

A case with ICF syndrome lost to rubella pneumonitis

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SUMMARY: Reisli İ, Yıldırım MS, Köksal Y, Avunduk MC, Acar A. A case with ICF syndrome lost to rubella pneumonitis. Turk J Pediatr 2005; 47: 85-88.

The immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is a rare autosomal recessive disorder characterized by variable immunodeficiency, instability of the pericentromeric heterochromatin, and facial dysmorphism. Here we report a new case of ICF syndrome who died of rubella pneumonitis. A six year-old-girl who was the first child of consanguineous parents was admitted to the hospital because of bronchopneumonia. Laboratory investigations revealed pan-hypogammaglobulinemia, lymphopenia, normal proportions of peripheral blood lymphocytes with an inverted CD4/CD8 ratio, and interstitial pneumonia with a positive serology of acute rubella infection. The ICF syndrome was diagnosed by centromeric instability in the standard cytogenetic analysis. An inclusion body was demonstrated in the lung biopsy after the death of the patient. Chromosomal investigation could be helpful along with other tests for diagnosis of variable immunodeficiency accompanied by facial dysmorphism.

Key words: ICF syndrome, immunodeficiency, centromeric instability, facial anomalies, rubella.

The immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is a rare autosomal recessive disorder. It is characterized by variable immunodeficiency, instability of the pericentromeric heterochromatin of, in particular, chromosomes 1, 9, and 16 in cultured peripheral lymphocytes, and a number of facial anomalies. Approximately 30 cases of this rare disorder have been reported in the literature^{1,2}. Patients with ICF syndrome also have mental retardation of variable degree and suffer from recurrent respiratory and/or gastrointestinal infections^{3,4}. Hypogammaglobulinemia involving two or more isotypes¹⁻⁴, an inverted CD4/CD8 ratio^{3,4}, rarely lymphopenia³, and severe/fatal viral infections³ have been reported in these patients. The majority of ICF cases display mutations in the DNA methyltransferase 3b (DNMT3B) gene^{1,4}.

Here we report a new case of ICF syndrome with pan-hypogammaglobulinemia, lymphopenia, and an inverted CD4/CD8 cell ratio, who died of interstitial pneumonitis caused by rubella.

Case Report

A six-year-old girl was admitted to the hospital with a history of fever, cough and respiratory distress. She was a child of first-degree consanguineous parents. A two-month-old female and a three-month-old male cousin died of respiratory tract infections. She had a history of recurrent respiratory and gastrointestinal tract infections occurring after 3.5 months of age. On her physical examination, she had a peculiar face characterized by roundness, high forehead, low hairline, low-set ears, hypertelorism with epicanthic folds, small nose with a flat nasal bridge, micrognathia, protrusion of the tongue (Fig. 1), tachypnea, cyanosis, bilaterally crackling rales, lymphoid hypoplasia and hepatosplenomegaly. She was mentally retarded with a normal head circumference. Laboratory evaluation revealed hemoglobin 111 g/L, white blood cell count $4.44 \times 10^9/L$, total lymphocyte count $0.58 \times 10^9/L$ and platelet count $300 \times 10^9/L$. A peripheral blood smear showed microcytic hypochromic



Fig. 1. Facial appearance of the patient.

erythrocytes. The results of the serological tests for cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, and herpes virus were negative, and the serology of acute rubella infection was positive. Serum alpha-fetoprotein concentration was normal. The biochemical measurements, bone marrow aspiration, urine-blood amino acid investigation and sweat test were normal. On chest X-ray, there was an

appearance of interstitial pneumonitis. Her immunological investigations revealed lymphopenia ($0.568 \times 10^9/L$), panhypogammaglobulinemia, normal proportions of the peripheral blood lymphocytes with inverted CD4/CD8 cell ratio, and decreased absolute numbers of lymphocytes (Table I). Conventional cytogenetic analysis revealed 46,XX karyotype. However, centromeric instabilities of the chromosomes 1, 16, and less frequently 9 were seen (Figs. 2a, 2b). The percentage of instability of chromosomes was 13.9% in normal metaphase chromosomes (16 metaphase), 26.1% in only chromosome 1 (30 metaphase), 3.3% in only chromosome 16 (36 metaphase), 0.9% in only chromosome 9 (1 metaphase), 24.3% in both chromosome 1 and 16 (28 metaphase), and 3.5% in all of them (4 metaphase). There were deletions particularly in several metaphases of long arm of chromosome 1. No chromosomal abnormality was detected on the cytogenetic investigation of lymphocytes of the parents or her sisters. She was treated with antiviral, antifungal, antibacterial agents and intravenous immunoglobulin, but died on the 52nd day of treatment from interstitial pneumonitis. An inclusion body was demonstrated in the lung tissue biopsy (Fig. 3).

