Schimke immuno-osseous dysplasia: case report and review of 25 patients

Jorge M Saraiva, Alexandra Dinis, Cristina Resende, Emília Faria, Clara Gomes, A Jorge Correia, Júlia Gil, Nicolau da Fonseca

Abstract

Immuno-osseous dysplasia is characterised by spondyloepiphysyal dysplasia, lymphopenia with defective cellular immunity, and progressive renal disease. We describe a patient with a severe form of the disease, review the features of another 24 patients, and discuss the previous classification. The differences between the two groups are not striking, and although similarities are greater between affected sibs, the same diagnosis of Schimke immuno-osseous dysplasia should apply to them all. The aetiology and physiopathology of this rare osteochondrodysplasia of presumed autosomal recessive inheritance remain unknown.

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Keywords: osteochondrodysplasia; immuno-osseous dysplasia; spondyloepiphysyal dysplasia; defective cellular immunity

Immuno-osseous dysplasia is a rare autosomal recessive osteochondrodysplasia (MIM 242900).\(^1\) It was first described in one patient by Schimke \(^2\) and to our knowledge 23 other cases have been published with this possible diagnosis.\(^3,15\) It is characterised by spondyloepiphysyal dysplasia, defective cellular immunity, and progressive renal disease.

We describe a Portuguese patient with immuno-osseous dysplasia, review the previous case reports and classification, and discuss the relevance of additional findings and variants.

Case report

The proband is the third child of non-consanguineous, Portuguese parents (mother 38, father 40 years old). Both parents and the older brother, aged 9 years, have normal stature and are healthy. A male twin of his brother was stillborn of unknown cause. The proband was born at 32 weeks of gestation by caesarean section following ultrasound prenatal diagnosis of intrauterine growth retardation. Birth length (38 cm), weight (1020 g), and head circumference (27.5 cm) were all less than the 3rd centile.

He was referred at the age of 5 years because of short stature and proteinuria. Herpes zoster had been diagnosed at 2 years. He had short stature with a short neck and trunk (fig 1) and normal development. His length was 79 cm (<5th centile), his weight was 10.42 kg (<5th centile), and his OFC was 47 cm (5th centile). He had a triangular face, a broad nasal bridge, bulbous nasal tip, and multiple lentigines. Blood pressure was normal (112/62 mm Hg). The voice was normally pitched and the hair, eyes, and teeth were normal. He had no ascites or oedema.

Skeletal x-rays showed an increased antero-posterior skull diameter, a J shaped sella turcica, small iliac wings, small ossification centres of the capital femoral epiphyses (fig 2), platyspondyly (fig 3), slightly short metacarpals, and carpal bone age delay. A previous brain ultrasound scan had been described as normal and abdominal ultrasound scan and karyotype (46,XY) were normal.

He had increased urinary glycosaminoglycans (38 mg/mmol creatinine, mostly chondroitin sulphate) with normal chromatography of both glycosaminoglycans and oligosaccharides. Plasma and leucocyte enzymatic activities were normal.

Haematological studies showed haemoglobin 14.2 g/l, platelet count 387 × 10^9/µl, 8.7 × 10^9/µl leucocytes with lymphopenia (absolute count 1.14 × 10^9/µl). Immunoglobulins IgG, IgM, IgA, IgE, IgG\(_1\), IgG\(_3\), and IgG\(_4\) serum levels were normal, but the IgG\(_2\) subclass level was decreased (<0.08g/dl). Circulating immuno-
complexes (<0.42 µg/ml, normal range <5.0 µg/ml) were normal.

Peripheral blood lymphocytes (flow cytometry) showed a decreased number of total CD3 T cells (52%) owing to a markedly decreased number of subpopulation helper CD4+ T cells (13%) with a decreased CD4/CD8 ratio (0.5%). The γδ T cell receptor CD3+ cells were increased (15%, normal range <7.5%). Activation molecules were slightly expressed in T lymphocytes: 25% of CD4+ lymphocytes were CD25+ and 18% were HLADR+. Also 50% of CD8+ T cells were HLADR+. The subpopulation of memory T lymphocytes (CD45RO+CD4+) was increased (69%) and CD45+CD4+ naïve lymphocytes were reduced (32%). Delayed hypersensitivity skin test to tetanus, diphtheria, tuberculin, streptococcus, candida, trichophyton, and proteus antigens was negative. Proliferative responses of T cells to the mitogens phytohaemagglutinin (PHA), pokeweed, and superantigen staphylococcus protein A were slightly reduced and the addition of recombinant interleukin 2 only enhanced the PHA induced proliferative response.

He had normal renal function and electrolytes, hypoalbuminaemia (30 g/l), and nephrotic proteinuria (80 mg/m²/h). A renal biopsy was performed that showed focal segmental glomerulosclerosis and a steroid therapy trial was unsuccessful. The patient developed anaasarca and hypertension in the third week of treatment that resolved with albumin perfusion, antihypertensive treatment, and prednisone decrease.

Discussion

Immuno-osseous dysplasia is characterised by spondyloepiphyseal dysplasia, cellular immune defect, and progressive renal failure with nephrotic proteinuria. The combination of all these features as previously described allows this diagnosis in the child reported here.

