DERMATOLOGICA SINICA 29 (2011) 50–54

Contents lists available at ScienceDirect

Dermatologica Sinica

journal homepage: http://www.derm-sinica.com

CASE REPORT

Omenn syndrome: a case report and review of literature

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ARTICLE INFO

Article history:
Received: May 10, 2010
Revised: Jul 28, 2010
Accepted: Aug 11, 2010

Keywords:
Omenn syndrome
Severe combined immunodeficiency

ABSTRACT

Exfoliative dermatitis or erythroderma in infancy is rare. Clinicians need to be alert to the possible diagnosis of Omenn syndrome (OS), a rare form of combined immunodeficiency in infants presenting with recurrent infections, erythroderma, lymphadenopathy, hepatosplenomegaly, eosinophilia, and increased serum IgE levels. OS is fatal unless treated by hematopoietic stem cell transplantation. We described a 26-day-old boy who had presented with diffusely thick scales on the scalp and some pustules on his face and trunk since birth. The rash was initially treated as presumed seborrheic dermatitis. At the age of 42 days, he developed extensive exfoliative dermatitis, lymphadenopathy, hepatosplenomegaly, and failure to thrive as well as eosinophilia and increased serum IgE levels. The histopathology of the skin and lymph node were consistent with the diagnosis of OS. He had been prepared for allograft bone marrow transplantation twice at 5 months and 7 months of age, but the procedure was not performed because of catheter-related sepsis. The patient eventually died of sepsis secondary to perianal cellulitis at 20 months of age.

Introduction

Omenn syndrome (OS, OMIM 603554, http://www.ncbi.nlm.nih.gov/omim/603554), a rare autosomal recessive disease, is characterized by symptoms of severe combined immunodeficiency (SCID) associated with erythroderma, hepatosplenomegaly, lymphadenopathy, and alopecia.[1,2] Similar to other patients with SCID, patients with OS typically present early in infancy with viral or fungal pneumonitis, chronic diarrhea, and failure to thrive. However, unlike typical SCID, patients with OS manifest erythroderma, lymphadenopathy, eosinophilia, and increased IgE levels.[1,2] Clinical diagnostic criteria for OS have been previously described as the clinical triad of hepatosplenomegaly, lymphadenopathy, and erythroderma in the absence of maternofetal engraftment and presence of either a raised IgE or peripheral eosinophil count, together with immunodeficiency.[3] Mutations of the recombination activating gene 1 and 2 (*RAG1* and *RAG2*) have been reported in most OS patients[4,5] and result in the absence of circulating B cells and nonfunctional oligoclonal T cells.[4] Unless treated with hematopoietic stem cell transplantation, OS patients usually succumb early in life to overwhelming opportunistic infections. Herein, we report an OS case and the result of mutation analysis.

Case report

A 26-day-old boy was born at full term as the first child after an uncomplicated pregnancy. There family history was unremarkable. The baby weighed 2.4 kg at birth. Diffuse thick scaling starting from the vertex of the scalp with progressive involvement of the forehead with some pustules on his face and trunk had been noted since birth. He was admitted to our Pediatric ward 26 days after birth with the diagnosis of seborrheic dermatitis associated with secondary bacterial infection. The initial laboratory tests showed eosinophilia (1035/μL) (white blood cell 6900/μL and lymphocytes 3519/μL), neutropenia (1380/μL), anemia (Hemoglobin 7.1 g/dL), and hypoalbuminemia (2.6 g/dL). A pus culture yielded heavy oxacillin-resistant *Staphylococcus aureus* and *Neisseria subflava*. After being treated with systemic antibiotics and topical hydrocortisone acetate 1% ointment, yellowish crusts decreased and he was discharged 1 week later.

