# Juvenile hyaline fibromatosis

Y. Kitano

SUMMARY

**Juvenile hyaline fibromatosis is a rare congenital disease with characteristic clinical and histopathological features. Clinical symptoms develop early in life, ranging from one month to four years of age. Tumors and nodules are the most outstanding symptoms. Whitish papules, hypertrophy of the gingiva and flexural contracture of joints are the essential symptoms. X-ray examination often reveals osteolytic or destructive bone lesions. Histopathology shows abundant deposition of hyaline substance in the tumor. In most cases, those main symptoms are not directly life-threatening, but ultimate prognosis is poor.**

KEY WORDS

**fibromatosis, congenital, tumor, papule, gingival hypertrophy, joint contracture, osteolysis, hyaline**

## Introduction

Juvenile hyaline fibromatosis (JHF) is a rare congenital disease characterized by tumors of the skin, whitish papules, hypertrophy of the gingiva and flexural contracture of the joints. The first report was made by Murray under the name of "peculiar cases of molluscum fibrosum" (1). In 1903, Whitfield and Robinson mentioned the follow-up of the three cases reported by Murray, and described that those cases did not belong to neurofibromatosis but should be placed simply in the category of multiple fibromata (2). Since then has been no report and the disease was nearly forgotten. In 1962, Puretić et al. described the condition under the name of "a unique form of mesenchymal dysplasia" (3), and then reports of this disease were increasing in number until now. This disease is distributed all over the world and case reports came from Japan, England, Kenya, Lebanon, Poland, Portugal, South Africa, Spain, USA and Yugoslavia. Recently, this disease was included in the textbooks under the name of 'juvenile hyaline fibromatosis' (4,5).

## Etiology

Family anamnesis shows the hereditary nature of the disease. The patients were born from apparently healthy parents often of consanguineous marriage, and sibling cases were occasionally reported. These strongly suggested an autosomal recessive trait of inheritance. Male and female ratio is 6:4.

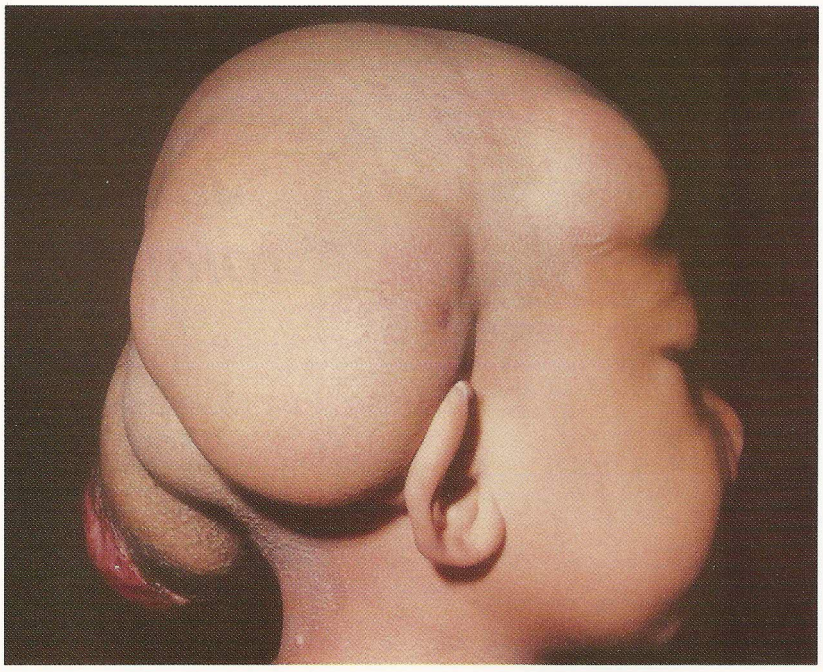


Fig. 1. Large tumors in scalp.

