

# Omenn's Syndrome

## A rare primary immunodeficiency disorder

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### متلازمة اومين اضطراب نادر لنقص المناعة الاولي

ابتسام النور، شاكيل احمد، كمال حليم، في نرمالا

**المخلص:** في السنوات ال 17 الماضية تم تشخيص انواع عديدة من نقص المناعة المركب الشديد في مستشفى جامعة السلطان قابوس . مسقط . متلازمة اومين حالة نادرة من الوراثة الصبغية الجسدية المتنحية لنقص المناعة لمركب الشديد . نعرض هنا رضيع عماني عمره ستة أسابيع كان باديا عليه الصفات السريرية والمناعية لتلك المتلازمة . ناقشنا من خلالها الجوانب لمناعية لهذه المتلازمة النادرة .  
**مفتاح الكلمات:** متلازمة اومين، نقص المناعة، نقص المناعة المركب الشديد، أولى، تقرير حالة، عمان.

**ABSTRACT:** Over the last 17 years different forms of severe combined immunodeficiency have been diagnosed at Sultan Qaboos University Hospital, Muscat. Omenn's syndrome is a rare autosomal recessive form of severe combined immunodeficiency. We report a 6 weeks old Omani infant who presented with the characteristic clinical and immunological phenotype of Omenn's syndrome. We take the opportunity to discuss and review the immunological aspect of this rare syndrome.

**Keywords:** Omenn's Syndrome; Immunodeficiency, severe, combined; Immunodeficiency, primary; Case report; Oman.

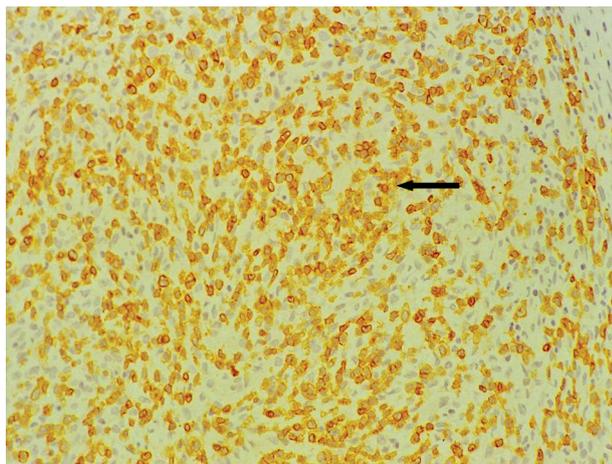
OMENN'S SYNDROME IS A RARE AUTOSOMAL recessive form of severe combined immunodeficiency. Omenn GS first described it in 1965. He described an extended American-Irish family with clinical features of recurrent infections, skin eruptions, eosinophilia, lymphadenopathy and hepatosplenomegaly with accompanied respiratory, gastrointestinal symptoms and failure to thrive. T lymphocyte numbers may be normal or high, but eosinophils are virtually increased. There is marked lymphocyte depletion in the thymus and lymphoid tissue. A given subset of T lymphocytes represents the majority of the blood T cells in each patient. Elevated numbers of T cells are found in the skin and gut, some of which have the phenotype of activated T cells. Omenn's syndrome is fatal if untreated. Patients have life-threatening bacterial, viral and fungal infections as in other forms of severe combined immunodeficiency. Allogenic haematopoietic stem cell transplant has treated the condition

successfully.

Omenn's syndrome is a genetically heterogeneous condition. Patients with similar immunophenotypes may have as yet unidentified gene defects. The majority of mutations are missense mutations in recombinase activating genes RAG-1 and RAG-2, which have been mapped to chromosome band 11p13. Mutation in RAG-1 and RAG-2 results in partial V(D)J recombination activity and dysregulation of T and B cell functions. Recent publications have described Omenn's syndrome in the absence of RAG mutations.

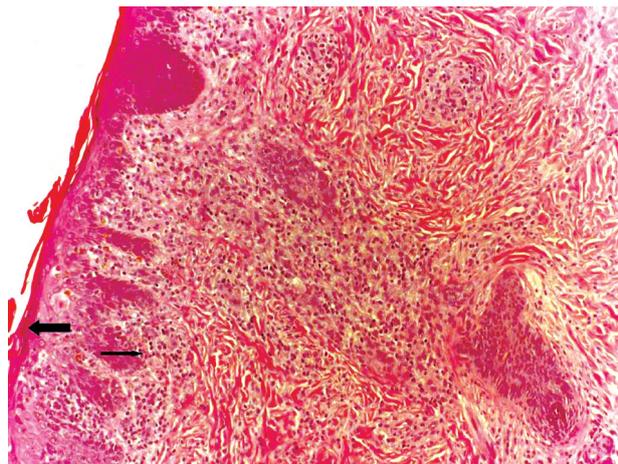
Omenn's syndrome has been reported in patients from North America, Europe and Asia. El-Arabi reported an infant with Omenn's syndrome from Qatar. To our knowledge, there is no other report from the Arabian area.<sup>1</sup>