At the age of 42 days, the child was admitted the Pediatric ward again because of fever and vomiting. Physical examination revealed generalized exfoliative dermatitis (Figure 1), alopecia, bilateral axillary and inguinal lymphadenopathy, mild hepatomegaly, and failure to thrive (weighed 2.92 kg, $<3^{rd}$ percentile). Microscopic examination of the clipped hairs revealed no bamboo hair. Laboratory tests revealed marked eosinophilia (2002/μL) (white blood

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doi:10.1016/j.dsi.2011.05.002

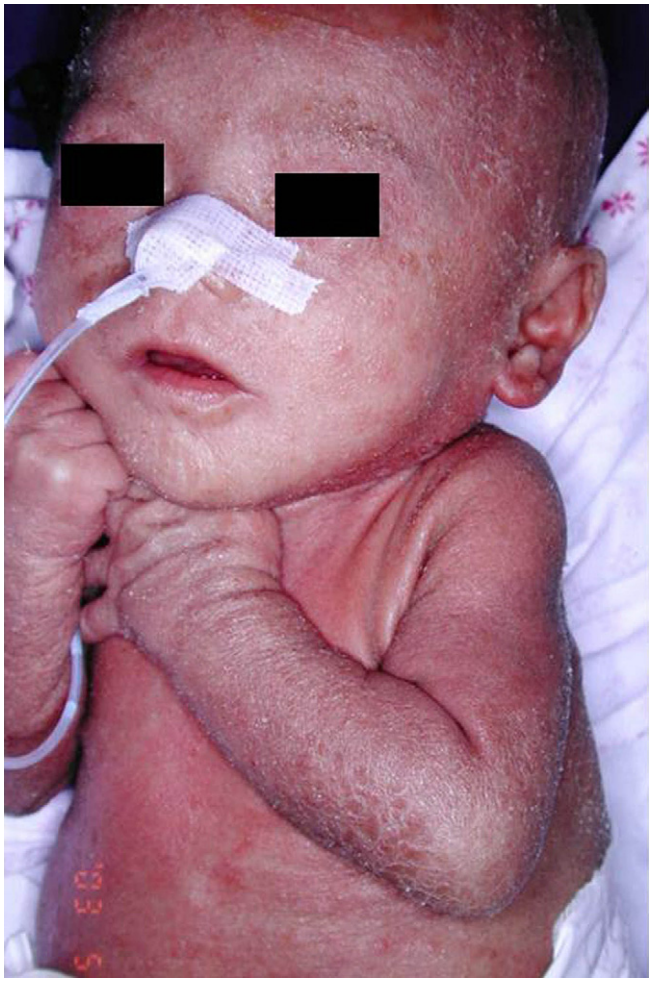

Figure 1 Two-month-old boy presented with generalized exfoliative dermatitis.

cell 7700/μL and lymphocytes 2772/μL), neutropenia (1694/μL), anemia (Hemoglobin 8.0 g/dL), and hypogammaglobulinemia. The total serum IgE level was elevated (3289 IU/mL), whereas IgG (273 mg/dL), IgA (<6.67 mg/dL), and IgM (32.5 mg/dL) levels were all below the lower limits. The flow cytometry showed a deficiency of T lymphocytes: T cells were decreased (24%); B cells (CD19) were increased (67%); natural killer cells were normal (7%) and T cells showed an abnormal distribution of CD4 and CD8 (8% of CD4 and 8% of CD8).[6] The chest X-ray revealed no obviously thymus aplasia.

A skin biopsy showed spongiotic psoriasiform hyperplasia with parakeratosis and infiltration of numerous small lymphocytes in the spongiotic foci as well as focal vacuolar interface changes (Figures 2A and 2B). There was infiltration of small lymphocytes obscuring the dermoepidermal interface with presence of a few single necrotic keratinocytes (Figure 2C). The papillary dermis showed extravasation of erythrocytes and a superficial perivascular and patchy lichenoid infiltrate consisting of small lymphocytes and a small number of neutrophils. Immunostaining revealed that the lymphocytes were CD3+ with about equal amounts of CD4+ and CD8+ cells in the infiltrate. The findings were compatible with OS but differed somewhat from those of the typical OS, which usually shows a predominance of CD4+ over CD8+ cells.[4,7] A lymph node biopsy revealed almost complete absence of germinal centers and marked reduction of lymphocytes in the cortical and paracortical areas where there was dense infiltrates of histiocytes and abundant eosinophils. The immunohistochemical staining revealed that the