## *Clinical symptoms*

The onset of the disease is very early, ranging from one month to four years of age. Tumors and nodules are the most outstanding symptoms. Hypertrophy of the gingiva and flexural contracture of the large joints of the extremities are also noted early.

The tumors in the scalp become large, and sometimes reach up to 15 cm in diameter (Fig.1). The

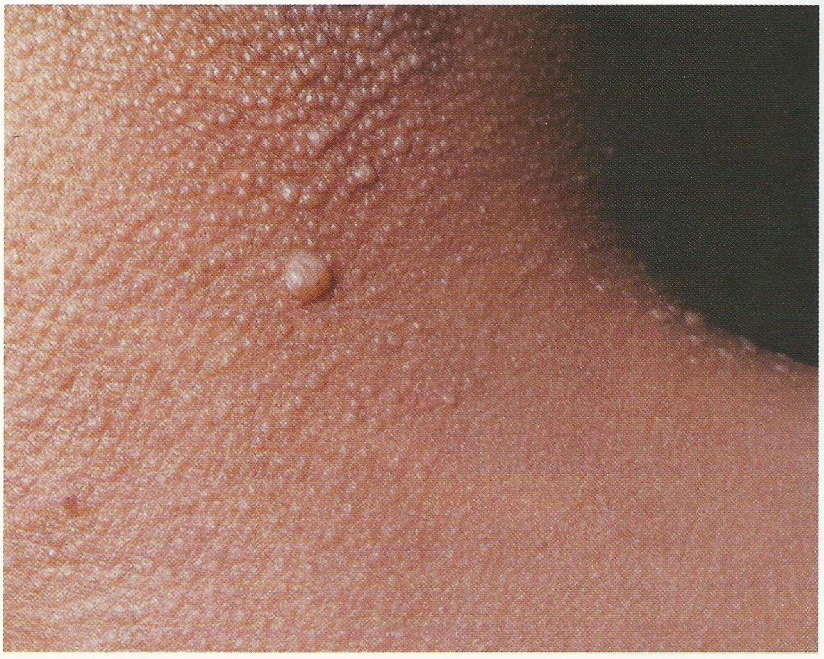


Fig. 2. Pale-pinkish papules in neck and shoulder.

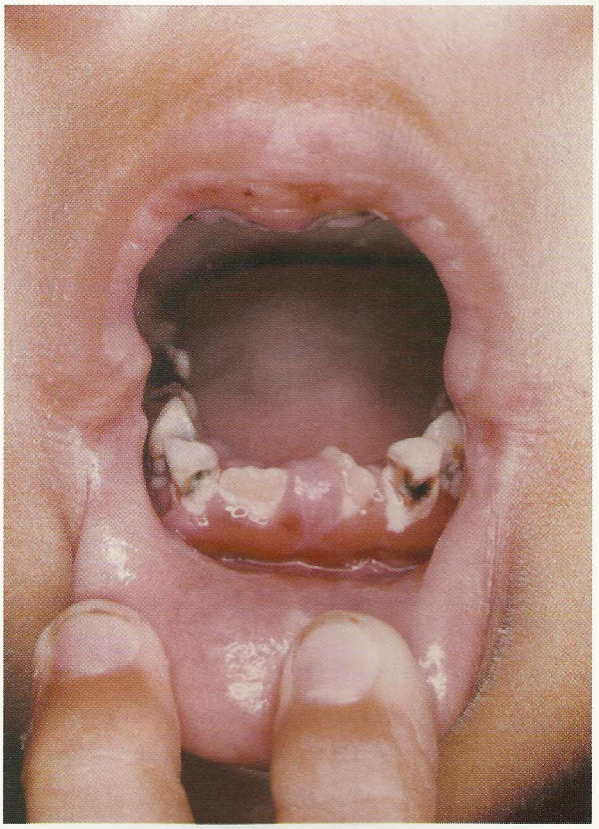


Fig. 3. Hypertrophy of gingiva.

