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I-CELL DISEASE*
A Case Report and Review of the Literature

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A four-month-old female infant having developmental delay, coarse facial features and dysostosis multiplex is reported with a special emphasis on the differential diagnosis among I-cell disease (ICD), Hurler syndrome and GM1 gangliosidosis. The lysosomal enzyme studies in cultured skin fibroblasts and serum sample of the patient certified the diagnosis of ICD.

Foamy cell infiltration of some organs, including the lungs, and microgyria formation were also noted. Genetic counselling was provided and prenatal diagnosis was offered to the couple to detect ICD in the next pregnancy. *Key words: I-cell disease dysostosis multiplex, microgyria, prenatal diagnosis.*

I-cell disease (ICD, mucolipidosis type II) is a rare. autosomal recessive lysosomal storage disorder. It was first described in 1967, and coarse cytoplasmic inclusions in the cultured skin fibroblasts (designated inclusion cell or I-cell) of two children were noted[1]. This disorder has been well defined clinically[1-6]. Manifesting at birth or in the first few months of life, ICD is characterized by developmental delay, short stature, coarse facial features with hyperplastic gums, and dysostosis multiplex clinically[2,3,5,6]. Affected patients may also have congenital dislocation of the hips, inguinal hernias, restricted motion in the shoulders, generalized hypotonia, thick and tight skin, and hepatomegaly[5,6]. The disease has a progressive clinical course resulting in a fatal outcome at 2-8 years of age (approximately 4 years). Death usually occurs due to intractable heart failure and/or pulmonary infection[1,2,6].

Histologically, vacuolation of cells is the most characteristic feature in patients with ICD, and this vacuolation is seen in various types of cells, such as myocardial fibers, hepatocytes, epithelial cells of renal glomeruli, renal tubular cells, splenic cells and neurons of the brain[2].

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In this report, because of its rarity, a case of ICD with its clinical, biochemical, and histological features is described and the relevant literature is reviewed.

Case Report

A four-month-old infant girl was admitted to Hacettepe University Children's Hospital because of difficulty in breathing, coughing and vomiting. She was born at full-term with a birth weight of 2000 g ($<5^{th}$ percentile) following an uncomplicated delivery. The child's psychomotor development was mildly delayed; head control was achieved at two months and she was able to recognize her mother at three months. She was the third child of the family. The parents were first cousins. The first child of the family was a five-year-old healthy female and the second child had died due to sepsis at 17 days of age.

On physical examination, the patient was 45 cm ($<5^{th}$ centile) in length and 3000 g ($<5^{th}$ percentile) in weight. Her head circumference was 33 cm ($<5^{th}$ percentile). Her general status was not good with mild lethargy and hypoactivity. Her skin was pale and cold with cutis marmoratus. Perioral and acral cyanosis was noted. She had coarse facial features characterized by bilateral mild exophthalmos, low-set ears, upturned nostrils, a long philtrum and hyperplastic gums (Fig. 1). She had a high-arched palate. The patient was tachypneic and had intercostal

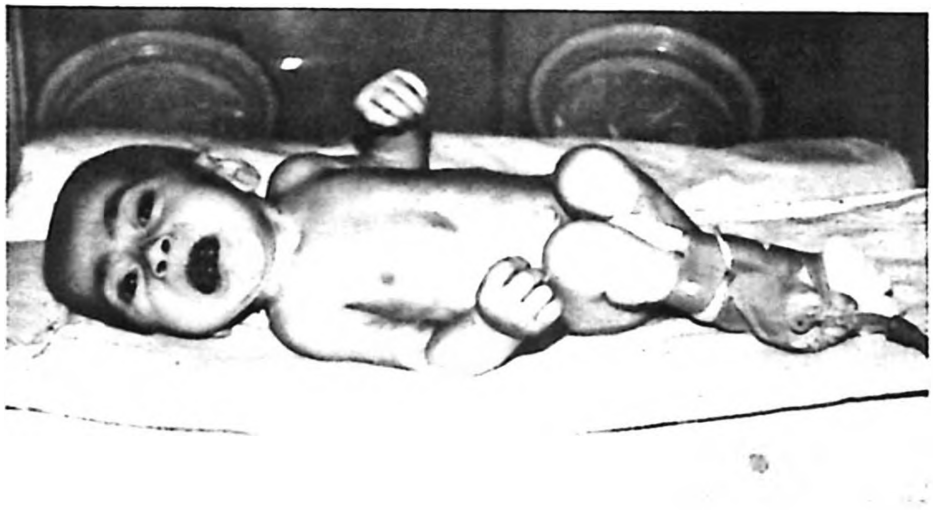

Fig. 1: The patient with coarse facial features, exophthalmos, low-set ears, upturned nostrils, long philtrum and hyperplastic gums.

and subcostal retractions. Crepitant rales were heard over the pulmonary fields. A III/VI degree systolic murmur was heard in the third and fourth left intercostal spaces. Diastasis recti was present. The liver was palpable 3 cm below the right costal arch. The abduction of both hip joints was limited. Bilateral pes equinovalgus deformity was present. Cortical fisting and crossing of legs were observed with hypoactive Moro reflex and poor suck.

