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ABSTRACT

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A CASE OF ORPHAN HYALINE FIBROMATOSIS SYNDROME IN UKRAINE

Background. Hyaline fibromatosis syndrome is a rare, highly dramatic, autosomal recessive multisystem disorder. The basis of the disease is the abnormal diffuse deposition of hyaline material in the connective tissue and internal organs. Mutations in the CMG2 gene (also known as the ANTXR2 gene) cause the disease. CMG2 encodes a transmembrane protein involved in endothelial development. Hyaline fibromatosis syndrome involves two allelic diseases that have the same phenotype. These are infantile systemic hyalinosis and juvenile hyaline fibromatosis. Common signs of these diseases are pain, joint contractures, skin lesions (thickening of the skin with areas of hyperpigmentation, pearl-sized nodules or papules), subcutaneous nodules on the head, neck, and extremities, gingival hypertrophy, osteopenia, protein-losing enteropathy, increased susceptibility to infectious diseases. Diseases differ in the time of the first clinical signs onset, the severity of the course, and the life expectancy of patients. In the case of infantile systemic hyalinosis, the prognosis is fatal. Hyaline fibromatosis syndrome is an orphan disease that is very difficult to diagnose. There is no pathogenetic treatment for the disease today.

Clinical case. We described a case of hyaline fibromatosis syndrome in a boy who was observed and treated at the Municipal Non-Profit Enterprise of Sumy Regional Council "Regional Children's Clinical Hospital" (Ukraine). The diagnosis was made based on medical and genetic analysis. The early manifestation of symptoms and the severe course of the disease forced us to think about infantile systemic hyalinosis in the child. Along with characteristic external phenotypic signs, severe enteropathy with protein loss and persistent infections were observed in the child. As far as we know, this is the first case of the disease diagnosed in Ukraine.

This publication aims to draw medical professionals' attention to the diversity of the course of genetic diseases in children. Comprehensive care, timely and symptomatic treatment make it possible to prolong the life of patients.

Keywords: ANTXR2, hyaline nodules, joint contractures, protein-losing enteropathy, multisystem failure.

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ВИПАДОК ОРФАННОГО СИНДРОМУ ГІАЛІНОВОГО ФІБРОМАТОЗУ В УКРАЇНІ

Синдром гіалінового фіброматозу – це рідкісне, дуже драматичне, аутосомно-рецесивне мультисистемне захворювання. В основі хвороби лежить аномальне дифузне відкладення гіалінового матеріалу у сполучній тканині та внутрішніх органах. Захворювання викликають мутації у гені CMG2 (також відомий як ген ANTXR2). CMG2 кодує трансмембранний білок, що бере участь у розвитку ендотелію. Синдром гіалінового фіброматозу включає два алельних захворювання, які мають однаковий фенотип: інфантильний системний гіаліноз і ювенільний гіаліновий фіброматоз. Загальними ознаками цих захворювань є біль, контрактури суглобів, ураження шкіри (потовщення шкіри з ділянками гіперпігментації, вузлики або папули розміром із перлину), підшкірні вузлики на голові, шиї та кінцівках, гіпертрофія ясен, остеопенія, ентеропатія з втратою білка, підвищена сприйнятливість до інфекційних захворювань. Захворювання відрізняються часом появи перших клінічних ознак, тяжкістю перебігу та тривалістю життя пацієнтів. У разі інфантильного системного гіалінозу прогноз фатальний. Синдром гіалінового фіброматозу – орфанне захворювання, його дуже складно діагностувати. Патогенетичного лікування захворювання сьогодні немає.

Випадок. Ми описуємо випадок синдрому гіалінового фіброматозу у хлопчика, який спостерігався та лікувався у Комунальному некомерційному підприємстві Сумської обласної ради "Обласна дитяча клінічна лікарня" (Україна). Діагноз було виставлено на підставі медико-генетичного аналізу. Думати про наявність у дитини інфантильного системного гіалінозу нас змусили рання маніфестація симптомів та тяжкий перебіг хвороби. Поряд із характерними зовнішніми фенотиповими ознаками, у дитини спостерігалися важка ентеропатія із втратою білка, персистуючі інфекції. Наскільки нам відомо, це перший випадок захворювання, що було діагностовано на території України. Метою цієї публікації є привернення уваги медичних фахівців до різноманіття перебігу генетичних захворювань у дітей. Ретельний догляд, своєчасне симптоматичне лікування дають змогу подовжити життя пацієнтам.