Table I. Immunological Data of Our Case

	Result		Normal values in age-matched Turkish children	
	(%)	Absolute number ($\times 10^9/L$)	(%)	Absolute number ($\times 10^9/L$)
CD3+	62.6	0.36	55-79	1.9-3.6
CD4+	29.8	0.17	28-51	0.7-2.0
CD8+	34.1	0.19	16-42	0.3-1.5
CD16+56+	22.6	0.13	5-28	0.2-1.2
CD19+	11.7	0.07	11-31	0.3-1.2
HLADR+	21.7		10-28	
Lymphoproliferative response to PHA	34%		65.8 $\pm$ 9.2	
PPD response	negative		(5-10)	
Candidin test	negative		(5-10)	
IgG (mg/dl)	347		745-1804 (*)	
IgA (mg/dl)	23		57-282 (*)	
IgM (mg/dl)	69		78-261 (*)	
IgE (IU/ml)	17.5		0-100	
Anti-A titer	1/4		>1/10	
NBT test	100%		100%	
CH50	Positive		Positive	

* See reference 5.



Fig. 2a: Centromeric instability of chromosomes 1, 9 and 16 in cultured peripheral lymphocytes.



Fig. 2b: Centromeric instability of chromosomes 1 (thin arrow) and 16 (thick arrow) in a metaphase.

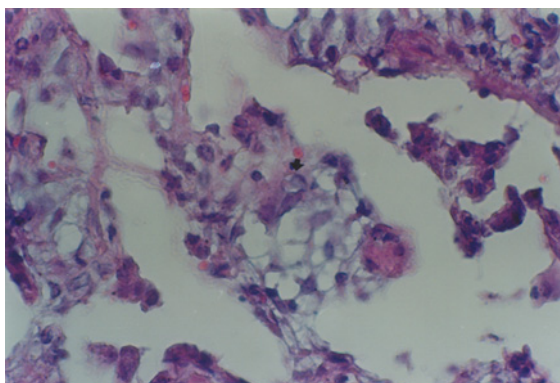


Fig. 3. Inclusion body in the lung biopsy.

Discussion

The common finding in ICF syndrome is recurrent respiratory infections secondary to variable immunodeficiency^{1,3}. However, the clinical features in the ICF syndrome are usually subtle, and of little diagnostic value¹. This patient presented with a history of recurrent respiratory infection, pan-hypogammaglobulinemia, lymphopenia, inverted CD4/CD8 cell ratio with normal proportions of peripheral blood lymphocytes and decreased absolute numbers of lymphocytes (Table I), but these were not diagnostic. In addition, our patient had most facial features, the presence of which may widely vary from one patient to another. Due to the facial anomalies, standard cytogenetic analysis was done, which revealed centromeric instability.

The ICF syndrome is associated with centromeric instability secondary to localized hypomethylation of classic satellite DNA⁶. The diagnostic finding is abnormal condensation of heterochromatin in chromosomes 1, 9 and 16^{1,6}. Chromosomal instability involves mostly chromosomes 1 and 16 and occasionally 9^{1,2}. Unbalanced chromosomes, chromosome breaks, translocations and isochromosome formation involve mainly the long arm of chromosome 1¹. Our patient also showed predominantly chromosome 1 and 16 involvement.

The ICF syndrome has variable expressivity in the clinical and phenotypic manifestations⁷. The mild phenotypic expression of the syndrome with no severe congenital malformations goes undiagnosed, and the recurrent infections indicate variable immunodeficiency². Similarly, our patient was not diagnosed because no cytogenetic study had been performed until admission to our hospital.

The viral infections seem to run a more severe course and widespread infections can cause death of the patient with ICF syndrome^{3,7}. Inclusion bodies such as cytomegalovirus can be shown in autopsy³. Our patient died of a severe interstitial pneumonitis caused by rubella. There was an inclusion body in lung biopsy.

We conclude that chromosomal investigation could be helpful along with other tests for diagnosis of variable immunodeficiency accompanied by facial dysmorphism.

REFERENCES

1. Ravel TJ, Deckers E, Alliet PL, Petit P, Fryns JP. The ICF syndrome: new case and update. *Genet Couns* 2001; 12: 379-385.
2. Smeets Moog U, Weemaes CM, et al. ICF syndrome: a new case and review of the literature. *Hum Genet* 1994; 94: 240-246.
3. Fasth A, Forestier E, Holmberg E, et al. Fragility of the centromeric region of chromosome 1 associated with combined immunodeficiency in siblings. *Acta Paediatr Scand* 1990; 79: 605-612.
4. Pezzolo A, Prigione I, Chiesa S, Castellano E, Gimelli G, Pistoia V. A novel case of immunodeficiency, centromeric instability, and facial anomalies (the ICF syndrome): immunologic and cytogenetic studies. *Haematologica* 2002; 87: 329-331.
5. Tezcan I, Berkel AI, Ersoy F, Sanal O. Sağlıklı Türk çocukları ve erişkinlerde türbidimetrik yöntemle bakılan serum immunoglobulin düzeyleri. *Çocuk Sağlığı ve Hastalıkları Dergisi* 1996; 39: 649-656.
6. Report of an IUIS Scientific Committee. Primary Immunodeficiency Diseases. *Clin Exp Immunol* 1999; 118 (Suppl): 1-28.
7. Gimelli G, Varon eP, Pezzole A, Lerone M, Pistoia V. ICF syndrome with variable expression in sibs. *J Med Genet* 1993; 30: 429-432.