microscopy, showed findings consistent with juvenile hyaline fibromatosis and an overlap with infantile systemic hyalinosis.

It is suggested that both disorders have a common cause⁽¹⁾ and can be considered as different parts of the spectrum of the same autosomal recessive disorder⁽²⁾

Introduction :

Infantile systemic hyalinosis appears at birth or during early infancy. An affected child develops intractable diarrhoea, diffuse colitis and in some patients hyaline material is found throughout the entire gastro-intestinal tract.⁽³⁾ Affected infants invariably die in early childhood⁽³⁾.

Patients show pearly papules on the face around the mouth, nose, ears and scalp margin, gingival hyperplasia, perianal nodules, diffusely thickened firm skin particularly over the trunk and hyper-pigmentation over the knuckles and maleoli, stiffness of the knees, shoulders and hips with fixed flexion deformities⁽⁴⁾.

Light microscopy of the skin shows hyaline deposition in the dermis. Electron microscopy (EM) shows fibrillo-granular material and a banding pattern in the dermis. This material is found also within membrane-bound vacuoles in macrophages and fibroblasts. The appearance and localization are identical with that of type VI collagen. This disease appears to be a distinctive disorder which may be due to excessive depositions of type VI collagen⁽⁵⁾.

Juvenile hyaline fibromatosis (JHF) is a rare autosomal recessive disease^(6,1,7) with only 38 cases being reported up to 1993⁽⁸⁾. The disease is characterized by large cutaneous nodules occurring especially around the head and neck and often involving the lips. JHF is also characterized by gingival hypertrophy, muscle tenderness and weakness, joint contracture of upper and lower limbs, claw deformity of the hands and osteolytic lesions.

JHF starts to appear during infancy or early childhood and the lesions become increasingly severe with age^(6,8,9). Plaques of confluent papules were described in the paranasal folds and extend to the cheeks, chin, medial canthi of both eyes, ears and neck⁽⁹⁾. A localized form of JHF, characterized by very slowly progressive localised lesions, has been described⁽¹⁰⁾. The radiological changes in JHF are characterised by lytic lesions in long bones and flat bones⁽⁹⁾ and acro-osteolysis in some cases.

Histopathologically there is deposition of amorphous hyaline material in the extracellular spaces of the dermis and any soft tissue. The collagen present is mainly type VI and I in the ratio of 4:1. Of the three chains of collagen VI (alfa one VI, alfa two VI, alfa three VI), the alfa three VI is the most abundant^(11,9). The glycosaminoglycans present in tumor tissue are mainly dermatan sulfate, chondroitin sulfate and hyaluronan. In normal skin hyaluronan is the most abundant. Type VI collagen is a normal component of connective tissue as in dermis, aorta, placental tissue, neurofibroma and nucleus pulpous. An increase in the content of type VI collagen might provide the pathological basis for JHF and infantile systemic hyalinosis and explain the inflexibility of the skin and stiffness of the joints⁽⁹⁾.

Case reports :

Patient No.1:

F.A., an 8-year-old Sudanese girl was born normally to second degree related parents. She had been suffering from chronic diarrhoea, recurrent colicky abdominal pain, multiple skin nodules of variable sizes, joint stiffness and failure to thrive which began at the age of six months with bouts of bloody

mucoïd diarrhoea and colicky abdominal pain. These attacks occurred every 2-4 weeks. At the age of one year she developed multiple small papules around the nose and mouth. At the age of eighteen months nodular skin lesions appeared mainly on the scalp, forehead and extremities. These increased in size gradually and were disfiguring but not painful.

Mentality was normal but the child was delayed in gross milestones. She started to walk at the age of two years and six months later the family noticed that the child had a stiff left knee. Later they noticed stiffness in various joints of the arms and legs and the child walked with a slight tip-toeing gait. The chronic watery mucoïd diarrhea continued intermittently and sometimes contained blood. There was a loss of appetite, poor weight gain and the nodu-

lar skin lesions slowly increased in size.

At the age of six years she developed gum hypertrophy and multiple dental caries. She continued to be weak, with an abnormal gait and difficulty in running, but her intelligence was normal. She was vaccinated as appropriate for her age. A younger sister (case No. II) has the same problem. Another sister died of malaria and gastroenteritis at the age of six months.

On examination she had fair general condition but was pale and weight and height were below the 5th centile. Her skin showed multiple nodules of variable sizes [Diagram 1; figs. 1-10) with the biggest nodule (9x10 cm) on the scalp, large nodules on both ears and small papules at the sides of the nose and chin. The nodules were firm and asymptomatic. The gingiva was hypertrophic and there