Ключові слова: ANTXR2, гіалінові вузлики, контрактури суглобів, ентеропатія з втратою білка, мультисистемна недостатність.

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INTRODUCTION / ВСТУП

Abbreviations

ALT – alanine aminotransferase

ANTXR2 – anthrax toxin receptor 2

AST – aspartate aminotransferase

CMG2 – capillary morphogenesis gene 2

HFS – hyaline fibromatosis syndrome

ISH – infantile systemic hyalinosis

vWA – Willebrand factor

RCCH – Municipal Non-Profit Enterprise of Sumy Regional Council "Regional Children's Clinical Hospital"

Hyalinosis is a change in the tissues of the body, characterized by the appearance of translucent dense protein masses outside the tissue cells. These formations seriously disrupt the function of various body organs and joints. The destruction of fibrous structures leads to a violation of tissue-vascular permeability; the tissue is infiltrated by plasma proteins.

The hyaline fibromatosis syndrome (HFS) (its variant: infantile systemic hyalinosis (ISH)) is a very rare systemic disease that is inherited in an autosomal recessive way and belongs to a heterogeneous group of genetic fibromatosis [1, 2]. ISH is characterized by widespread deposition of hyaline material similar to type VI collagen and abnormal proliferation of hyalinized fibrous tissue in the dermis, joints, skeletal and cardiac muscles, thyroid, adrenal glands, spleen, and gastrointestinal tract. The brain does not suffer. ISH usually manifests at birth or immediately after birth (usually in the first 3 months of life). Clinical manifestations of ISH persist and progress throughout the child's life. This is a fatal disease. Due to multisystem failure, patients die within the first 2 years of life [2, 3]. HFS is caused by a gene mutation in the extracellular protein-binding domain of a protein called capillary morphogenesis protein-2 (CMG2). The CMG2 gene encodes a type I membrane protein that is ubiquitously expressed in the human body, except for the brain. In 2003, CMG2 was identified as the second receptor for anthrax toxin, hence its official name, anthrax toxin receptor 2 (ANTXR2). This gene encodes a transmembrane protein that is responsible for binding laminin and type IV collagen through the von Willebrand factor (vWA) domain A and, as a result, participates in the construction of the basement membrane and the morphogenesis of endothelial cells [4]. Fun Fact: One week after the horrific terrorist attacks on September 11, 2001, letters were sent to several news outlets. The letters contained anthrax spores, which posed a great danger. These events boosted anthrax-related research and put ANTXR2 in the spotlight. Just then, ANTXR2 was identified as the gene responsible for a rare autosomal recessive human disease – HFS [5].

Case history. The boy S. was repeatedly treated in the Municipal Non-Profit Enterprise of Sumy Regional Council "Regional Children's Clinical Hospital" (RCCH) for four years and 8 months of his life. The child was from the first pregnancy. Prenatal ultrasound determined the breech presentation of the fetus. The delivery was performed by cesarean section at 40 weeks gestation. Assessment on the Apgar scale was 7–9 points. The boy was born with a body weight of 3050 g and a height of 50 cm. He was put to the breast 3 hours after the birth. The child was discharged from the maternity hospital on the 5th day of life in a satisfactory condition. According to the parents, no genetic problems were observed in the family. In the neonatal period, the child's phenotype was normal; the parents had no complaints. During a preventive examination at the age of 1 month, the pediatrician noted hypotonus of the upper limbs and limitation of extension in the knee joints. The diagnosis was a perinatal lesion of the central nervous system. A massage was prescribed.

At the age of 3 months, the boy was hospitalized for the first time in RCCH with complaints from parents about the child's anxiety, bouts of painful crying, and "stiffness" of the joints. The diagnosis was made: spastic-tonic syndrome, movement disorders; hip dysplasia. Treatment: physical therapy, massage, electrical stimulation of the upper and lower limbs, cinnarizine, cortexin. No positive changes were observed as a result of the treatment. The child was in pain. At the age of 4 months, the patient developed painful limitations of upper and lower limb movements in several large and small joints. Contractures of these joints have formed. Enlarged gums attracted attention. The boy did not suck the breast very well, so the mother expressed milk and spoon-fed him.