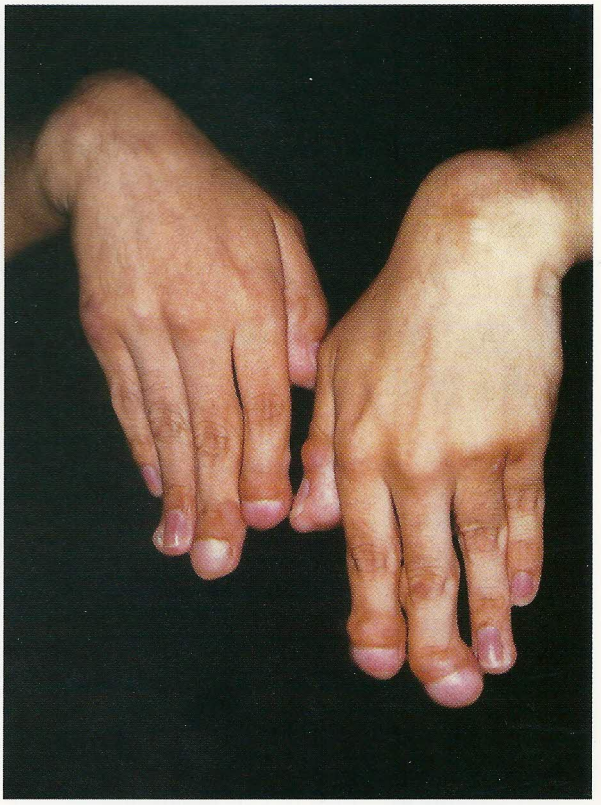


Fig. 4. Club-like enlargement of tips of fingers.

tumor is dome-shaped or protrudes globally. The surface is smooth, and covered with normal skin. When the tumor is large, the covering skin is stretched and often ulcerated. Semitranslucent pinkish tumor tissue can be observed. The newly appeared tumor is rather soft and elastic. At first it enlarges rapidly, and after a while stops to enlarge. The tumor becomes increasingly hard, and after several years has cartilage-like consistency. The tumors usually adhere to the skin and are movable on the underlying bone. The tumors can develop in any site of the body. But the sites of predilection are the scalp, post-auricular folds, the extensor aspects of shoulder, elbow and knee joints and the perianal region. Papules of 2-3 mm size have been described in a half of the cases. These are whitish or pale-pinkish in color and have a waxy surface (Fig. 2). The sites of these papules are limited to the both sides of ala nasi, post-auricular region and neck.

The gingiva is so hypertrophic that sometimes the teeth are buried in it. The hypertrophic gingiva is flesh-colored, semitranslucent and granular on the surface (Fig. 3). The nodules of perioral region often impair opening of the mouth. The perianal area is also undulated by the nodules and incontinence is noted.

Flexural contractures of the large joints of the extremities, such as shoulder, elbow, hip and knee are essential symptoms. The contracture appears early, and often as the first symptom. Some patients have never walked due to the severe contractures of the hip and knee joints, which appear within one year after birth. The tumor is often noticed around these joints. Muscle atrophy is often described. Enlargement of the distal portions of the fingers and toes occur at a late stage (Fig.4).

There are no essential symptoms involving the nervous, respiratory, cardiac, and digestive systems. Few reports describe mental retardation possibly due to inadequate education.

## *Laboratory examination*

Hypochromic anemia was reported in several cases. Other routine laboratory examinations do not reveal any specific abnormality.

On X-ray examination, osteolytic or destructive bone lesions are often found. The lesions are classified in three types.

1) Destruction of bone of large joints of extremities, such as humeral head (Fig.5). There is no mobility of the joint.

2) Round or oval, punched-out osteolytic lesions of the skull, and long bones of the extremities.

3) Osteolysis of honeycomb-appearance of the distal phalanges of fingers and toes (Fig.6). This change results finally in complete destruction of the phalanx. The finger takes the shape of club.