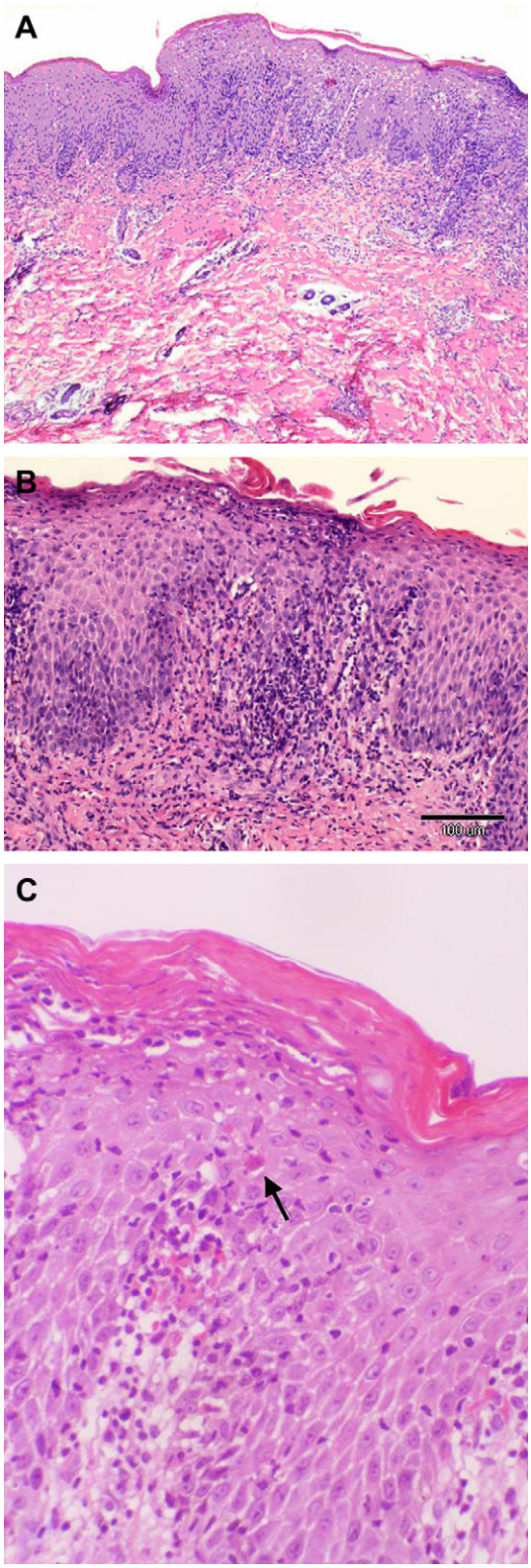

Figure 2 (A–C) The epidermis shows spongiotic psoriasiform spongiotic psoriasiform hyperplasia with parakeratosis and infiltration of numerous small lymphocytes in the spongiotic foci as well as focal vacuolar interface changes (hematoxylin and eosin; original magnification for A: ×40; B: ×100). (C) The dermoepidermal interface is obscured by the infiltration of small lymphocytes. Note the presence of a few single necrotic keratinocytes (hematoxylin and eosin; original magnification ×200).