The complete blood count revealed a hemoglobin value of 9.2 g/dl and a hematocrit value of 27% with hypochromia and anisocytosis in erythrocyte morphology. Mild leucocytosis (13.000/µl) with a predominance of polymorphonuclear cells and stabs was present. Granulation was observed in the cytoplasm of lymphocytes. The mean corpuscular volume and transferrin saturation were below normal, indicating iron deficiency anemia. The urinalysis and serum electrolytes were within the normal range. The chest roentgenogram revealed cardiomegaly and a diffuse pulmonary infiltration. The EKG revealed findings compatible with right ventricular hypertrophy and ST and T changes. Echocardiography displayed 58 mm of systolic gradient in the mitral valve. Urinary mucopolysaccharide excretion was normal. Serum and urine amino acids were normal. Skin specimens for fibroblast culture were obtained. Lysosomal enzyme studies were performed in cultured skin fibroblasts. The lysosomal enzyme activities were found to be high in serum and low in fibroblasts (Table I).

Table I: Lysosomal Enzyme Studies in The Patient

	Activity (mU/mg)	
Enzyme		
FIBROBLASTS	Patient	Normal Range
o-Iduronidase	0.046	1.36-4.40
β-Glucuronidase	0.464	3.05-7.65
α-Galactosidase	0.109	7.53-14.3
SERUM		
o-Ac-α-Glucosamin	0.9844	0.183-0.697
β-Glucuronidase	13.4236	0.281-1.991
α-Fucosidase	19.6403	1.017-11.13
α-Mannosidase	17.8642	0.109-1.173
Hexosaminidase A	10.7205	1.125-4.249
Total Hexosamin	423.694	8.916-27.07

The patient had interesting skeletal findings which may be grouped together under the term "dysostosis multiplex". Except for the skull bones, the skeleton was characterized by a low density and an abnormal texture which gave a fibrillar or lacunar appearance to the bones. The roentgenographic findings of the patient will now be summarized, beginning from the proximal:

Skull : The skull was microcephalic with a mildly deep posterior fossa. There was sclerosis in the skull base.

Spine : The anteroposterior diameter of the lumbar bodies was small. The bodies were longer posteriorly than anteriorly. The end-plates of the vertebral bodies were convex. The second lumbar body was hypoplastic with a "hook" configuration. There was slight concavity at the anterior borders of the vertebral bodies of L2 and L3 (mild hook configuration). There was thoracal scoliosis.

Pelvis : Bilateral hip dislocation with supraacetabular constriction was observed. The iliac wings were flared.

Long Tubular Bones : The shaft of the long bones had a poorly defined contour (a contour with a double line image, resembling periosteal apposition). Especially in both femurs and tibiae, the double outline (cloaking) involved almost the entire shaft. The cortices were thin and the medullary canals were enlarged (Fig. 2).

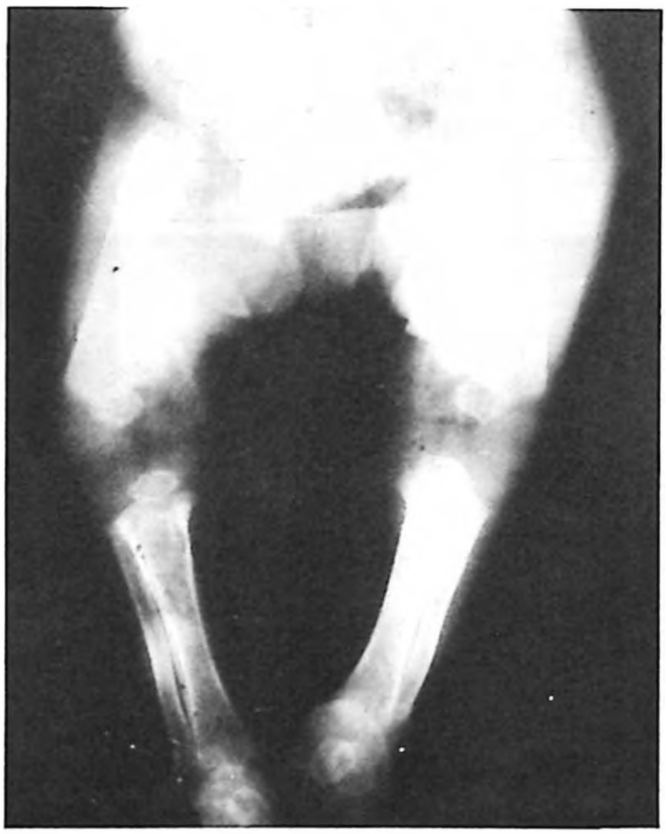

Fig. 2: Cloaking of both femurs and tibiae with enlarged medullary canals.