## *Histopathology*

The histopathologic findings of JHF are characteristic. The tumor is located in the dermis. It is fairly well circumscribed from the surrounding dermal connective tissue, but does not have a capsule. The tumor is composed of tumor cells and abundant ground substance. The tumor cells have oval or elliptic nuclei and a fine granular or vesicular cytoplasm, which is stained pale pink in HE staining. The cells are buried in the ground substance in groups of a few to several cells and the tissue looks like cartilage. The ground substance is eosinophilic and homogeneous with some wavy filaments (Fig.7). In the early growing stage there are many dilated blood vessels. After the tumor stops to grow and becomes hard (in consistency), the number of tumor cells decreases and the amount of fibrous elements increases in the ground substance. The substance is strongly positive to PAS staining and resistant to amylase digestion. Alcian blue staining is negative and metachromasia is partially seen with toluidine blue. Congo red did not stain the substance. The epidermis overlying the tumor is atrophic.

The hypertrophic gingiva shows deposits of amorphous eosinophilic substance with several tumor cells beneath the oral epithelium. The histopathologic picture of the papule is also characteristic. A deposit of an amorphous substance is observed beneath the epidermis. A few tumor cells, dilated blood vessels, and an infiltration of inflammatory cells are seen in the ground substance.

Electron microscopic examination of the tumor tissue revealed that the ground substance is composed mostly of delicate filaments (6,7). Uniform fine particles are occasionally seen mixed with the filaments. The fibrils with a cross-banded structure of 60-100 nm periodicity are occasionally observed (8) (Fig.8). The cross-banded structure corresponded to so-called zebra body, which was recently suggested to be composed of type VI collagen. Numerous intracytoplasmic granules with a limiting membrane characterize tumor cells (Fig.9). The granule contains delicate filaments and fine particles similar to those of the ground substance. Dilated rough endoplasmic reticulum contains fine particles of the same electrondensity as the ground substance. The Golgi apparatus is well developed, and contains the same substance as the granules. A connection between the Golgi vesicles and the granules is seen. Electron microscopic observation shows that the ground substance is produced by the tumor cells.

Biochemical analysis of the tumor tissue showed that the tumor glycosaminoglycans consist of chondro-

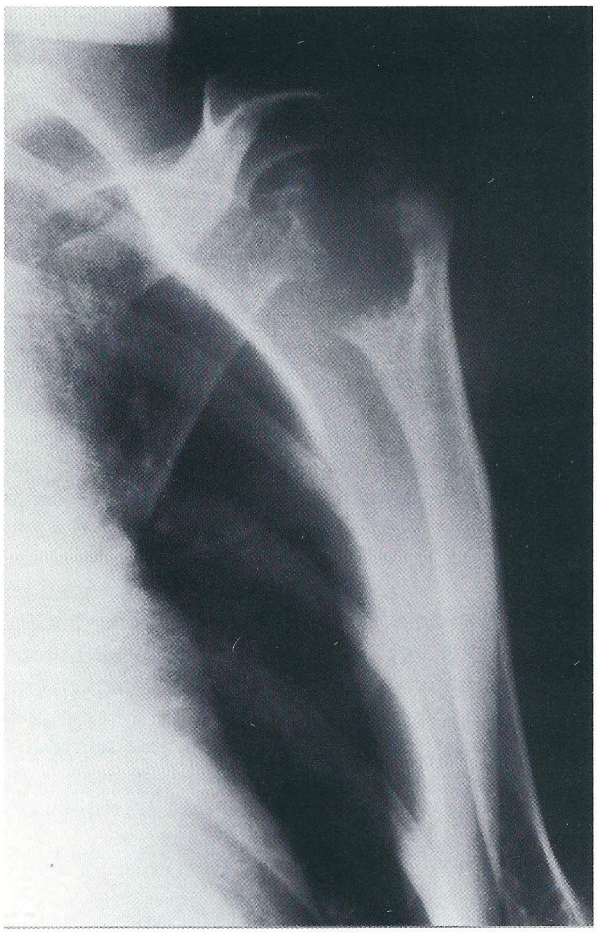


Fig. 5. Destruction of humeral head.