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**Figures 1: Omenn's Syndrome Lymph node biopsy**

Immunohistochemistry staining showing T lymphocyte (CD3+) proliferation. Majority of the cells are CD30. Immunoperoxidase x 200



**Figures 2: Omenn's Syndrome Skin Biopsy**

Skin with Parakeratosis (↔) and lymphohistocytic infiltrate. The lymphocytes expressed CD3+ (→) and were mostly CD8+. The histocytes in the skin were S-100 non reactive. Hematoxylin and eosin x 200.

### CASE REPORT

A 6 weeks old Omani male infant was referred to Sultan Qaboos University Hospital with generalized lymphadenopathy and gross hepatomegaly. He was the second child of consanguineous parents, delivered normally with a birth weight of 3.5 kg. He received the BCG and the first dose of oral polio vaccine (OPV), together with hepatitis B vaccines immediately after birth according to the routine schedule of immunization in Oman. The first child in the family was normal. Symptoms were first noticed at the age of 3 weeks with progressive diffuse erythrodermic scaly skin rashes, which spread over the whole body including the scalp. This was diagnosed and treated as extensive seborrheic dermatitis. Two weeks later, the mother noticed swelling of the face, neck and at the subaxillary areas. Physical examination revealed a febrile and sick baby who had generalized lymphadenopathy with huge cervical lymph nodes, oedema of the face and the extremities, diffuse erythrodermic scaly ichthyotic skin rashes over the entire body and hepatosplenomegaly of 4cm each. Cardiovascular, respiratory and neurological examinations were normal. A complete range of hematological, immunological and biochemical tests was performed. Blood test showed haemoglobin of 9.3g/dl, leukocyte count of  $40.3 \times 10^9/l$ , of which the neutrophil count was  $7.92 \times 10^9/l$  and lymphocyte count was  $11.8 \times 10^9/l$ . The eosinophils count was very high ( $17.4 \times 10^9/l$ ). The platelet count was normal. Flow cytometry analysis of peripheral blood cells revealed lymphocytosis with virtually absent B cells as marked by anti CD20. All lymphocytes were CD3+.

There was oligoclonal predominance of activated memory cells CD4+/CD29, [Table 1]. Bone marrow aspiration confirmed the absence of B cells and T cells were present. Human leukocyte antigen typing revealed that the child was not identical to his mother.

Serum immunoglobulin levels were low except for extremely high serum IgE levels. In the absence of B cells, IgG level was certainly of maternal origin. IgE level was 19188.0 kiu/l and later rose to 25200 kiu/l [Table 2].

Evaluation of cytokines revealed normal interleukin 4 < 5pg/ml and high interleukine 5 level 25 pg/ml (normal < 13 & < 3 pg/ml respectively).

TORCH screening for congenital infections gave similar results in the mother and child, with positive IgG and negative IgM immunoglobulins for Epstein Barr virus, cytomegalovirus virus, rubella and toxoplasmosis infections suggestive of vertical transmission. HIV 1 and 2 were negative as well as screening for mycobacterium infections. Post vaccination hepatitis B surface antibody titer was 10-100 iu/L.

Radiological assessment revealed bronchopneumonia on the chest X-ray. Computed tomography of the chest showed normal sized thymus and no hilar lymphadenopathy.

Histopathological examination of lymph node showed loss of follicular architecture with preserved hilar structure and sinusoids. Polymorphous population of small lymphocytes, large activated lymphoid cells and numerous eosinophils replaced the lymph

**Table 1: Result of Lymphocyte subsets**

Lymphocyte type	Numbers	Percentage (%)	Reference range 0-3 months
Total	19.5	-	2.9-8.8 x10 <sup>9</sup> /L
CD3+	18.779	96.3	2.1-6.5 x10 <sup>9</sup> /L
CD20+	0.0	0.0	0.4-1.0 x10 <sup>9</sup> /L
CD3+/CD4+	14.430	74.0	1.5-5.1 x10 <sup>9</sup> /L
CD4+/CD29+		73.4	
CD4+/CD45RA		0.7	
CD3+/CD8+	4.349	22.35	0.7-2.5 x10 <sup>9</sup> /L
CD8+/CD11a+		2.7	
CD8+/CD11a-		19.4	
CD4:CD8 Ratio	3.3:1	-	1.3-3.5 x10 <sup>9</sup> /L
NK cells	0.644	3.3	0.3-0.7 x10 <sup>9</sup> /L

