

Omenn's syndrome: lessons from a red baby

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Summary

Exfoliative dermatitis and erythroderma in infancy are rare. Clinicians need to be alert to the possible diagnosis of Omenn's syndrome (OS), a rare form of combined immunodeficiency in infants presenting with exfoliative dermatitis, erythroderma, recurrent infections, eosinophilia and raised IgE. OS is fatal unless treated by bone-marrow transplantation (BMT). We describe a 3-week-old girl who presented with a widespread scaly erythematous rash and stomatitis, and was initially treated for presumed atopic eczema and primary herpes stomatitis. Aged 3 months, she developed erythroderma, diarrhoea and hepatosplenomegaly associated with eosinophilia, raised serum IgE and low IgG, IgA and IgM levels, abnormal lymphocyte populations and skin histology, consistent with a diagnosis of OS. She remains well 16 months after a human leucocyte antigen-matched bone-marrow transplant from an unrelated donor.

Neonatal and infantile erythroderma are rare. When faced with such a patient, a systematic approach leads to the correct diagnosis and appropriate, sometimes life-saving treatments. Misdiagnosis can be fatal in cases of immunodeficiency syndromes such as OS, which may first present to the clinician as erythroderma. We describe an infant with OS and her progress following bone marrow transplantation (BMT), and discuss the salient features of OS as illustrated by this case.

Report

A 3-week-old girl presented with stomatitis and a widespread scaly erythematous rash. She had been born at full term to non-consanguineous parents after an

uncomplicated pregnancy, and had normal skin at birth. Family history was unremarkable. She was treated with intravenous aciclovir for presumed primary herpes stomatitis, and topical emollients and corticosteroids for atopic eczema. During the following 2 months, despite regular intermittent courses of topical corticosteroids, the rash flared. Aged 3 months, the child developed exfoliative dermatitis and erythroderma with pustules and crusting on the palms and legs associated with pyrexia, lethargy and watery diarrhoea, requiring hospital admission. Examination also revealed tachycardia and hepatosplenomegaly, but no lymphadenopathy. Growth and developmental milestones were appropriate for her age.

Results of investigations at the age of 3 weeks and 3 months old are shown in Table 1. At the age of 3 months, her lymphocyte numbers were preserved, but subpopulations were grossly imbalanced, with a predominance of activated CD3+ cells (73%, predominantly CD25+, DR+), CD4+ cells (71%) and low CD8+(3%) and CD19+(<1%) cells. A skin biopsy showed marked focal basal cell vacuolation, spongiosis and parakeratosis. A mild lymphocytic infiltrate and eosinophils were seen within the upper and mid dermis. Immunocytochemical staining of the skin biopsy showed CD3+ (T cells) (Fig. 1) but no CD20+ (B cells) (Fig. 2) in the

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Table 1 Summary of investigation results before and after bone-marrow transplantation.

Blood investigations	Aged 3 weeks	Aged 3 months (pre-BMT)	Aged 10 months (5 months post-BMT)	Aged 17 months (1 year post-BMT) ^a	Aged 21 months (16 months post-BMT) ^a
Haemoglobin, g/dL (11–15)	16.6	11.5	10.0	12.3 (10–13.5)	13.4
White blood count, $\times 10^9/L$ (6–12.5)	7.5	16.6	12.2	7.3 (5–15)	7.18
Eosinophils, %	2	43	41	N/A	N/A
Eosinophils, $\times 10^9/L$ (0–0.8)	0.2	7.1	5.1	N/A	0.08 (0.1–0.3)
Lymphocytes, %	67	31	17	–	–
Lymphocytes, $\times 10^9/L$ (5.5–8.5)	5	5.1	2.7	3.55 (3–13.5)	4.11
CD3	–	73	–	73	74
CD19	–	1	–	15	19
IgE, kU/L (<15)	–	2466	–	N/A	N/A
IgG, g/L (2.05–5.39)	–	<1	7.9 ^b	9.53 ^b (3.1–13.8)	N/A
IgA, g/L (0.05–0.34)	–	<0.04	>0.06	0.37 (0.3–1.2)	N/A
IgM, g/L (0.17–0.66)	–	0.08	>0.3	0.32 (0.5–2.2)	N/A
Albumin, g/L (31–47)	–	25	35	46	–