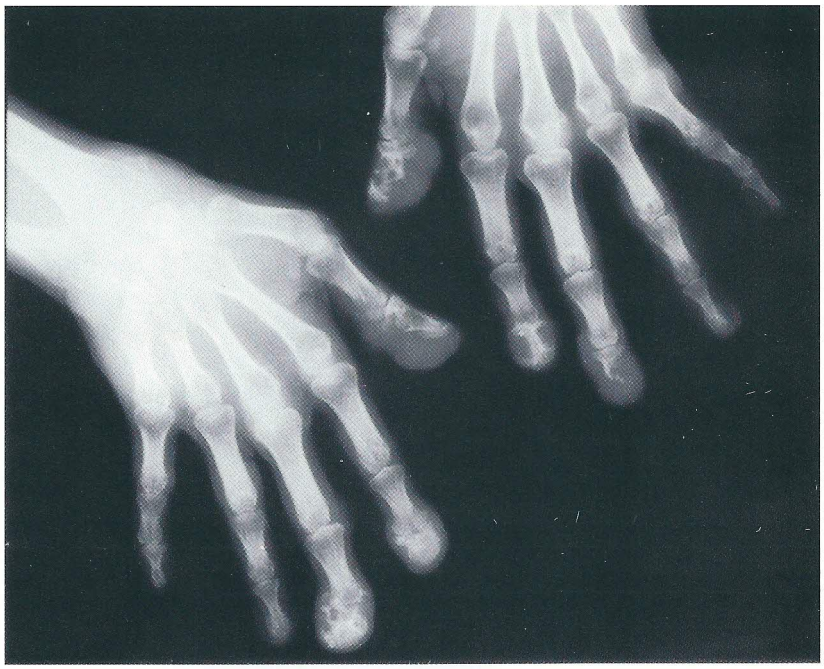


Fig. 6. Osteolysis of distal phalanges. Some have honeycomb-appearance.

itin sulfate, dermatan sulfate and hyaluronic acid. The proportion of each glycosaminoglycan varied from report to report. Characterization of collagen showed that the hyaline substance mainly consisted of type VI collagen (9).

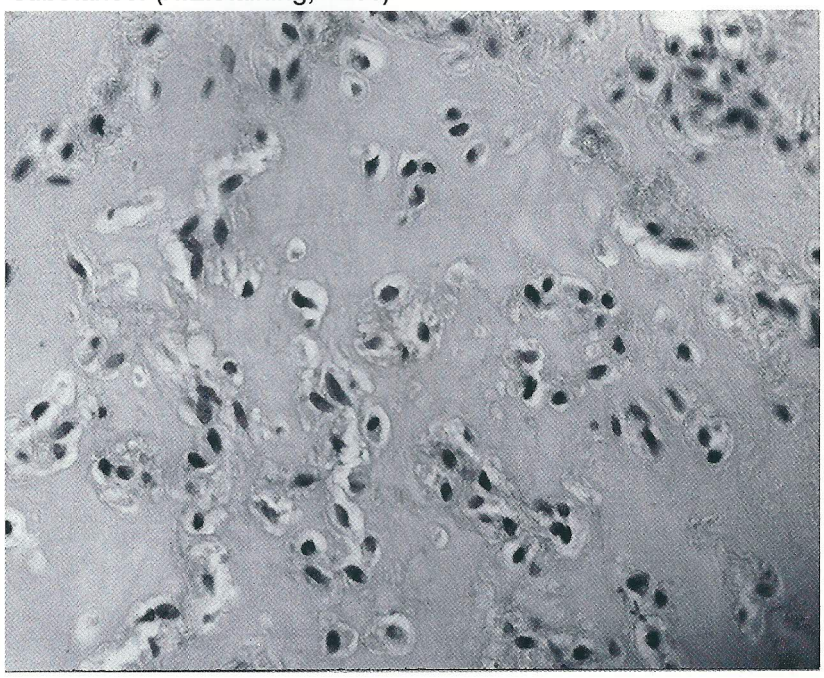
The findings of histopathology, electron microscopy and biochemical analysis suggest that the tumor cells proliferate at first and produce the ground substance. The substance is secreted and the cells are embedded into the substance. The ground substance consists of collagen, probably type VI, and glycosaminoglycans.