At the age of 5 months, the boy spontaneously developed swelling in almost all joints of the limbs: hand, wrist, elbow, knee, foot, and ankle joints. Swelling of the joints was accompanied by severe pain syndrome. The skin over the affected joints was purplish-bluish. Movements in the joints were sharply limited and painful. The prescribed therapy (nonsteroidal anti-inflammatory drugs, prednisone) was not sufficiently effective. By the 7th month of life, the boy had new symptoms: small papular nodules on the face, apparent hyperplasia of the gums; hypertrophy of the alveolar processes of the upper jaw; reddish-bluish, thickened, and compacted skin in the neck and back. Episodes of diarrhea appeared (2–3 days a week), for which the child was examined and treated in the infection department. The examination showed that he was low on serum albumin, and had a normal globulin index. With the help of several immunological tests, an infectious genesis of chronic enteropathy was excluded. Diagnosis: malabsorption of unspecified genesis.

At the age of 9 months, the child was consulted at the Sytenko Institute of Spine and Joint Pathology National Academy of Medical Sciences of Ukraine (Kharkiv, Ukraine). Conclusions: dysplasia of the hip joints, contractures of the joints of the upper and lower limbs, osteoporosis; consolidated fractures of the proximal parts of both femurs, bones of the left forearm. Accumulation disease (maybe mucopolysaccharidosis) was suspected. Based on clinical data, a diagnosis of Farber's lipogranulomatosis was made in the medical-genetic center.

At the age of 13 months, the boy was treated for acute pneumonia for 12 days at the RCCH. At that time, the child had a specific phenotype: coarse facial features (broad face); hyperplasia of the gums; high palate; short neck; wide short chest; contractures of the elbows, knee joints, hand joints; pigmentation of the skin over the joints; hyperpigmentation of the scrotum; hygromas on the hands; chondromas on the feet and elbows; papilloma on the right ear; hyperemia of the skin areas of the scalp, back, sacrum; slight nodular rash on the face; dark erythematous plaques on the lower back above bony projections and perianal sessile nodules (Fig. 1–5). The patient could not stand on his own and reacted painfully to examinations. But he smiled and tried to speak ("mom," "no", "yes", "window"); according to his mother, he liked to "read" books and listen to songs.

At the age of 15 months, the child was sent for consultation at the Ohmatdyt National Specialized Children's Hospital of the Ministry of Health of Ukraine. A diagnosis was made: infantile systemic hyalinosis. Differential diagnosis was carried out between accumulation diseases, Farber's lipogranulomatosis, and tuberculous lesions of the bone and joint system. To verify the diagnosis, a biopsy of the affected skin in the back, and lateral bone of the left lower limb was performed. Pathohistological findings: fragment of skin and soft tissues with collagen fibrosis, foci of hyalinosis; ulcer areas with an inflammatory reaction in the tissues, and the presence of capillary sinusoids. Diagnosis: infantile systemic hyalinosis (ISH) with the autosomal recessive type of inheritance. The repeated genetic risk in this marriage is 25%.