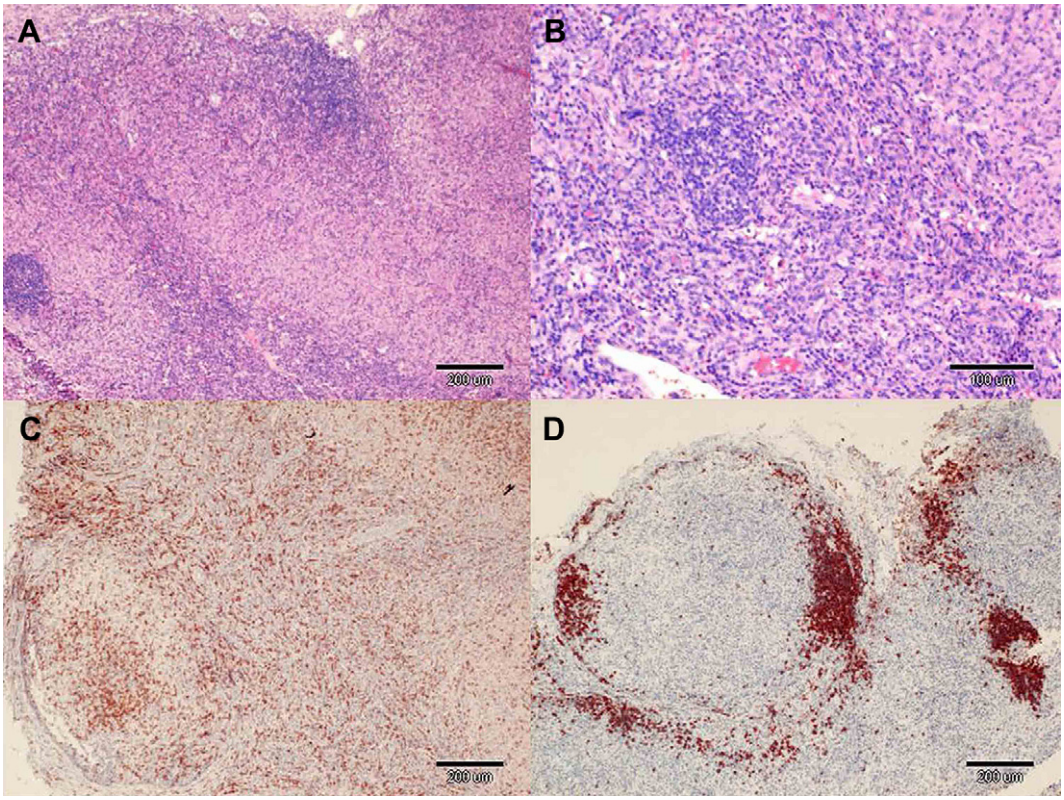

Figure 3 (A and B) A lymph node biopsy revealed almost complete absence of germinal centers and marked reduction of lymphocytes in the cortical and paracortical areas replaced by histiocytes and abundant eosinophils (hematoxylin and eosin; original magnification A: ×40; B: ×100). (C) The immunohistochemical staining revealed the infiltrating lymphocytes were CD3+ cells(original magnification ×40). (D) CD20+ B cells were present in small foci in the residual primary lymphoid follicles (original magnification ×40).

lymphocytes were CD3+ with about equal amounts of CD4+ and CD8+ cells. CD20+ B cells were present in small foci in the residual primary lymphoid follicles. Large numbers of S100-positive histiocytoid cells were present in the cortical and paracortical areas (Figure 3). The findings were consistent with OS.[7–10]

Mutation analysis of *RAG1*, *RAG2*, *ARTEMIS*, and *SPINK5* were performed. No mutation was identified in our patient and his parents. In view of the clinical and laboratory findings, the clinical diagnostic criteria of OS were reached and the patient had been prepared for allograft bone marrow transplantation at the age of 5 months and 7 months. However, the transplantation was not done because of catheter-related sepsis. Thirteen months later, the patient died of sepsis secondary to perianal cellulitis.

Discussion

OS, originally reported as "familial reticuloendotheliosis with eosinophilia" by Omenn[1] in 1965, is a rare autosomal recessive form of SCID. The frequency is 1:5,000,000 and the male to female ratio is about 1. Clinically, OS manifests as exfoliative dermatitis, followed by lymphadenopathy, hepatosplenomegaly, alopecia, diarrhea, failure to thrive, and recurrent life-threatening infections. Eighty percent of the patients present the clinical triad of former three manifestations. In general, the onset is during the 1st day of life and mostly before the age of 8 weeks.[1,2,4]

In the present case, the clinical and laboratory findings of hepatosplenomegaly, lymphadenopathy, erythroderma, alopecia, recurrent severe infection, failure to thrive, eosinophilia, and elevated IgE together with immunodeficiency met the diagnostic criteria of OS despite that no mutation in *RAG1*, *RAG2*, and *ARTEMIS* gene were identified in the patient and his parents. These results did not change the diagnosis as OS is a genetically heterogeneous condition and patients may have as yet unidentified gene defects. The histopathology of the erythrodermic skin and lymph node was also consistent with the diagnosis of OS.