Autopsy was done in one case (6). There were deposits of hyaline substance in the tongue, esophagus, stomach, small intestine, thymus, spleen and lymph nodes as well.

## *Diagnosis and differential diagnosis*

Tumors, especially the large tumors on the scalp, whitish papules, hypertrophy of the gingiva and flexural contracture of the large joints of the extremities are

Fig. 7. Histopathology of tumor. The tumor cells are buried in the eosinophilic homogenous ground substance. (H.E.staining, ×200)



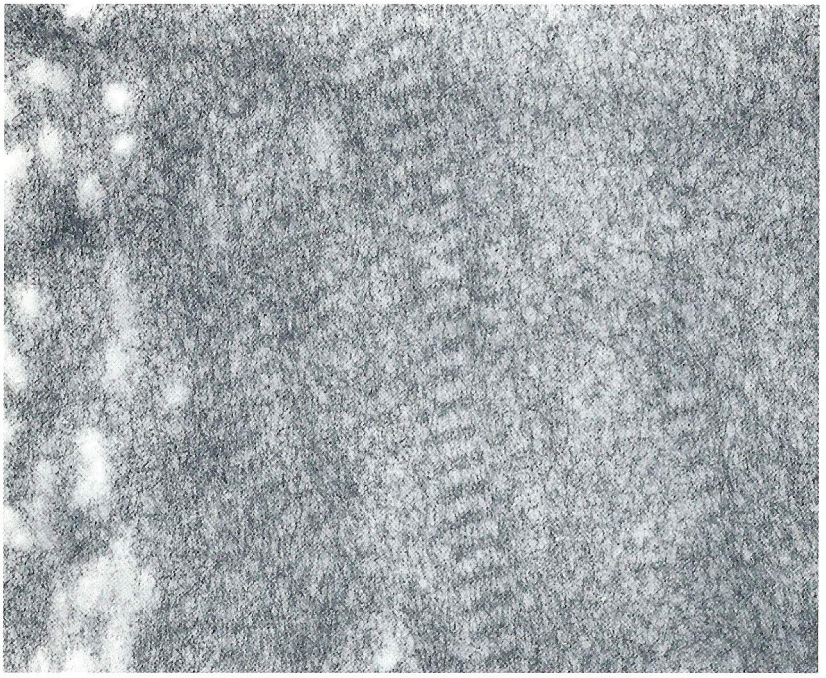
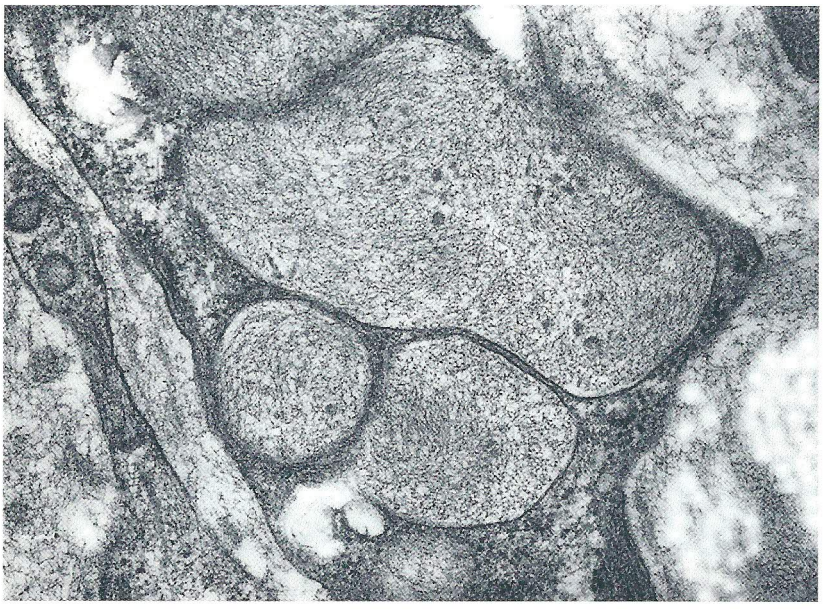