node architecture. The lymphoid cells are predominantly T lymphocytes (CD3 positive) with occasional B cells (CD20 Positive). Considerable proportions of CD30 positive T cells were present. Large dendritic cells of the node were shown which immunoreact for marker S-100 [Figures 1]. The epidermis in the skin biopsy showed parakeratosis. The dermis contained a moderately heavy lymphohistocytic infiltrate. Marked exocystosis was present associated with basal cell vacuolation and focal keratinocyte necrosis [Figure 2]. The lymphocytes cells were immunoreactive for marker CD8 and did not express CD4 (CD3+/CD8+). The histocytes expressed marker CD68 and were negative for S-100, ruling out the possibility of a Langerhans' cell infiltrate in the skin.

Although the child was treated with broad-spectrum antibiotics and immunoglobulin infusions, he continued to have recurrent bronchopneumonia and died at the age of 4 months of coagulase negative staphylococcus septicaemia and septic shock.

## DISCUSSION

Omenn's syndrome is a genetic disorder with recessive autosomal inheritance, characterized by lymphocytic infiltration of the skin, gut, liver and spleen, leading to erythroderma and protracted diarrhoea with failure to thrive.<sup>2-6</sup> In 1965, Omenn presented a kinder with 12 children suffering from skin eruptions followed by hepatosplenomegaly, generalized lymphadenopathy,

eosinophilia, poor growth and recurrent infections.<sup>2</sup> Skin lesions are very similar to those observed in graft-versus-host disease. All children had fatal outcomes within two to six months of life. Other features include extremely elevated serum immunoglobulin E levels and hypogammaglobulinaemia. A series of case reports expanded the clinical picture.<sup>3-6</sup> T lymphocyte number may be normal or high, but eosinophils are virtually increased. A given subset of T lymphocytes represents the majority of the blood T cells in each patient.<sup>7</sup> There is undue susceptibility to serious infections of the skin, lungs, joints and septicemia. Pneumonia and septic shock are the usual cause of death in this syndrome. Unless treated with allogenic haematopoietic stem cell transplantation, the prognosis of Omenn's syndrome will prove fatal within the first two to six months of life.<sup>8-20</sup> Poor clinical status before stem cell transplantation results in high transplantation related mortality.

Omenn's syndrome is genetically a heterogeneous condition. The majority of mutations are missense mutations in recombinae activating genes RAG1 and RAG2, which have been mapped to chromosome band 11p13.<sup>11-12</sup> The remainder of the mutations are nonsense, deletion, frameshift, duplication and splice mutations. Recent reports described Omenn's syndrome in the absence of RAG mutations. Ege et al. described a patient with Omenn's syndrome due to ARTEMIS mutation.<sup>13</sup> Giliani et al. described an infant with the phenotype picture of Omenn's syndrome and IL7RA

**Table 2: Immunoglobulin levels**

Immunoglobulin	Level	Normal range
IgG	3.6	2.1 - 7.7 G/L
IgA	<0.07	0.05 - 0.4 G/L
IgM	0.16	0.08 - 0.4 G/L
IgE	19188.0	10 - 29.2 Kiu/L
Anti Staphylolysin antibodies	< 1.0	<2 IU
Anti-corps anti Staphylolysin gamma	10	160 IU

gene mutation.<sup>14</sup> Patients with similar immunophenotypes may have as yet unidentified gene defects.<sup>15</sup>

The recombination activating enzymes RAG1 and RAG2 are essential in the assembly of V(D)J segments, which form the variable portions of immunoglobulin and T cell receptors (TCR) proteins.<sup>16</sup> Mutations in either the RAG1 or RAG2 genes were identified to cause severe combined immunodeficiency with markedly reduced numbers of T and B cells (T-B-NK+ phenotype).<sup>17</sup> Missense mutations of RAG1 or RAG2 in Omenn's syndrome lead to partial activities of RAG1 or RAG2,<sup>18</sup> and impair variable diversity joining V (D) J recombination, which is required for the development of mature T and B cells. There is marked lymphocyte depletion in the thymus and lymphoid tissue. Rudimentary thymus tissue shows poorly formed and decreased Hassall corpuscles with few lymphocytes.<sup>19</sup> Predominance of few T cell receptors clonotype is detectable in the thymus and is further selected in the periphery, with a different distribution of clonotype in different tissues. The gut lacks lymphocytes in Peyer's patches and in the lamina propria. Elevated numbers of T cells are found in skin and gut, some of which has the phenotype of activated T cells. Skin biopsy shows an activated autologous T cell infiltrate and psoriasiform hyperplasia of the epidermis, parakeratosis, cellular dyskeratosis and necrosis.<sup>20</sup> Reactive lymph nodes show infiltrating eosinophils and histocytes, but they lack germinal centers and cortical lymphocytes.<sup>21</sup>