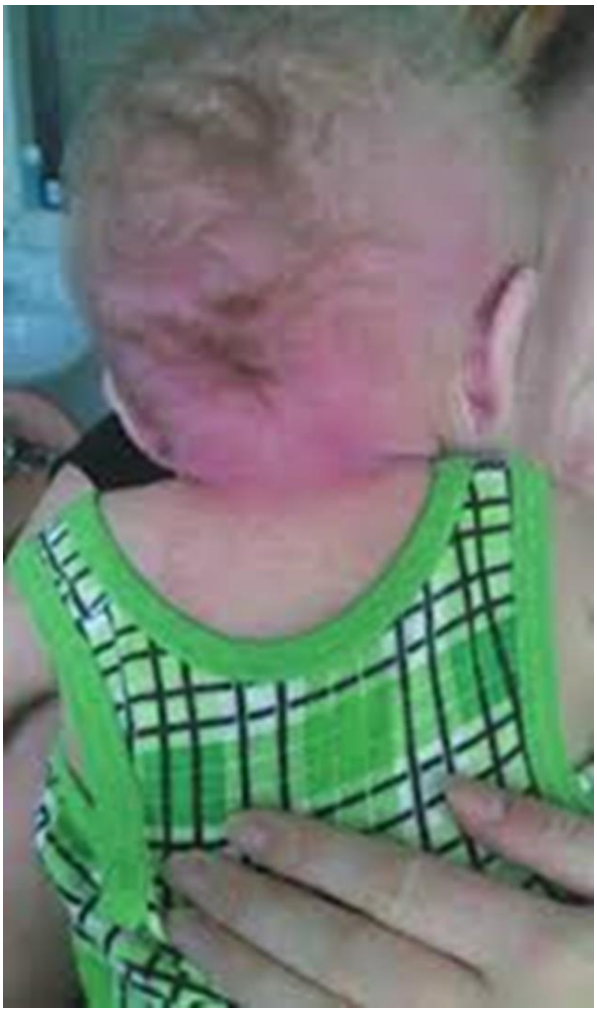

Figure 1 – Hyperpigmentation of the skin [10]

Unfortunately, the parents did not permit us to re-photograph the child. We have shown here a photo of the boy taken at Ohmatdyt. The child is 15 months old [10].

Figure 2 – Hyperpigmentation of the skin. Erythematous plaques on the lower back over bony prominences and perianal sessile nodules [10]

Further, we observed the patient at the age of 18 months. The boy was sick with SARS for 3 days, then profuse diarrhea appeared; he vomited twice, and refused to eat. The parents watered the child (ORS) but to no avail. Examination: the phenotypic status was the same, and the pain syndrome was pronounced (the child was examined extremely sparingly). There were obvious signs of dehydration: a body weight deficit of 8% (the mother weighed her son every day). Laboratory findings: the level of serum albumin = 1.2 g/dL (the norm in children under 3 years of age = 1.7); anemia of mixed genesis of moderate severity, moderate leukocytosis with lymphomonocytic predominance, thrombocytosis, high level of C-reactive protein up to 6.0 g/l. In the intensive care unit, the child received full parenteral nutrition, and infusion therapy, including 10% albumin 10–15 ml/kg/day, a broad-spectrum antibiotic.

At the age of 2 years and 10 months, our patient had another pneumonia complicated by sepsis (osteomyelitis of the right hip, enteropathy with protein loss worsened, disseminated intravascular coagulation). The child received detoxification therapy, albumin in a volume of 20 ml/kg/day, vancomycin, immunoglobulin, and symptomatic treatment. For 4 days, the child was treated in the intensive care unit, then another 2 weeks in the somatic department.

At the age of 4, the boy was hospitalized three times at the RCCH. Manifestations of the main diagnosis progressed (characteristic phenotype, chronic diarrhea with frequent episodes of severe dehydration, pneumonia). Growth retardation and body weight deficiency (15–20%) were noted. Phenotypically, "only the eyes looked healthy", but the eyes were "adult" and sad. The intellectual status of the patient should be noted. Despite the constant debilitating pain, the boy was quite friendly, and communicated easily with the staff, although his speech was difficult. The child watched cartoons with pleasure, loved music, listened to books with great interest, knew numbers and counted within 20, and knew all the letters. It was noticeable that the parents took great care of their son, and treated him with great love.

For the last time, we observed the child when she was 4 years and 8 months old. The patient came to the hospital with pronounced pain and asthenic syndromes, with respiratory failure (Sa O_2 = 88%) and severe low-level protein enteropathy. Attention was drawn to general pastiness and swelling of the lower limbs and hands. Ultrasound revealed signs of fluid in the pericardium. An X-ray revealed signs of osteoporosis of the hands, lower legs, hips, hip joints, and fractures of both tibia and thighs, bones of the left forearm. Clinical blood analysis showed signs of anemia (hemoglobin = 8.2 g/dL) and thrombocytosis ($654x10^9$/L). Serum albumin = 0.8 g/dL (the norm for a 5-year-old child = 1.55), the values of ALT, AST, and creatinine were higher than the norm. In the intensive care unit, the boy underwent mechanical ventilation, intensive rehydration, albumin infusion, antibiotic therapy, and immunoglobulin. But against the background of multisystem failure, the boy died. No pathological examination was performed.

Our Kyiv colleagues were the first to describe this case of ISH [10]. We observed the child for more than 3 years. So far, this case remains the only literature-registered case of ISH in Ukraine. Now the girl is growing up in the family. She is 3 years old. She did not have any signs of the disease. Medical-genetic counseling was not carried out.