Hands and Feet : The metacarpal and metatarsal bones were shortened and rectangular in shape with coned proximal ends. The proximal and middle phalanges were shortened and bullet-shaped. Distal phalanges were markedly hypoplastic. The cortex of these bones was inapparent and their texture was fibrillar or lacunar (Fig. 3).

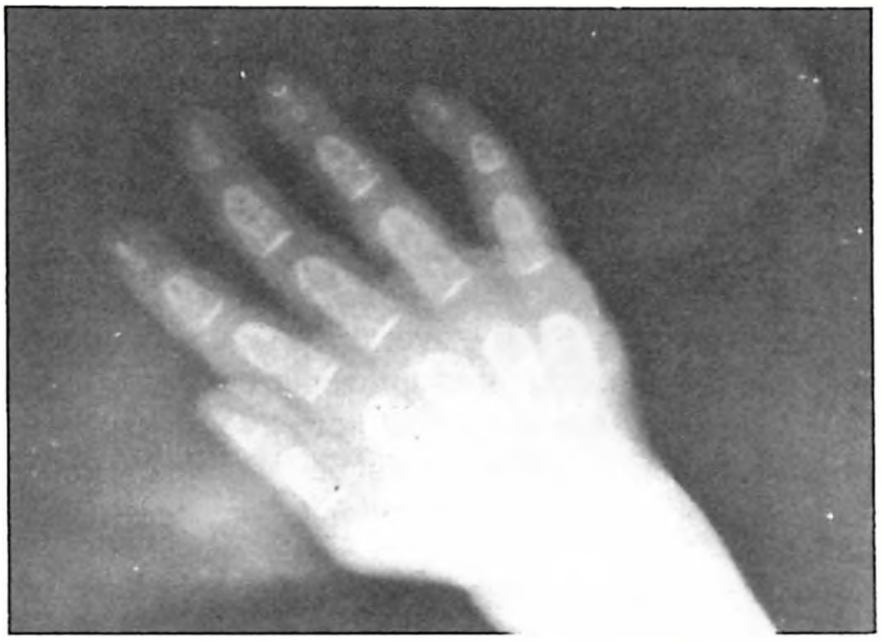

Fig. 3: Short and rectangular metacarpal bones with coned proximal ends. Bullet-shaped proximal and distal phalanges and hypoplastic distal phalanges.

Ribs : The ribs were oar-shaped with widening of the lateral and anterior part (Fig. 4).

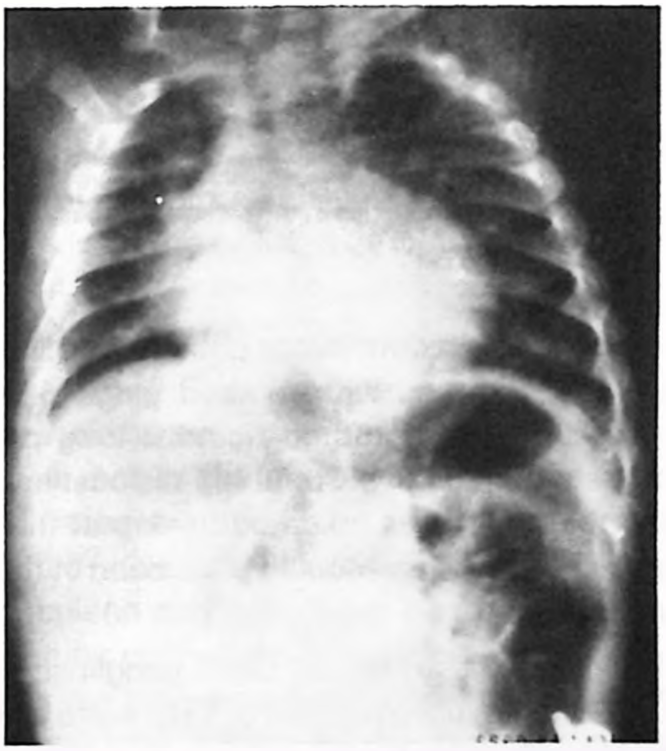

Fig. 4: Thoracal scoliosis and oar-shaped ribs. This figure also reveals the cardiomegaly of the patient.