Immunological abnormalities in this syndrome may include normal to high T lymphocytes count with variable distribution ratio of CD4+:CD8+ subsets. B cells are absent and NK cells are present. (T-B+NK+ phenotype).<sup>21</sup> An oligoclonal T<sub>H</sub>2 population is expand-

ed, possibly as a result of increased exposure to inadequately cleared antigen, or to an aberrant response to infection by non-antigen specific T cells receptors, leading to massive release of inflammatory cytokines. Those autoreactive cells have a highly restricted receptor repertoire.<sup>19-21</sup> Oligoclonicity of T cell repertoire in Omenn's syndrome is due both to intrathymic restriction and to the peripheral expansion.<sup>19, 20, 22</sup>

Lymphocyte stimulation with mitogens, phytohemagglutinin (PHA), concavalin A (con A) and Pokeweed Mitogen (PWA) are absent or profoundly reduced. In contrast, response to anti-CD3, phorbol myristate acetate (PMA) may be detectable.<sup>15</sup> Immunoglobulin levels show absent immunoglobulin A and M levels and increased immunoglobulin E level. Immunoglobulin G level is of maternal origin. Interleukin-4 (IL-4) and interleukin (IL-5) levels are typically increased.<sup>22</sup> The increased level of IL-5 suggests TH2 cells activation and favor eosinophils differentiation. T helper 2 cells usual function is to promote IgE production, but they it also have and inhibitory effects on macrophages. Therefore, it is accepted that elevated IgE production also goes along with T cell dysfunction.

Our patient had the typical clinical features of Omenn's syndrome. He presented with progressive diffuse erythrodermic scaly ichthyotic skin eruptions started at the age of 3 weeks. Then he developed generalized lymphadenopathy, hepatosplenomegaly, pneumonitis and loss of weight. Although treated with broad-spectrum antibiotics and immunoglobulin infusions, he continued to be sick with persistent pneumonitis and died of staphylococcal septic shock at the age of 4 months. Investigation showed leucocytosis, lymphocytosis and severe eosinophilia. Lymphocyte subsets' analysis of

our patient showed a virtual absence of B cells on both peripheral blood and bone marrow. CD4+ and CD8+ numbers were increased with oligoclonal expansion of T<sub>H</sub>2 cells (CD4+/CD29) typical of Omenn's syndrome. With virtually absent B cells, the IgG level is certainly of maternal origin. Immunoglobulin studies showed very high serum IgE and IL-5 levels. The increased level of IL-5 suggests TH2 cells activation and favours eosinophil differentiation. Lymphocyte transformation tests were not available in our laboratory, but there was poor response to hepatitis B vaccination with low anti hepatitis B surface antibody level. Pathological lymph node examination was diagnostic of Omenn's syndrome. There was loss of follicular architecture. The lymphoid cells were predominantly T lymphocytes (CD3 positive). Considerable proportions of CD30 positive T cells were present. The epidermis in the skin biopsy showed parakeratosis and marked exocystosis. The lymphocytes cells were immunoreactive for marker CD8 and did not express CD4 (CD3+/CD8+).

Early presentation, ichthyotic scaly skin lesion, absence of B cells, low immunoglobulin levels and negativity of antistaphylococcal antibodies signal towards Omenn's syndrome and not towards hyper IgE syndrome. Although the skin biopsy mimicked graft-versus host disease, heavy lymphohistocytic infiltrate and parakeratosis exclude graft-versus host disease.<sup>23</sup> The child's and mother's human leukocyte antigens were not identical, excluding materno-foetal engraftment. The histocytes in the skin biopsy expressed marker CD68 and were negative for S-100, ruling out the possibility of a Langerhans' cell infiltrate in the skin.

### CONCLUSION

In summary, the clinical picture of Omenn's syndrome resembles infantile histiocytosis. Our patient presented with a clinical and immunological picture consistent with previous reviews of this syndrome. At the time of presentation, neither lymphocyte stimulation tests nor bone marrow transplantation were available for children with primary immunodeficiency. Recognition of different forms of severe combined immunodeficiency in our hospital has led to improvement of the clinical immunological services for our patient, as well as availability of haematopoietic stem cell transplant for patients with primary immunodeficiency. Genetic evaluation for all types of severe combined immunodeficiency is in process. We should shortly be able to confirm whether

this child had a RAG 1 or RAG 2 mutation. There was no family history suggestive of immunodeficiency in this child. Physicians at the secondary care and primary health care levels should withhold all life-attenuated vaccines whenever there is family history suggestive of primary immunodeficiency. BCG vaccination at birth as well as live poliovirus vaccine could be fatal in these patients.

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