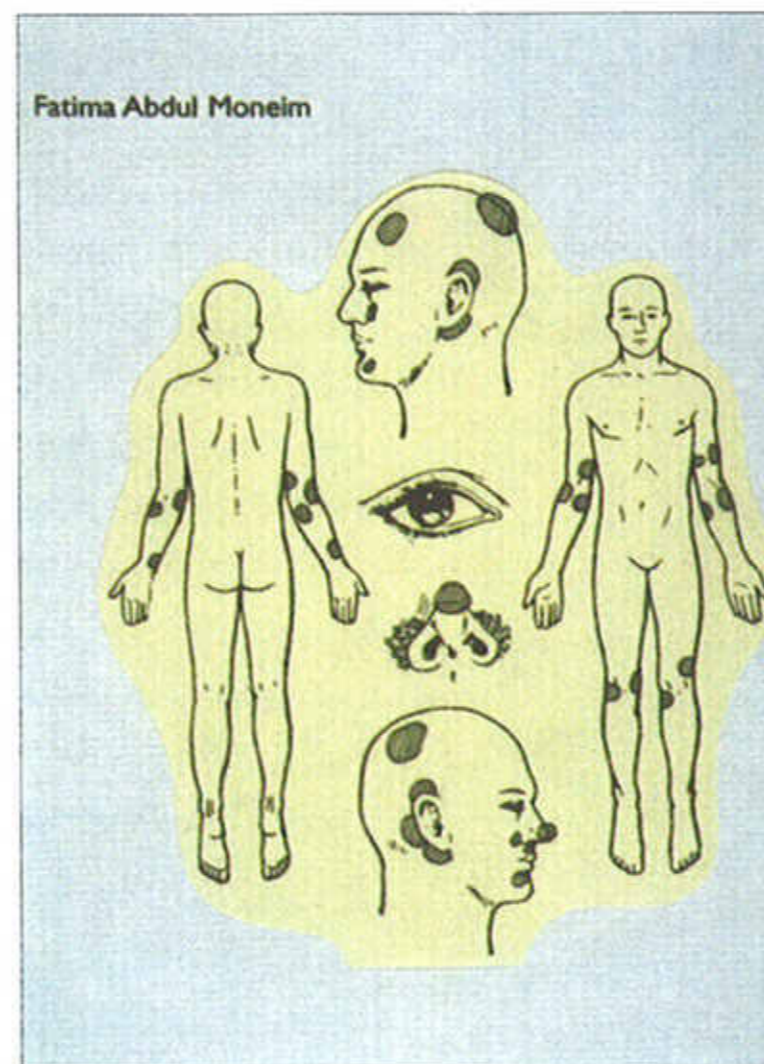


Diagram (1) = Distribution of skin lesion of first case.



Fig. (1) Case 1 = Papules around nose, mouth and chin.



Fig. (2) Case 1 = Nodules of forehead.



Fig. (3) Case 1 = Nodules of the ear.



Fig. (4) Case 1 = Thickened pigmented skin of the knuckles.



Fig. (5) Case 1 = Nodules of palms.



Fig. (6) Case 1 = Nodules of both knees and stiff flexed knee joint.



Fig. (7) Case 1 = Swollen ankle and skin nodules.



Fig. (8) Case 1 = Swollen ankle and skin nodules.



Fig. (9) Case 1 = Swollen lower gum.



Fig. (10) Case 1 = Swollen upper gum.

was multiple dental caries. The skin over the knuckles was dark and thickened. Joints were stiff with generalized muscle wasting and hypotonia and a tip-toeing gait. The cardiovascular system and the chest showed no abnormalities. The abdomen was distended with slight tenderness on deep palpation but no organomegaly. Rectal examination showed fissures and perianal papulo-nodules.

Laboratory tests showed a hypochromic microcytic anaemia, normal LFT, low albumin, and occult blood in the stool which contained no ova or parasites.

A CT scan of the head, EMG, N.C.V., and abdominal ultrasound were all normal. Colonoscopy showed colitis with early bleeding lesions and a barium enema showed diffuse infiltrative large bowel disease with mucosal ulceration and nodularity. Colonic biopsy showed hyalinization of the lamina propria and an inflammatory process replacing the glands.

A radiological skeletal survey revealed osteopenic bones which were somewhat slender in the extremities but with no evidence of metaphyseal or diaphyseal osteolytic lesions and no periosteal reaction or soft tissue calcification. There was soft tissue swelling around the left ankle. The bones of the vault and base of the skull appeared normal with no intracranial calcification.

The patient improved on a full dose of steroid that was gradually reduced. The attacks of diar-

rhea and abdominal pain became less frequent and the iron deficiency anemia improved on iron supplementation. The gum hypertrophy was treated surgically and she started a course of physiotherapy to reduce the stiffness of the joints and to strengthen the muscles.

Patient No. 2 :

M.A., a six-year-old, was the second child in the same Sudanese family. She was born normally after an unremarkable pregnancy. At the age of six months she developed attacks of chronic bloody mucoid diarrhea every four weeks. At one year she had small painless, gradually enlarging nodular lesions over the nose and later developed similar nodules over the scalp and ear pinnae. At 2-1/2 years her joints were noticeably stiff and her gums were hypertrophic. However, in general, her condition was less severe than her elder sister. She developed normally and was vaccinated appropriately for her age.