Proper alimentation (first oral then intravenous), antibiotics, digitalization, supportive therapy and ventilation were administered. The patient's clinical status worsened daily, and she died following a cardiopulmonary arrest on the eighth day of hospitalization. Permission for autopsy was given by her parents.

On histopathological examination, congestion and hemorrhage in some alveolar spaces and findings consistent with interstitial pneumonitis were observed. Some of the macrophages in the alveolar spaces were vacuolated and stained light blue with Hale's colloidal iron[9] (Fig. 5). The liver displayed fatty degeneration. In the kidneys, some of the glomerular epithelium displayed foamy changes and were also stained light blue with Hale's colloidal iron. In addition there were foci of mononuclear cell infiltration revealing interstitial nephritis. There was no other marked histopathological change in the other organs and tissues.

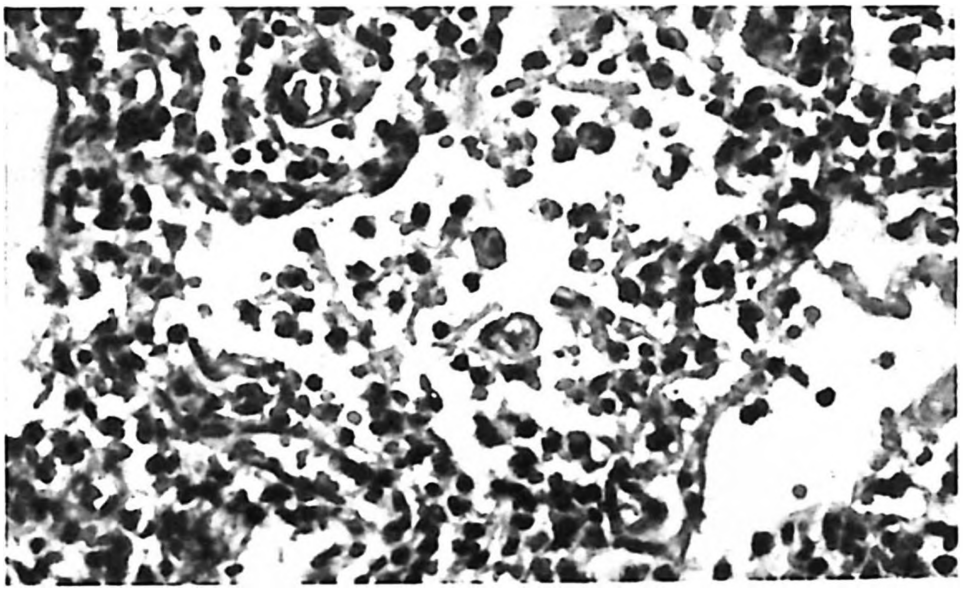

Fig. 5: The vacuolated macrophages in the alveolar spaces. (H+, x100).

Discussion

The major clinical abnormalities present in our patient were developmental delay, microcephaly, coarse facial features with marked gingival hyperplasia, bilateral mild exophthalmos, low-set ears, upturned nostrils, long philtrum, high-arched palate, diastasis recti, hepatomegaly, bilateral hip dislocation and pes equinovalgus deformity. At first, these features made us think that the patient might have an inborn error of metabolism. This error could have been in the mucopolysaccharide (MPS) or lipid metabolism.

Mucolipidosis type II (I-cell disease, ML-II). GM1 gangliosidosis, and mucopolysaccharidosis type I (Hurler syndrome, MPS I-H) were the main issues for differential diagnosis. Patients with Hurler syndrome appear normal at birth, and during the first year of life only slight developmental delay is noted. Infants with

MPS I-H usually have macrocranium and they are usually tall (in contrast to our patient), but the coarse facial features are also seen in Hurler syndrome. Presence of a marked gum hypertrophy and the detection of normal excretion of urinary mucopolysaccharides made this diagnostic consideration less likely. The radiographic findings in our patient were consistent with dysostosis multiplex. The early onset of clinical findings and no detection of a cherry red spot in the macula were against the diagnostic consideration of GM1 gangliosidosis in our patient. As GM1 gangliosidosis presents with the same skeletal changes as mucolipidosis type II, radiologic differentiation between these conditions was not possible.