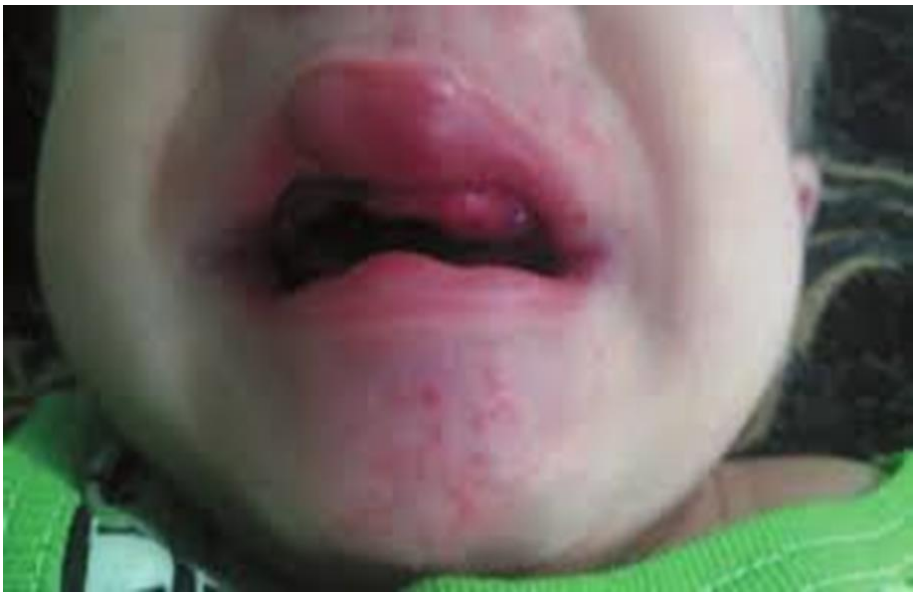

Figure 3 – Gum hypertrophy [10]

Discussion. Clinical signs of HFS were first described in 1873 by Murray J. The disease was named "Molluscum Fibrosum". Almost 100 years later (Drescher et al., 1967) called the disease "juvenile hyaline fibromatosis". A little later (1986), the name "infantile systemic hyalinosis" appeared [6]. According to the literature, about 250 cases of HFS have been registered in the world, including about 50 cases of ISH. The prevalence of this pathology is less than 1 case per 1,000,000 of the global population. ISH is a fatal disease. A milder form of HFS, juvenile hyaline fibromatosis, has a similar clinical picture. The prognosis for patients with juvenile hyaline fibromatosis is generally better: but patients who survive even to adulthood suffer from crippling joint deformities [5, 7, 8]. In the case of ISH, recurrent purulent infections, chronic diarrhea, and severe osteoporosis develop already in the first year of life. Intense arthralgias and contractures with limited range of motion in the joints lead to immobility. Congestion in the lungs and respiratory failure develop. In connection with the hyaline infiltration of the intestinal wall and the developing enteropathy, there is a loss of protein and, as a result, problems with feeding, protein-energy deficiency, and cachexia. Death occurs as a result of secondary sepsis with multiple organ failure, usually before the age of two years [7].

Clinical features of HFS. Skin nodules and pearly white to pink papules several millimeters in size are often found on the face and neck. Fleshy lesions may appear in the perianal region. These lesions develop and become more numerous over time. The skin is dense on palpation and thickened.

Contractures progress (60%). There may be congenital contractures. Pain or excessive crying (100%). Severe pain during passive movements,