At the time of presentation there were multiple large skin nodules mainly on the scalp, ear pinna and extensor surface of the arm. These varied in size with the largest being on the scalp. [Diagram 2; figs 11-16]

The stiffness of her joints limited movement and affected her gait. A CT scan showed her head to be normal but the walls of the colon were thickened. Biopsies for examination by light and electron mi-

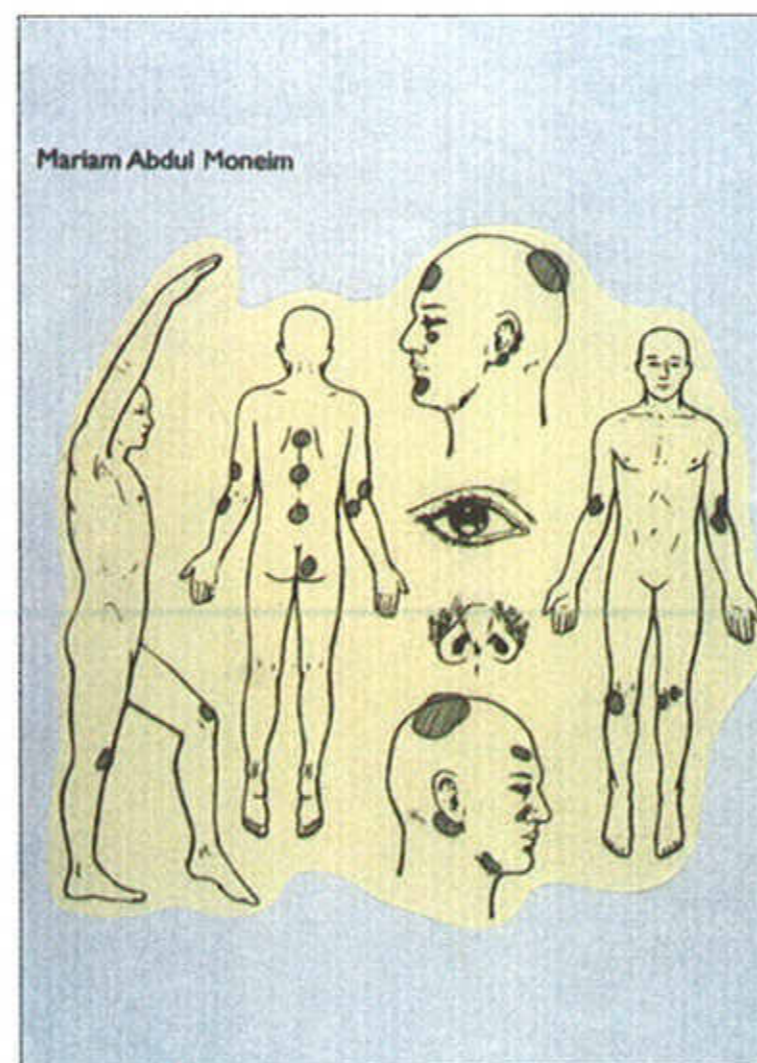


Diagram (2) = Distribution of skin lesions - second case.



Fig. (11) Case 2 = Big nodule of forehead.



Fig. (12) Case 2 = Big nodule of scalp.



Fig. (13) Case 2 = Nodules of forehead.



Fig. (14) Case 2 = Nodules of ears.



Fig. (15) Case 2 = Gum hypertrophy.



Fig. (16) Case 2 = Papules on the back.

croscopy were taken of the skin nodules and gingiva.

Radiological skeletal survey demonstrated a soft tissue swelling in the right parietal area. There were no bony or sutural abnormalities and the rest of the skeletal examination was normal without any evidence of marrow infiltration or bone destruction. Her lung fields were clear with normal cardio-mediastinal shadows. She responded well to systemic steroid and physiotherapy.

The combination of clinical examination and results of dermal connective tissue morphology by light and electronmicroscopy were compatible with the diagnosis of juvenile hyaline fibromatosis in both sisters [cases 1 & 2; Figs.17-26].

Discussion:

The main published features of J.H.F. can be summarized as follows:

The manifestations of J.H.F. occur early in infancy or childhood (between 3 months and 4 years)

and increase with advancing age. Growth is retarded but intelligence develops normally. Cutaneous nodules of various sizes occur on the scalp, forehead, nose, ears ^(6, 8), and sometimes near big joints or on the trunk. Small papules, usually 2 mm diameter, are seen on the alae nasi, in the post-auricular fold, on the commisures of the lips, the chin, the neck and the perianal region. New lesions continue to appear while older ones do not change in size or shape. There is gum hypertrophy with decayed irregular teeth. The lesions have a characteristic histopathology which is described later in this review.

Joint lesions usually precede the skin lesions. Some joints may be swollen and there are painful flexural contractures of hips, knees, shoulders, elbows, wrists, some fingers and ankles.