Biochemically, elevated serum levels of many lysosomal enzymes, decreased intracellular activities of some of them and normal excretion of urinary mucopolysaccharides characterizes I-cell disease (ICD)[3,4]. The primary defect in ICD is a deficiency of a specific N-acetylglucosamine phosphotransferase. This enzyme phosphorylates newly formed lysosomal enzymes and generates the common phosphomannosyl recognition markers of lysosomal enzymes. Thus, lacking these phosphate groups that serve as a recognition marker, the newly synthesized enzymes do not enter the lysosomes but are excreted from the cell. This explains the striking elevation in the serum levels of lysosomal hydrolases and their deficiency in fibroblasts associated with ICD. Other body fluids (tears, amniotic fluid, etc.) also show this increased activity of several lysosomal enzymes. On the other hand, some cells and tissues do not express the lysosomal enzyme deficiency (leukocytes) and others express it partially (liver, brain)[3,6].

For the definite diagnosis and differentiation of the two conditions (GM1 Gangliosidosis and ICD), lysosomal enzyme studies were required in cultured fibroblasts, culture medium and serum. When this enzymatic study was performed, the lysosomal enzyme activities were found to be high in serum and low in fibroblasts. The diagnosis of ML-II (ICD) was confirmed in our patient in this way.

The death of patients with ICD occurs mostly due to intractable pulmonary infections or cardiac failure[2,6]. The same occurred in our patient despite the effort to cure her. No cardiac abnormality was detected in our patient except for a systolic gradient of 58 mm in the mitral valve. On the other hand, the relation between histological changes in the lungs and the cause of death in ICD patients is still being investigated[2]. Characteristic foamy changes in the organs such as the heart, kidneys, liver, spleen and brain have been reported in the literature[2]. The changes in the glomerular epithelium of the patient's kidneys were in accordance with those reported in the literature. Foamy changes in the alveolar epithelium of the lungs is a relatively rare finding in the literature which attracts attention especially when recurrent respiratory infections are being considered as a major cause of death in ICD; this rare finding is also found in our patient. In addition,

marked microgyria formation was observed in the frontal lobe of the cerebrum of our patient. To the best of our knowledge, this finding has not before been reported in ICD patients; this may be a new finding in ICD patients.

The importance of recognizing the index case in metabolic diseases is once more emphasized by this case report. This family was provided with thorough genetic counseling; thus the next pregnancy was evaluated in utero. Since the fetus was found to be affected, the pregnancy was terminated.

Acknowledgements

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REFERENCES

1. Okada S, Owada M, Sakliyama T, Yutaka T, Ogawa M, et al. I-cell disease: clinical studies of 21 Japanese cases. Clin Genet 1985; 28: 207-215.
2. Yuasa Y, Yoshinaga M, Kitahara T, Miyata K, Shimozono I, Yoshida H. A case of I-cell disease. Acta Paediatr Jpn 1990; 32: 670-674.
3. Poenaru L, Mezard C, Akli S, Dury JF, Dumez Y, Boue J. Prenatal diagnosis of mucolipidosis type II on first-trimester amniotic fluid. Prenat Diagn 1990; 10: 231-235.
4. Yamaguchi K, Hayasaka S, Hara S, Kurobane I, Tada K. Improvement of tear lysosomal enzyme levels after treatment with bone marrow transplantation in a patient with I-cell disease. Ophthalmic Res 1989; 21: 226-229.
5. Kamiya M, Tada T, Kuhara H, Kishimoto H, Wada Y, Hashizuma Y, et al. I-cell disease: a case report and review of the literature. Acta Pathol Jpn 1986; 36: 1679-1692.
6. Matalon RH. Mucolipidoses. In: Behrman ER, Kliegman RM, Nelson WE, et al. (eds). Nelson Textbook of Pediatrics (14th ed). Philadelphia: W.B. Saunders Co; 1992: 351-352.
7. Pazzaglia UE, Beluffi G, Campbell JB, Bianchi E, Colavita N, Diard F, et al. Mucolipidosis II: correlation between radiological features and histopathology of the bones. Pediatr Radiol 1989; 19: 406-413.
8. Pazzaglia UE, Beluffi G, Bianchi E, Castello A, Coci A, Marchi A. Study of the bone pathology in early mucolipidosis II (I-cell disease). Eur J Pediatr 1989; 148: 553-557.
9. Spranger JW, Langer LO, Wiedemann HR. Bone Dysplasias. An Atlas of Constitutional Disorders of Skeletal Development. Philadelphia: W.B. Saunders; 1974: 144-148, 179-182.
10. Sandoval IV, Chen JW, Yuan L, August T. Lysosomal integral membrane glycoproteins are expressed at high levels in the inclusion bodies of I-cell disease fibroblasts. Arch Biochem Biophys 1989; 271: 157-167.