Most OS cases show an autosomal recessive inheritance pattern with mutations in the *RAG1* or *RAG2*, which encode RAG1 and RAG2 enzymes. Normally, RAG1 and RAG2 enzymes, which are restricted to immature lymphocytes, initiate a V (D) J (Variable, Diversity, Joining) recombination that leads to both T- and B-cell development. The absence of V (D) J recombination results in SCID, such as OS.[7,11,12] In OS, the defect in V (D) J recombination is partial and characterized by presence of only a small number of T cell clones, which infiltrate the skin, gut, liver, and spleen leading to clinical manifestations. The number of peripheral blood lymphocytes can be decreased, normal, or increased with variable B cell counts and hypogammaglobulinemia. Recently, other studies suggested that defects in genes other than *RAGs*, such as *ARTEMIS*, *IL7RA*, and RNase mitochondrial RNA processing RNA gene may cause OS.[13–15] Indeed, in a study of nine patients with clinical and immunological features of OS, seven had no detectable mutations in the *RAG* or *ARTEMIS* genes, suggesting that mutations in as yet undiscovered genes may cause an immunodeficiency syndrome immunologically and phenotypically similar to OS.[3] A low to absent number of CD19+ B cells is characteristic of OS associated with mutations in RAG1, RAG2, *ARTEMIS*, or DNA ligase 4. However, B cells are normal in other forms of OS without these mutations similar to our case.[10]

Pruszkowski et al[16] conducted a retrospective study of 51 cases of neonatal erythroderma. On average, the etiological diagnosis was established 11 months after the onset of erythroderma. The underlying causes observed included immunodeficiency (30%), simple or complex ichthyosis (24%), Netherton syndrome (NS,

OMIM 256500) (18%), and eczematous or papulosquamous dermatitis (20%).[17] Atopic dermatitis and seborrheic dermatitis were less frequent in neonatal erythroderma. Other causes of erythroderma include fungal infections, graft-versus-host disease (GVHD), and drug eruptions. The cause remains unknown in 10%.[17] Differential diagnosis of erythroderma with immunodeficiency and failure to thrive in neonates lies mainly among OS, GVHD, and NS. Clinical presentation in these neonates may be very similar; therefore, blood investigation, skin biopsy, immunocytochemistry, and molecular genetic analysis are needed to establish the diagnosis (Table 1).

GVHD can be present in newborns with SCID because of maternal-fetal transfusion or as a consequence of blood transfusion.[18] Symptoms of maternal-fetal GVHD in SCID patients may vary from a transient morbilliform eruption to erythroderma with alopecia. NS is a rare severe autosomal recessive disease characterized by congenital ichthyosiform erythroderma, ichthyosis linearis circumflexa, “bamboo hair” (trichorrhexis invaginata), and atopic diathesis with elevated IgE. Most patients with NS are typically born with a generalized erythroderma, which can be difficult to distinguish clinically from other types of infantile erythroderma initially. The erythroderma can persist throughout life or evolve into a milder phenotype known as ichthyosis linearis circumflexa. Diagnosis of NS may be delayed because the pathognomic trichorrhexis invaginata or ichthyosis linearis circumflexa often does not become evident until after the 1st year of life.[19] Mutations in serine protease inhibitor Kazal-type 5 (*SPINK5*) have been identified in NS. In this case, the mutation analysis of *SPINK5* was negative.

Both GVHD and NS were excluded in the present case. OS and GVHD can be differentiated histologically from NS by the presence of epidermal basal vacuolization and apoptosis of keratinocytes.[20,21] Both were present in the biopsy of our patient, thereby making a diagnosis of NS highly unlikely. Furthermore, no bamboo hairs were found. Skin biopsies in OS can look very similar to those in GVHD. However, in OS, there is always acanthosis and parakeratosis, whereas the epidermis in GVHD is generally flat and rarely with parakeratosis.[21] Inflammation is more marked in OS, with a high lymphocyte/macrophage ratio, whereas in GVHD, this ratio is between 1:1 and 1:4.[8] Additional clinical findings, such as eosinophilia and pronounced lymphadenopathy, can help to differentiate the erythroderma in OS from GVHD. Genetic markers may also be used to distinguish nonautologous cells from autologous cells.[22]

OS is fatal if untreated; the most frequent causes of death are recurrent infections, particularly respiratory infections and septicemia. Therapeutic options include bone marrow transplantation or cord blood stem cell transplantation; however, the mortality is still 46%. Early diagnosis of OS is very important to initiate appropriate treatment because OS is often rapidly fatal because of life-threatening infections when bone marrow transplantation is delayed.