Osteolytic lesions in the skull, long bones and distal phalanges are the main radiological findings in J.H.F. There is diffuse demineralization of bones partially due to immobilization by the painful joint contractures and there may be cortical erosion and

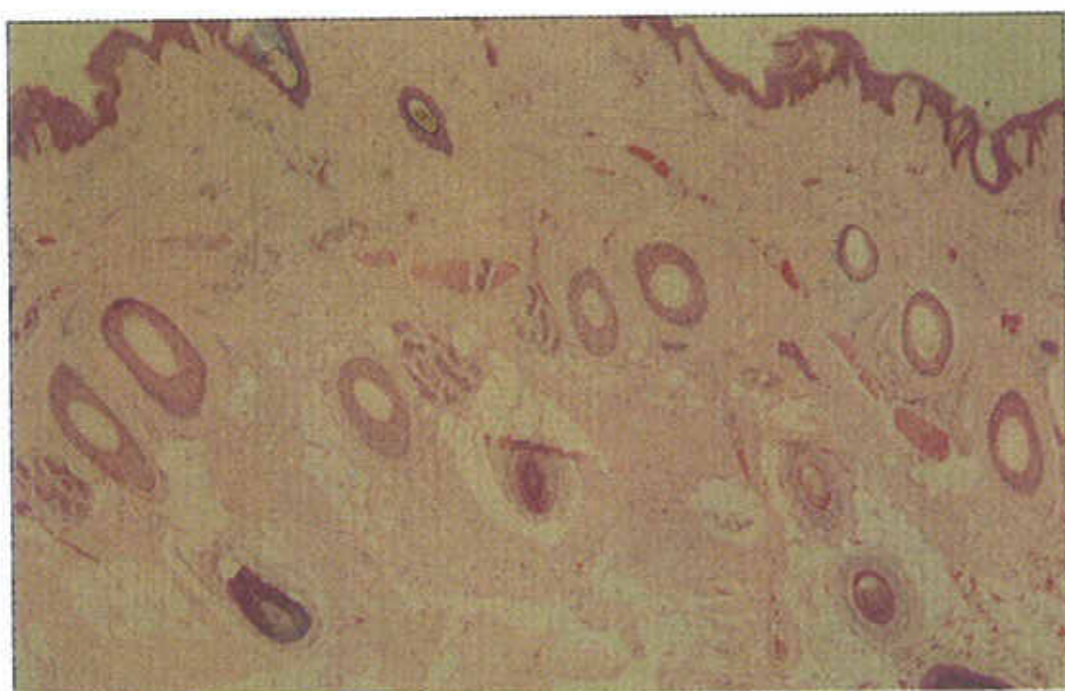


Fig. (17) (H1) = Hair bearing skin and subcutaneous tissue containing large areas of hyaline material.

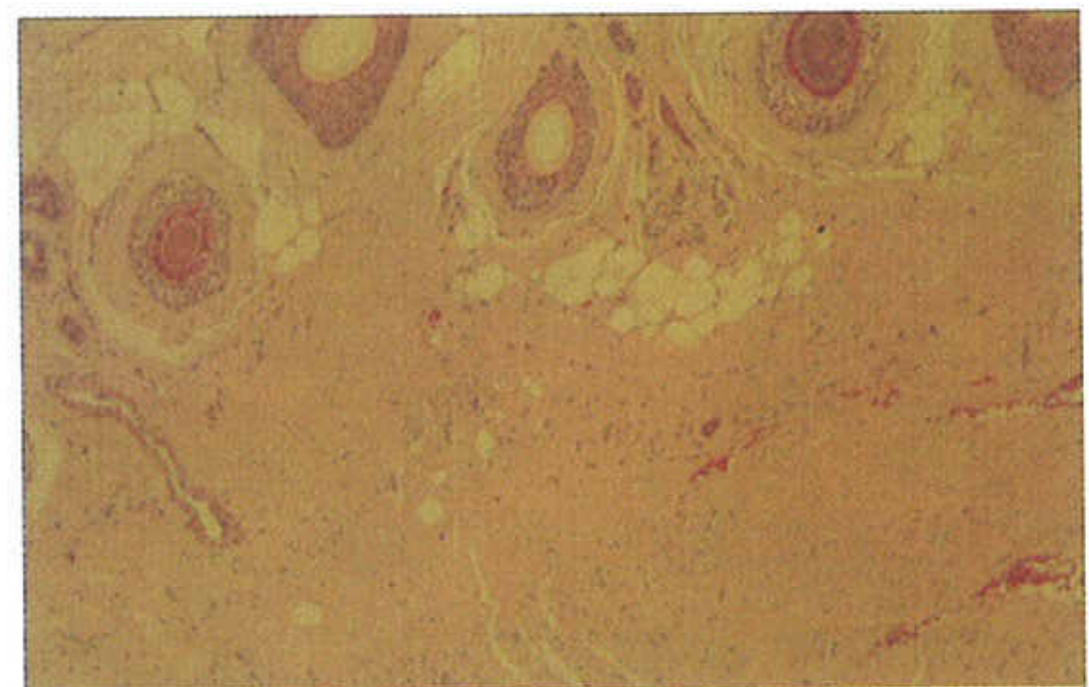


Fig. (18) (H2) = Higher power showing the hyaline material predominantly in the subcutaneous tissue.

