The Turkish Journal of Pediatrics 2003; 45: 258-260 *Case*

A rare cause of protein-losing enteropathy and growth retardation in infancy: infantile systemic hyalinosis

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SUMMARY: Büyükgebiz B, Öztürk Y, Arslan N, Özer E. A rare cause of protein-losing enteropathy and growth retardation in infancy: infantile systemic hyalinosis. Turk J Pediatr 2003; 45: 258-260.

Infantile systemic hyalinosis is a rare, progressive, fatal condition with a presumably autosomal recessive mode of inheritance. It is characterized by widespread deposition of hyaline material in many tissues. We present a three-month-old girl with hypoproteinemia, growth retardation, and generalized stiff and edematous skin, who was diagnosed as protein-losing enteropathy. A final diagnosis of systemic hyalinosis was made. In this report, we present a very rare entity of infantile systemic hyalinosis, which is a cause of protein-losing enteropathy and growth retardation in infancy, and review the relevant literature.

Key words: infantile systemic hyalinosis, protein-losing enteropathy, growth retardation, thickness of skin.

Infantile systemic hyalinosis is a rare, progressive, fatal condition with a presumably autosomal recessive mode of inheritance[1]. It is characterized by widespread deposition of hyaline material in many tissues such as skin, gastrointestinal tract, adrenals, skeletal muscles, and other loci[1,2]. Clinical features include thickness and focal nodularity of skin, relatively short limbs and neck, gum hypertrophy, hypotonia and reduced movement, joint contractures, osteoporosis, growth failure, diarrhea, and recurrent infections. The symptoms become apparent soon after birth and death usually occurs before the age of two years[1-3].

In this report, we present a case with hypoproteinemia, growth retardation, and generalized stiff and edematous skin who was diagnosed as protein-losing enteropathy (PLE), and review the relevant literature. A final diagnosis of systemic hyalinosis was made.

Case Report

D.Ö., the first child of healthy, third-cousin parents, was born at full-term weighing 2,200 g (<5th percentile). She appeared well until one month of age when her parents noticed that she disliked being held or touched. A couple of weeks after birth, her parents were aware of the stiffness of her body. By two months of age, the joints of her arms and legs began to fell stiff, and she screamed whenever she was touched. She had no history of infection except for one short-term diarrheal attack.

On physical examination, at three months of age, she appeared pale and sweaty and was not gaining weight. Her skin was diffusely thickened, most obviously over the trunk and upper limbs, with hyperpigmentation over the metacarpophalangeal joints and over the malleoli (Figs. 1, 2). There was no focal nodularity in her skin and the anal margins were normal. Both her length and weight were less than the fifth percentile and she had relatively short limbs. She had a relatively large head with a circumference of 40 cm (50-75th percentile). She looked miserable, and she

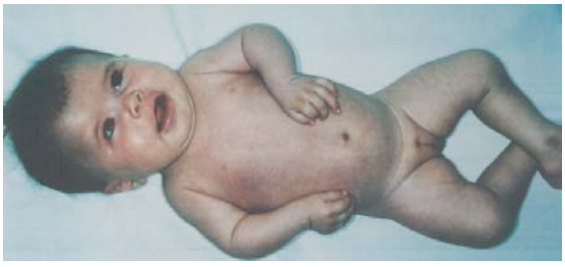

Fig. 1. Patient showing characteristic posture at three months of age. Her skin was diffusely thickened.

was lying in a supine frog-like position (Fig. 1). She had a distinctive appearance with a small mouth, gingival hypertrophy (Fig. 3), a short neck and a prominent forehead (Fig. 1). The mobility of the spine, shoulder, elbow, finger, wrist, hip, knee, and ankle joints was extremely limited. The elbow and wrists were swollen and appeared tender but not hot or erythematous. Her motor development was impaired, presumably as a result of limited joint mobility. The remainder of her physical examination was normal.

On the laboratory tests, hematological and biochemical investigations were normal, except or marginally low total protein level of 4.4 g/dl (normal range: 4.6-7.4 g/dl), and low serum albumin level of 3.0 g/dl (normal range: 3.9-5 g/dl). Serum immunoglobulins, C_3 and C_4, and VDRL test were normal. Skeletal survey showed normal bone structures.

The stool fat globules and reducing substance were negative. Her fecal alpha-antitrypsin level was increased (2.91 mg/g dry weight of stool; normal <0.95 mg/g dry weight of stool).

Barium studies were consistent with intestinal lymphangiectasia. A skin biopsy was done from the right thigh skin. By light microscopy with hematoxylin and eosin stain, hypocellular hyaline areas were highly concentrated in papillary dermis. Where hyaline material was not evident in the papillary dermis, the collagen stains exhibited pallor and some rarefaction of the collagen fibers, particularly evident in perivascular regions. The deeper dermis appeared normal. Some mild hyperkeratosis was evident, and epidermis and adnexal structures and vessels were normal (Fig. 4).

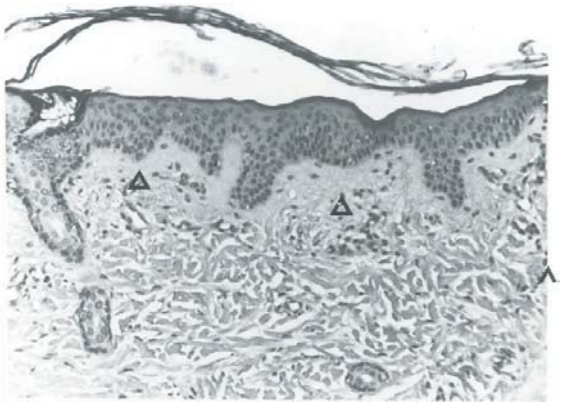

Fig. 4. Skin biopsy taken from right thigh. Hypocellular hyaline areas are highly concentrated in papillary dermis and are visible on hematoxylin and eosin (H & E) staining (Paraffin section, H & E x 40).