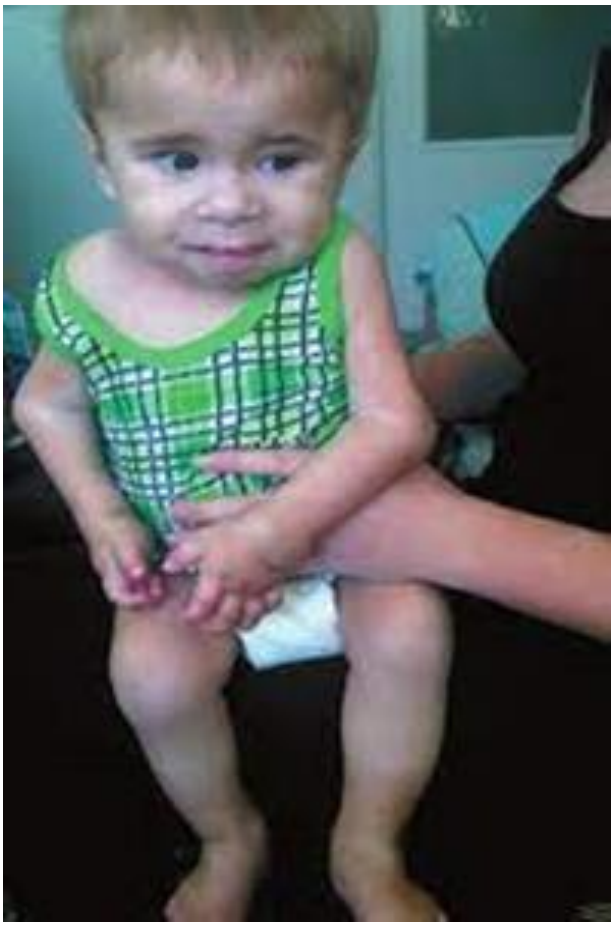

Figure 4 – Joint contractures [10]

osteopenia, and bone fractures are characteristic. Postnatal growth deficiency is the most common phenomenon. Villous atrophy, edema, and intestinal lymphangiectasia lead to malabsorption. 50–75% of children with ISH develop chronic severe diarrhea with protein loss due to intestinal hyalinosis. The cartilage is thickened in > 90%, these lesions are very problematic; they disrupt the patency of the respiratory tract and interfere with oral intake of food, causing dental anomalies. Excessive sweating is typical. Hyperpigmentation of the skin over bony protrusions (a sign present in 100% of patients). Characteristic purple spots appear on the medial and lateral bones, metacarpal-phalangeal joints, spine, and elbows. Characteristic facies: a depressed bridge of the nose, defects in the development of the auricle (large or low-set ears, preauricular skin tags), and rough facial appearance. Cognitive function is preserved [3]. Recurrent infections are due to a violation of the cellular immune response and a decrease in the level of immunoglobulin.

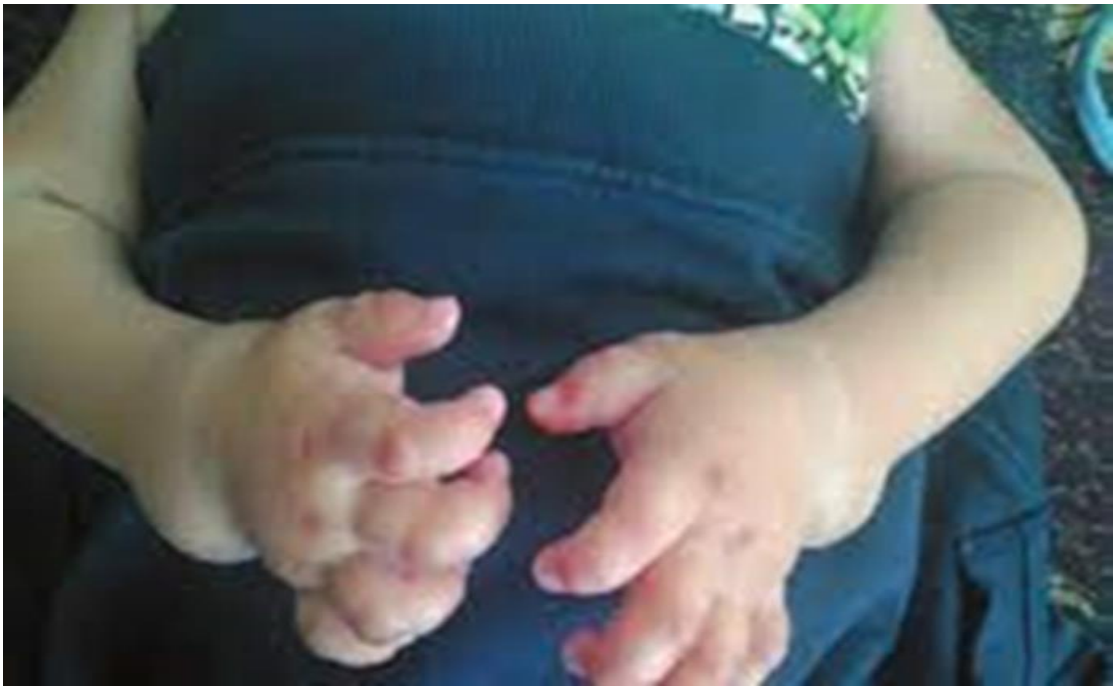

Figure 5 – Contractures of the hands [10]