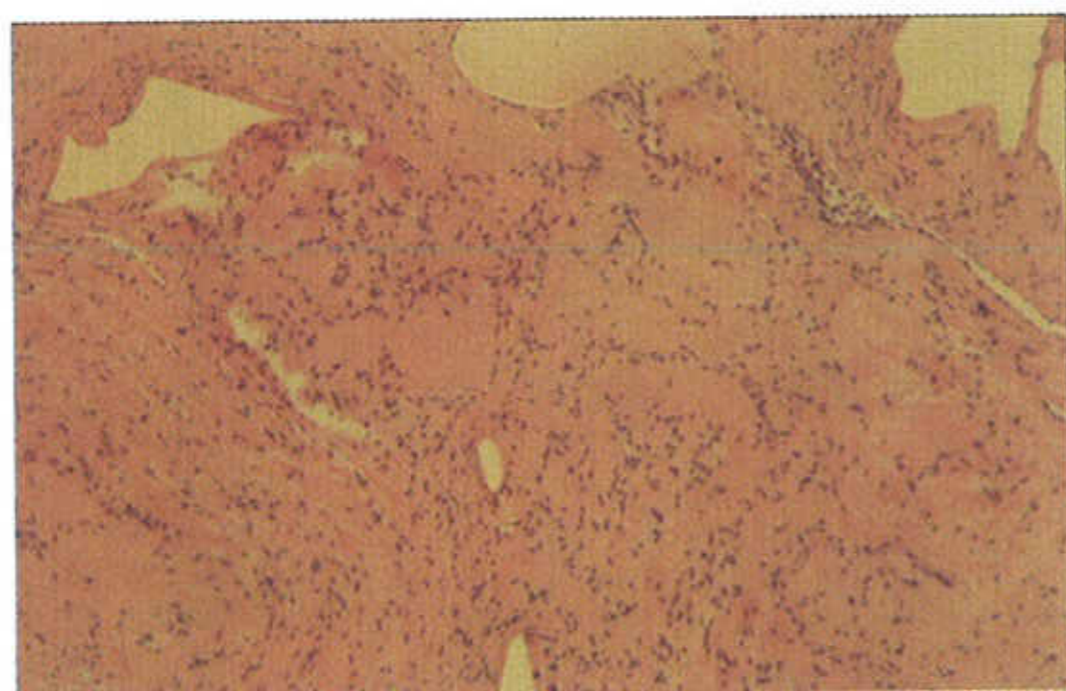


Fig. (19) (H3) = Multiple dilated vascular spaces in the hyalinized connective tissue.

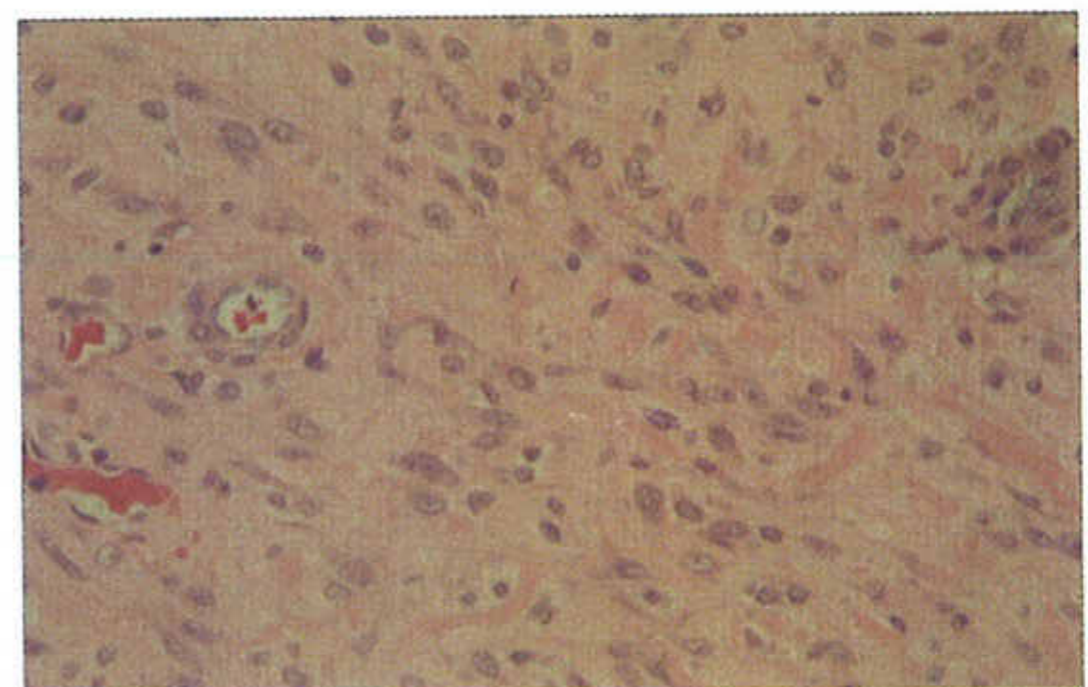


Fig. (20) (H4) = Higher power of the hyalinized material containing fibroblasts and occasional macrophages.



Fig. (21) (H5) = Gingiva-stromal connective tissue showing changes similar to those seen in the skin including dilated vessels.