The combination of abnormalities of the immune and skeletal systems is also present in other osteochondrodysplasias, such as cartilage-hair hypoplasia, as well as progressive renal disease and skeletal dysplasia which are features of asphyxiating thoracic dysplasia, but it has been claimed that the presence of the immune, skeletal, and renal abnormalities is specific to immuno-osseous dysplasia.

The association of focal segmental glomerulosclerosis with spondyloepiphyseal dysplasia has also been described in two patients without mention of the diagnosis of immuno-osseous dysplasia. These two patients, the one described here, and the 22 case reports where this diagnosis was quoted can be classified into two different groups as was previously suggested, a severe form and a more benign variant.

The features of the 17 patients with intruterine growth retardation and severe growth failure since birth (group 1) and those of the other group of eight patients (group 2) are similar (table 1). They all are intellectually normal.

In group 1, patients develop nephrotic syndrome aged 3 to 14 years. Immunosuppressive therapy has never been noted to be beneficial, with the one exception of cyclosporin that decreased the proteinuria in one patient. If the patients do not die of severe infection (one death from sepsis at the age of 5 years (case 2)), another from bacterial pneumonia at the age of 5 years, another from sepsis at the age of 6 years or because of absence of treatment of the renal failure (patients 1 and 2 died at the age of 8 years of renal failure, patient 4 at 5 years of pulmonary embolism), they progress to end stage renal failure aged 5...
<table>
<thead>
<tr>
<th>Feature</th>
<th>Group 1 (17)</th>
<th>Group 2 (8)</th>
<th>All patients (25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal onset short stature</td>
<td>17/17</td>
<td>0/8</td>
<td>17/25</td>
</tr>
<tr>
<td>Dysmorphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triangular face</td>
<td>4/17</td>
<td>0/8</td>
<td>4/25</td>
</tr>
<tr>
<td>Broad nasal bridge</td>
<td>10/17</td>
<td>3/8</td>
<td>13/25</td>
</tr>
<tr>
<td>Bulbous tip of nose</td>
<td>10/17</td>
<td>2/8</td>
<td>12/25</td>
</tr>
<tr>
<td>Hair abnormalities</td>
<td>5/17</td>
<td>1/8</td>
<td>6/25</td>
</tr>
<tr>
<td>Multiple lentigines</td>
<td>14/17</td>
<td>3/8</td>
<td>17/25</td>
</tr>
<tr>
<td>High pitched voice</td>
<td>5/17</td>
<td>0/8</td>
<td>5/25</td>
</tr>
<tr>
<td>Normal intelligence</td>
<td>16/16</td>
<td>8/8</td>
<td>24/24</td>
</tr>
<tr>
<td>Spondyloepiphyseal dysplasia</td>
<td>17/17</td>
<td>8/8</td>
<td>25/25</td>
</tr>
<tr>
<td>Cellular immune deficiency</td>
<td>17/17</td>
<td>6/6</td>
<td>23/23</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>16/17</td>
<td>8/8</td>
<td>24/25</td>
</tr>
<tr>
<td>Global/focal segmental</td>
<td>10/13</td>
<td>4/5</td>
<td>14/18</td>
</tr>
<tr>
<td>glomerulosclerosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Corneal opacities (3), microdontia (1), coarse, low voice (1), autoimmune haemolytic anaemia with thrombocytopenia (2), autoimmune enteropathy (1), mesangio proliferative glomerulonephritis (1), ventricular septal defect (1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The cellular immune deficiency is usually described as recurrent lymphopenia and reduced stimulation to mitogens, often with failure to perform cytogenic study of blood specimens. There is previous evidence of a decreased number of CD4+ T cells with reduction in CD4+ T cells. The percentages of activated and memory T lymphocytes were increased and peripheral blood CD3+ T cells expressed an abnormally high proportion of γδ TCR and reduced αβ TCR (case 3). The increase in peripheral blood immature γδ TCR CD3+ T cells may reflect a defect in intrathymic T cell differentiation or selection pathways. The histological study of one thymus (case 1) had the appearance seen in other T cell immunodeficiencies.

The progressive renal disease is described as an immune complex nephritis with proteinuria which progresses to focal and segmental glomerulosclerosis and chronic renal failure. Histological and ultrastructural studies of the kidney have been described both from biopsy and at necropsy.
After end stage renal failure, biopsy specimens are described as focal segmental glomerulosclerosis with foci of tubular atrophy and fibrosis of the interstitium (case 1) and necropsy studies mention diffuse and global sclerosis, atrophic or wide tubuli, fibrotic interstitium, and thickened and hyalinised arterioles (cases 1 and 2).

The increased urinary excretion of chondroitin-6-sulphate first reported by Schimke et al was not present in any of the other patients with immuno-osseous dysplasia except for the one reported here and two cases described as having slightly increased urinary mucopolysaccharide levels, composed of chondroitin-6-sulphate and chondroitin-4-sulphate (case 1). It also disappeared in the proband described by Schimke as he became older.

The aetiology and physiopathology of Schimke immuno-osseous dysplasia remain unknown. Although it is likely that a primary immune disease may affect the kidney, it is more difficult to accept that it may interfere with bone growth starting before birth as happens in the severe spectrum of the disease.

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