A case with ICF syndrome lost to rubella pneumonia

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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 pneumonia. 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.

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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 4.44x10⁹/L, total lymphocyte count 0.58x10⁹/L and platelet count 300x10⁹/L. A peripheral blood smear showed microcytic hypochromic
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 x 10⁹/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>
<thead>
<tr>
<th>Table I. Immunological Data of Our Case</th>
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<tbody>
<tr>
<td>Result</td>
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<tr>
<td></td>
</tr>
<tr>
<td>CD3+</td>
</tr>
<tr>
<td>CD4+</td>
</tr>
<tr>
<td>CD8+</td>
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<tr>
<td>CD16+56+</td>
</tr>
<tr>
<td>CD19+</td>
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<tr>
<td>HLADR+</td>
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Lymphoproliferative response to PHA 34% 65.8 ± 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.
Discussion

The common finding in ICF syndrome is recurrent respiratory infections secondary to variable immunodeficiency\textsuperscript{1,3}. However, the clinical features in the ICF syndrome are usually subtle, and of little diagnostic value\textsuperscript{1}. 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 DNA\textsuperscript{6}. The diagnostic finding is abnormal condensation of heterochromatin in chromosomes 1, 9 and 16\textsuperscript{1,6}. Chromosomal instability involves mostly chromosomes 1 and 16 and occasionally 9\textsuperscript{1,2}. Unbalanced chromosomes, chromosome breaks, translocations and isochromosome formation involve mainly the long arm of chromosome 1\textsuperscript{1}. Our patient also showed predominantly chromosome 1 and 16 involvement.

The ICF syndrome has variable expressivity in the clinical and phenotypic manifestations\textsuperscript{7}. The mild phenotypic expression of the syndrome with no severe congenital malformations goes undiagnosed, and the recurrent infections indicate variable immunodeficiency\textsuperscript{2}. 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\textsuperscript{3,7}. Inclusion bodies such as cytomegalovirus can be shown in autopsy\textsuperscript{3}. 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