Fig. (22) (H6) = Gingiva higher power showing multiple fibroblasts in hyalinized stroma.

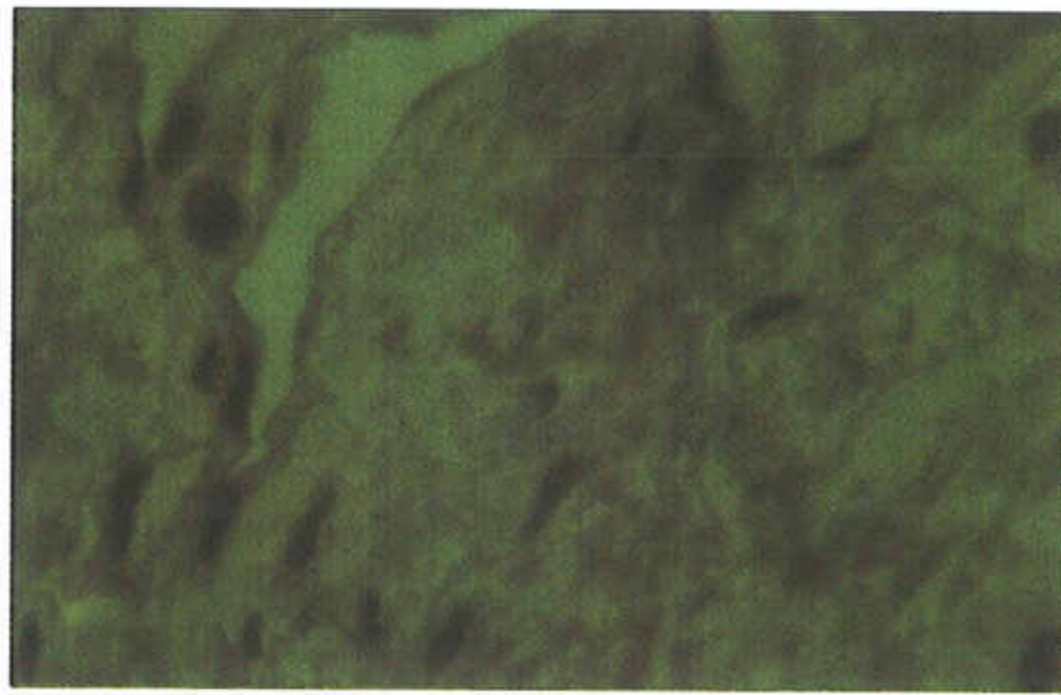


Fig. (23) (H7) = Ultrathin section showing fibroblasts in a fibrillogranular ground substance.

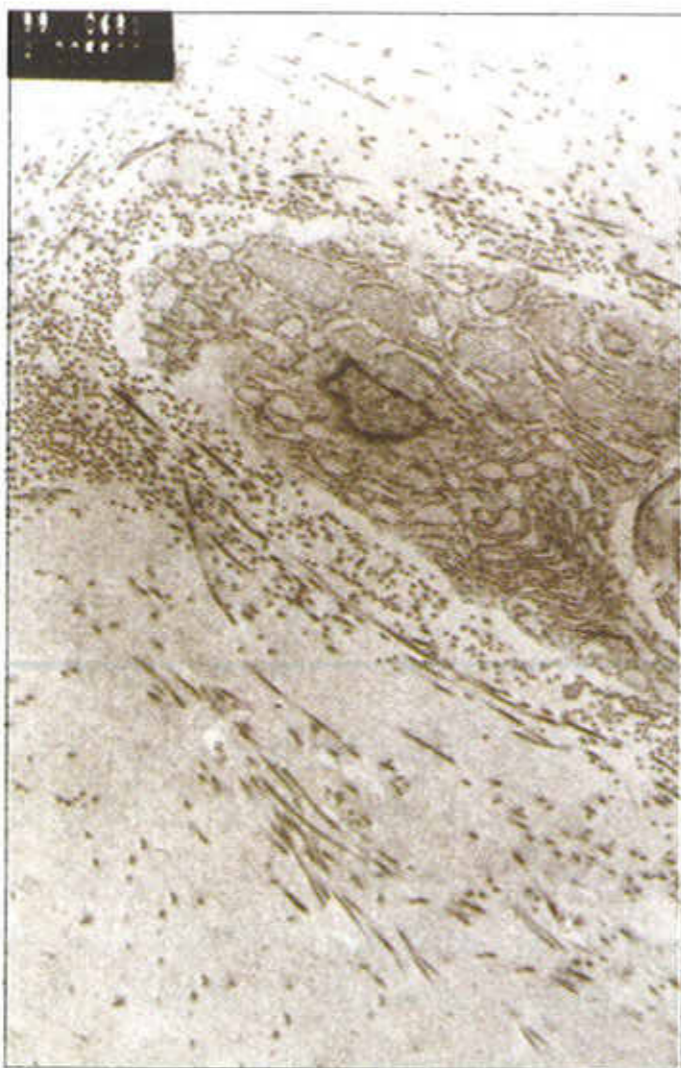


Fig. (24) (H8) = Electron Microscopy showing prominent rough endoplasmic reticulum and Golgi apparatus. Granulofilamentous material is present in and around fibroblasts.