Discussion

Systemic hyalinosis is genetic generalized fibromatosis characterized by an accumulation of hyaline in the dermis. Two distinctive syndromes are described in the literature: infantile systemic hyalinosis and juvenile hyaline fibromatosis[4].

Infantile systemic hyalinosis is a presumably autosomal recessive, progressive, and painful disorder of a yet unknown pathogenesis.

In systemic hyalinosis, immunohistochemistry reveals widespread presentation of type VI collagen in the connective tissue with particularly intense staining in the hyaline material[3]. The clinical features of inflexible skin and stiff joints, in combination with immunohistochemical

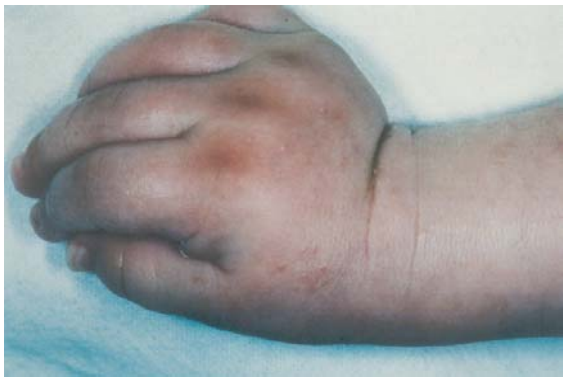

Fig. 2. Hyperpigmentation over the metacarpophalangeal joints.

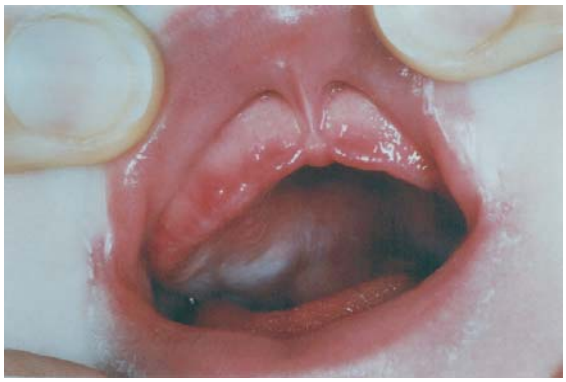

Fig. 3. Gingival hypertrophy.

studies and electron microscopic findings, suggest that an increase in the amount of collagen type VI might provide the pathological basis for these disorders[2]. On the other hand, ultrastructural examination of skin biopsies reveals a distinctive fibrillogranular appearance around fibroblasts and blood vessels[2,5]. Electron microscopic inves-tigations of skin biopsies demostrate deposition of a floccular amorphous substance that is abundant around, and appeared to orginate from, small blood vessels in the dermis, partially interfering with collagen fiber formation. It has been suggested that the amorphous material may orginate from blood circulation[6].

Joint contracture, massive hyperplasia of gingivae, diffuse skin papules and subcutaneous nodules occupying the scalp, face, perianal area, palms, soles and chest are present in juvenile hyaline fibromatosis. Cases of juvenile hyaline fibromatosis live until aldthood. Mucopolysaccharide abnormalities have been shown in juvenile hyaline fibromatosis[6]. Jujenile hyaline fibromatosis and infantile systemic hyalinosis have been described as different entities by Landing et al[1]. However Glover et al.[2] proposed the opposite. There are striking histological similarities between juvenile hyaline fibromatosis and infantile systemic hyalinosis. In addition, the electron microscopic appearance of the hyaline material in infantile systemic hyalinosis is the same as in juvenile hyaline fibromatosis. Therefore it has been suggested that infantile systemic hyalinosis and juvenile hyaline fibromatosis represent different expressions of the same disorder, infantile systemic hyalinosis being a more severe form with early onset and juvenile hyaline fibromatosis being a milder from with a later onset[2].

Growth retardation is a very important finding in infancy and serious considerations should be given to these cases. In our case striking physical findings led us to the diagnosis of infantile systemic hyalinosis. In this disorder, growth retardation is due to inadequate nutritional intake as a cause of perioral stiffness, irritability due to generalized painful body, and excess energy and protein loss from the intestine. Although physical findings were obvious, skin biopsies supported the diagnosis, showing hypocellular hyaline areas highly concentrated in papillary dermis.

Protein-losing enteropathy (PLE) has been described in many of the cases with infantile systemic hyalinosis. PLE is not a specific disease but a pathophysiologic process[7]. It is well known that PLE occurs with various mechanisms as a result of mucosal erosion and ulceration[8]. Intestinal lymphangiectasia is the underlying cause of PLE in infantile systemic hyalinosis[2].

The prognosis of this entity is very poor. Because many of the cases with infantile systemic hyalinosis result in death within the first two years of life[1,2], this disorder has not been clarified completely. However, follow up of a case with infantile systemic hyalinosis for more than three years was presented by Stucki et al.[6]. In this case, skin lesions and painful joint contractures progressed in spite of intense physical therapy and rehabilitation. At three years, the child had marked motor disability but central nervous system was intact and the infant showed normal mental development.

There is no known specific treatment for infantile systemic hyalinosis. Physical therapy and nutritional support improve the quality of life of the patient.

In conclusion, we present a very rare entity of infantile systemic hyalinosis, which may be a cause of protein-losing enteropathy and growth retardation during infancy.

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