In conclusion, we report a case of OS in a Taiwanese infant, in which the diagnosis was established as early as 3 months of age. Although the diagnosis had been made early enough for an early allograft bone marrow transplantation, the procedure was unfortunately aborted twice because of catheter-related sepsis. The child eventually died of sepsis secondary to perianal cellulitis at the age of 20 months. Clinicians should be familiar with the key clinical findings of OS, which consist of neonatal erythrodermia, hepatosplenomegaly, and lymphadenopathy with recurrent life-threatening infections and failure to thrive, and the characteristic

Table 1 Differential diagnosis of this case.

Disease	Cause	Cutaneous characteristics	Extracutaneous symptoms	Diagnosis	Histology[20,21]
Omenn syndrome	Mutation in *RAG 1*/*RAG 2* gene, rarely in *IL-7R*, *RMPR*, or *ARTEMIS* gene	Erythroderma and alopecia	Hepatosplenomegaly, lymphadenopathy, thymus hypoplasia, diarrhea, failure to thrive, recurrent serious infections (pneumonia, sepsis, and so on)	Blood differential: eosinophilia, IgE ↑, infectious disease diagnosis, lymphocyte phenotyping, molecular genetic analysis	Skin: always acanthosis, almost always parakeratosis, predominantly lymphocytic infiltrate (IHC of LCA), dyskeratosis, basal vacuolation Lymph node: abnormal architecture typically with an absence of germinal centers and paracortical expansion of S100 staining interdigitating reticulum cells
Maternal-fetal GVHD	Persistence of maternal T cells in patients with SCID	Variety (transient morbilliform eruption to erythroderma and alopecia)	Hepatopathy (icterus, transaminase elevation), diarrhea, anemia, fever, failure to thrive	Transaminases ↑, bilirubin ↑, specific: chimerism analysis for detection of maternal lymphocytes	Skin: flat epidermis, rarely parakeratosis, dyskeratosis, basal vacuolation, relatively more macrophages in infiltration (IHC of CD68).
Netherton syndrome	Mutation in *SPINK-5* gene	Erythroderma, alopecia, later ichthyosis linearis circumflexa, trichorrhexis invaginata	Hypertensive dehydration. Later: bronchial asthma, allergic rhinoconjunctivitis, enteropathy, delayed growth, recurrent infections	Hair shaft analysis, IHC (LEKTI)	Skin: psoriasiform acanthosis, thickening of the basement membrane, prominent dermal blood vessels, a dermal infiltrate with lymphocytes and macrophages equally represented.
Present case	No mutation in *SPINK-5*, *RAG 1*/*RAG 2*, and *ARTEMIS* gene	Erythroderma and alopecia	Hepatosplenomegaly, lymphadenopathy, diarrhea, failure to thrive, recurrent serious infections (pneumonia, abscess, sepsis, and so on)	Eosinophilia, IgE ↑, infectious disease diagnosis	Skin: spongiotic psoriasiform hyperplasia with parakeratosis and vacuolar interface changes with necrotic keratinocytes. Lymph node: consistent with OS.

GVHD = graft-versus-host disease; IHC = immunohistochemistry; LCA = leukocyte common antigen; LEKTI = lymphoepithelial Kazal-type-related inhibitor.

laboratory findings, which include eosinophilia and high IgE levels, so that an early diagnosis could be established for bone marrow transplantation in a timely fashion. Molecular diagnosis procedures are now available to determine the diagnosis or to serve as a tool for genetic counseling and prenatal diagnosis.

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