Fig. (25) (H9) = Higher power of granulofilamentous material.

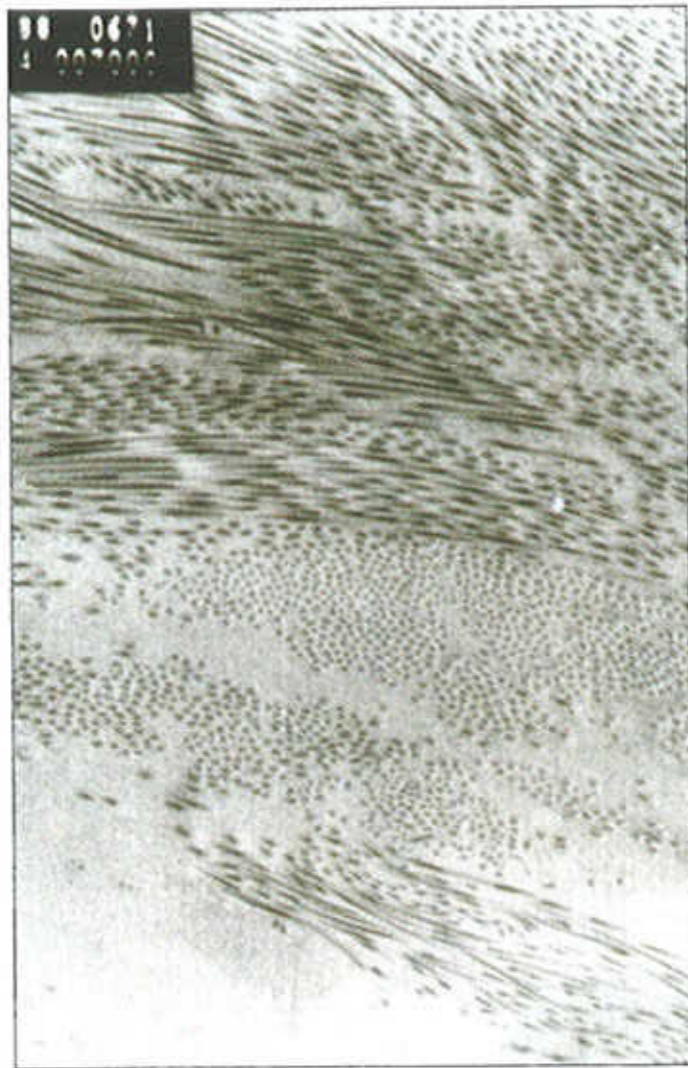


Fig. (26) (H10) = Fibrillar material in longitudinal and cross section.

A banding pattern is visible in the fibrillar or filamentous material.

calcification of soft tissues around the joint.

Laboratory examinations that might be needed for diagnosis of these patients include blood counts; immunologic studies; levels of urinary mucopolysaccharides and amino acids; screening for lysosomal enzyme defects in leukocytes and cultured fibroblasts (especially for ceramidase deficiency); serology for syphilis, cytomegalovirus, toxoplasma and rubella; karyotyping; and histopathology of lesions on skin and mucous membranes. These tests might reveal hypochromic microcytic anemia, hypoproteinemia, hypoglycemia and a slightly elevated erythrocyte sedimentation rate with no change in levels of serum calcium and phosphorus. Although they have recurrent infections or attacks of diarrhea, these patients often have a normal immunity.

X-rays of bones and joints, abdominal sonography, electro-myograms, ECG and EEG, are also important diagnostic tools.

Histopathologically the gingiva showed beneath the gingival epithelium deposits of amorphous hyaline material with several dilated hyperplastic blood vessels surrounded by inflammatory cells, mainly lymphocytes, plasma cells and histiocytes. There is fibroblastic proliferation with fragmentation of collagen fibres by thin fibrillar material. Examined by both light and electron microscopy, mucosal lesions show hyperactive spindle-shaped

fibroblasts and dysplastic mesenchymal cells⁽²⁾ within the cytoplasm of which can be seen dilated endoplasmic reticulum, prominent Golgi complexes and multivesicular bodies as well as single membrane vesicles filled with fibrillogranular material. Many of the fibrillogranular vesicles contain smaller vesicles and there are also invaginations of cell membrane containing fibrillogranular material similar to that seen in the single membrane vesicles, suggesting engulfment of an extracellular substance. The stroma contains both normal and serrated collagen fibrils, microfibrils and two types of fibrillogranular material, one of which has a characteristic banding pattern⁽²⁾.