Possible laboratory findings: serum albumin may be low; anemia and/or thrombocytosis; immunoglobulin levels may be low and cellular immune responses suppressed. Histopathology: deposition of amorphous fibrillar hyaline material, similar in appearance to type VI collagen, in areas of damage. Electron microscopy shows hyaline material deposited between endothelial cells and pericytes, supporting the suggestion that ISH may result from leakage of plasma components across the basement membrane into the perivascular space. Histopathology: deposition of amorphous fibrillar hyaline material, similar in appearance to type VI collagen, in areas of damage. Electron microscopy shows hyaline material deposited between endothelial cells and pericytes, supporting the suggestion that ISH may result from the leakage of plasma components through the basement membrane into the perivascular space [8].

Differential diagnosis is very important for the diagnosis of ISH (Table 1) [9].

HFS is classified as grade 1 or mild (skin and/or gum involvement), grade 2 or moderate (joint and/or bone involvement), grade 3 or severe (internal organ involvement with or without clinical manifestations), and stage 4 or fatal outcome (severe clinical decompensation). Enteropathy with protein loss, sepsis, or organ failure is associated with the most severe forms [8].

Treatment of patients with ISH involves supportive therapy. Analgesia with the help of non-steroidal anti-inflammatory drugs and opiates. Physiotherapy, if the patient tolerates it. It is possible to consider the possibility of surgical removal of skin lesions, and partial gingivectomy, although relapse is possible [2, 6, 7, 8].

Table 1 – Differential diagnosis of ISH [9]

Disease	Inheritance type, age at onset	Initial manifestations	Clinical features	Survival	Pathology
Infantile systemic hyalinosis	Autosomal recessive, first 3 months of life	Diffusely thickened skin, small nodular thickenings, gingival hypertrophy	Joint contractures, osteopenia, growth failure, frequent infections, protein-losing diarrhea	More common in the first 2 years of life	Hyaline depositions
Juvenile hyaline fibromatosis	Autosomal recessive, more common in children over 2 years of age	Nodular skin lesions, gingival hypertrophy	Joint contractures, osteopenia	More often adulthood	Hyaline depositions
Neonatal onset multisystemic inflammatory disease	Most sporadic, first months of life	Widespread urticarial papules and plaques	Periodic fever, chronic aseptic meningitis, short stature, arthropathy	Adulthood	Neutrophilic infiltration
Congenital generalized myofibromatosis	Most sporadic, before age 2	Nodules in skin and subcutis	Nodules in muscle, bone, and internal organs	Survival depends on the location of the lesions	Hyperproliferation of myofibroblasts
Mucopolysaccharidosis type II (Hunter syndrome)	X-linked recessive, before age 2	Generalized skin thickening, ivory-colored papules in scapular area and other sites of trauma, hypertrichosis, coarse facies	Dysostosis with dwarfism, hepatosplenomegaly, cardiovascular disorders, deafness	Severe, 15 years; mild, adulthood	Metachromatic granules within fibroblasts and extracellular deposits between collagen bundles and fibers
Winchester syndrome	Autosomal recessive, first months of life	Patches of thickened leathery skin, coarse facies, gingival hypertrophy	Short stature, severe joint contractures, peripheral corneal opacities, dissolution of carpal and tarsal bones, osteoporosis	Adulthood	Proliferation of fibroblasts in the reticular dermis, followed by collagen appearing homogenized with few fibroblasts
Lipoid proteinosis (Urbach-Wiethe disease)	Autosomal recessive, birth to first few years of life	Pustules that crust and heal with “icepick” acneiform scars; later yellowish, waxy papules, nodules, or plaques; beaded papules on eyelid margins	Hoarse voice, intracranial calcifications	Adulthood	Accumulation of hyaline deposits

CONCLUSIONS / ВИСНОВКИ

The clinical manifestations of our patient's disease are generally identical to the symptomatic characteristics of ISH. The child lived for 4 years and 8 months. This fact contradicts information from literary sources, according to which patients with ISH do not live up to 2 years. But the great desire of the parents to help the child (impeccable care), and the team management of pediatricians, neurologists, orthopedists, surgeons, and dermatologists contributed to the boy's life expectancy. Despite groundbreaking research into the management of HFS, there are still very few advances in treatment. Only supportive care remains helpful.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

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