Fig. 8. Electron microscopy of tumor tissue. The ground substance is composed of fine fibrils which occasionally show a cross-banded structure of 60-100 nm periodicity. (×3,000)

Fig. 9. Intracytoplasmic granules of tumor cell. The granule has a limiting membrane and contains delicate filaments and fine granules. (×3,000)



characteristic symptoms of JHF. Early onset is also important. Histopathology of the tumor tissue confirms the diagnosis.

So-called juvenile fibromatosis, such as congenital generalized fibromatosis, juvenile aponeurotic fibroma, calcifying fibroma and infantile myofibromatosis, are to be differentiated. The tumors in this disease may contain hyalinized portions or cartilage-like substance. But these histological structures do not permeate the whole tumor tissue. In hyalinosis cutis et mucosae, deposition of hyalinoid substance is observed around blood vessels of the upper dermis.

There are several cases reported under the diagnosis of infantile systemic hyalinosis (ISH) (10,11). These cases showed stiff skin and painful joint contractures in the first few months after birth. Other features were small papules, perianal nodules, hyperpigmentation over the metacarpophalangeal joints and the malleoli, gingival hyperplasia, persistent diarrhea, and failure to thrive. Most patients were dead by the age of 20 months. Hyaline material was found in the papillary dermis. Ultrastructurally, the hyaline material had fibrillogranular appearance in which a banding pattern could be observed. There are striking similarities in clinical features and histological findings between JHF and ISH and it is proposed that JHF and ISH represent different expressions of the same disorder (11,12).

Winchester syndrome is characterized by short stature, coarse facial features, peripheral corneal opacities and joint stiffness and contractures. Cutaneous changes are diffuse thickening, hypertrichosis and hyperpigmentation. Radiological examination reveals destructive changes at the epiphyseal articular margins of the hands, wrists, feet and ankles. The histological findings of gum and skin biopsies showed an abundance of fibrillogranular material (13). The multiple large tumors and nodules were not reported in Winchester syndrome.

## *Treatment and prognosis*

When the tumor becomes large, disfiguring and causes functional disturbance, excision is indicated. Sometimes, intratumoral injection of corticosteroid is effective when the tumor is still soft and fast growing in the stage of early development (6). Radiation therapy is not effective (3). Hypertrophic gingiva can also be excised, but recurs in a short period (13,14,15). Orthopedic surgery, including capsulotomy, was performed to make the contracted knee joints movable. After a few months of rehabilitation, the patient could stand and walk with the aid of long leg braces. But the contracture recurred soon (7).

In JHF, neurological abnormality is not found, and mental development is essentially not retarded. Disfiguring tumors and joint contracture deprive the patients of the normal social life. The patients with ISH and two severe cases reported by Bedford at al. were dead before the age of 24 months (10,11,16). The reported longest survivor was 51 years old. A patient reported in 1972 and followed by myself is 39 years old by now (6). He is disabled by contractures of joints of extremities, but his internal organs, including heart, lung, liver and kidney do not show functional disturbance.

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**AUTHOR'S ADDRESS** *Yukio Kitano MD, professor of dermatology, Department of Dermatology, Hyogo College of Medicine, 1-1 Mukogawa-cho Nishinomiya, Hyogo 663-8501, Japan*