In the skin lesions there are groups of cells in the dermis with abundant granular cytoplasm and oval or elliptical nuclei. These cells are embedded in an eosinophilic homogeneous hyaline ground substance formed of glycosaminoglycans and glycoproteins, strongly PAS-positive, negative to alcian blue, toluidine blue, congo red and resistant to amylase digestion⁽¹²⁾. Elastic fibres are not disorganized but reticulin is. By electron-microscopy collagen fibres are scarce and short in abundant granular material. Proliferating fibroblasts show a prominent cystic dilated rough endoplasmic reticulum and a hypertrophic Golgi apparatus containing cystic Golgi vesicles filled with fibrillar and granular material.^(8,13)

Immuno-histochemistry of cells of the skin lesions has shown them to contain vimentin,⁽¹⁴⁾ alpha-1-antichymotrypsin and alpha-1-antitrypsin. The spindle-shaped cells were negative for alpha smooth muscle actin and S-100 protein. The hyaline ground substance was positive for type I and type III collagen but negative for type II and type IV collagen and tenascin⁽¹⁵⁾ and so the disease is considered a hereditary disorder of collagen metabolism⁽¹⁶⁾. Type I collagen synthesis and degradation was found to be increased in fibroblasts of Juvenile Hyaline Fibromatosis compared with control fibroblasts⁽¹⁷⁾.

Juvenile hyaline fibromatosis is a rare condition and its pathogenesis is unknown. It is suggested that the hyaline material might be collagen type VI and the increase in that collagen might be the pathological basis for the hard skin and stiff joints⁽⁵⁾. Clinically it must be differentiated from arthrogryposis multiple and congenita, lipid proteinosis, mucopolysaccharidosis, Farber lipo-granulomatosis, congenital generalized fibromatosis, connective tissue

inflammatory disease of infancy, gingiva fibromatosis, Winchester syndrome, and infantile systemic hyalinosis (ISH).

Farber lipo-granulomatosis, is characterized by ceramidase deficiency. Gingiva fibromatosis is autosomal dominant and is limited to the gums and commonly occurs when teeth erupt.

Congenital generalized fibromatosis is characterized by subcutaneous and osseous fibrous lesions present since birth. Microscopically the nodules show proliferation of elongated spindle cells having the features of myofibroblasts ultrastructurally and macroscopically might suggest J.H.F but the lesions regress in 3 years^(18, 19). There may be visceral involvement with fibromatous nodules most commonly in the gastro-intestinal tract, lungs and heart. Lung involvement has a poor prognosis and most such affected infants die shortly after birth.

Winchester syndrome was described 1969⁽²⁰⁾. It is characterized by short stature, failure to thrive, painful joint stiffness and contracture with radiological changes resembling rheumatoid arthritis with negative serology and osteoporosis. Patients also have peripheral corneal opacities, coarse facial features, gum hypertrophy, papular lesions 0.5cm on buttocks, neck and ears. Patches of leathery skin with hypertrichosis may develop. Gross abnormality of the small intestine with multiple nodular filling defects and intestinal lymphangiectasis has been shown by jejunal biopsy. Patients also suffer from persistent diarrhea and protein-losing enteropathy. There is enhanced collagen turn over, active synthesis of collagen and active collagen phagocytosis. Patients are in relative good health and survive to adulthood. This syndrome shares most of the characteristics of infantile systemic hyalinosis with which it may be confused.

Infantile systemic hyalinosis (ISH) affects infants and children who show thickened hard skin with hyperpigmentation, especially over knuckles and malleoli; papular skin lesions around the nose, mouth, chin, upper eyebrows, behind the ears and the nape of the neck and nodules in the perianal region and around the nose and mouth.. Gingival hy-

perplasia is a major characteristic. Patients show limitation of joint mobility in the first few weeks of life. They suffer from persistent diarrhea, failure to thrive and recurrent severe infections and generalized osteopenia. Colonoscopy has shown diffuse colitis with no obvious ulceration. Hyaline material is deposited in the skin, gastrointestinal tract, heart, trachea, spleen, muscles, thyroid, thymus and lymph nodes. In rectal biopsies electron microscopy shows deposits of fibrillogranular material at the tips of the lamina propria. Similar deposits are described in the deep dermis with numerous macrophages and fibroblasts containing intralysosomal fibrillogranular material whose appearances and localizations are identical with that of type VI collagen. ISH appears to be a distinct disorder which may be due to excessive deposition of type VI collagen⁽²¹⁾.

The two sisters reported here are siblings of a second degree consanguineous marriage. There is no family history of a similar condition although three uncles and one aunt have diabetes mellitus. In both sisters the clinical manifestations could be characteristic of both JHF and ISH. As there is also a striking similarity in the histology of both conditions when examined by light and electron microscopy, it is suggested that ISH and J.H.F. represent different expressions of the same disorder with ISH being a severe form with early onset and JHF being a milder form with a later onset.^(5, 1, 2, 22)

There is no satisfactory treatment for J.H.F. although many treatments have been tried. Large skin nodules may be removed successfully surgically but some report that they tend to recur⁽²⁴⁾. Gum hypertrophy is treated successfully surgically by partial gingivectomy. Systemic steroid and intralesional steroid treatments have been tried as have also orthopedic therapy, physiotherapy and penicillamine. Proteolytic enzymes are still under trial⁽⁵⁾. Dimethylsulfoxide and ketotifen were attempted in treatment of JHF⁽²⁵⁾. Calcitriol was tried and had limited effect⁽¹⁾.

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