Data in parentheses in column 1 are normal ranges; data in parentheses in the last two columns are BMT, bone-marrow transplantation; N/A, not available. ^aNote change in normal range for ages between 17 and 21 months; ^bOn intravenous IgG 7.5 g every 3 weeks.

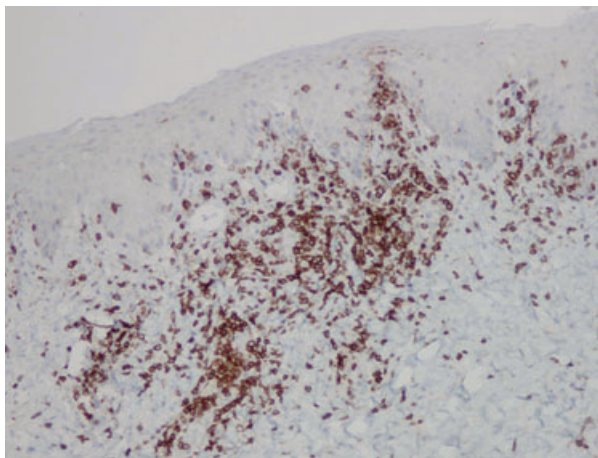


Figure 1 Immunocytochemical staining of the skin biopsy shows CD3 staining, indicating the presence of T lymphocytes in the dermis (original magnification $\times 100$).

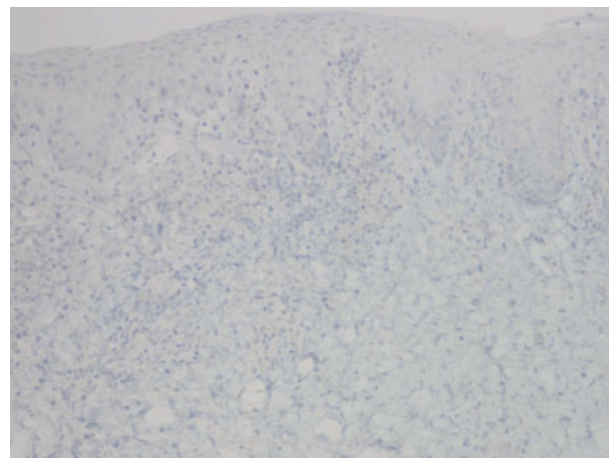


Figure 2 Immunocytochemical staining of the skin biopsy shows no staining with CD20, indicating the absence of B lymphocytes in the dermis (original magnification $\times 100$).

dermis, with a predominance of CD4+ over CD8+ cells, characteristic of Omenn's syndrome (OS).

Her general condition improved within 24 hours of supportive treatment with topical emollients, topical corticosteroids, intravenous broad-spectrum antibiotics and antifungal agents (tazocin, gentamicin, fluconazole), nasogastric feeding and intravenous fluid replacement. A full septic screen was performed, which was negative except for the skin swabs taken from several sites, which showed a heavy growth of *Staphylococcus aureus*.

Based on the clinical findings and investigation results, our patient was diagnosed with OS (T+, B–,

NK+, RAG-deficient phenotype with mutation in the *RAG1* gene) and referred for bone-marrow transplantation (BMT) to a specialist paediatric haematology unit. After conditioning with cyclophosphamide, fludarabine and monoclonal antibodies (anti-CD45 and alemtuzumab), the child had a successful BMT from a human leucocyte antigen-matched unrelated female donor 8 weeks after the diagnosis of OS.

The post-transplantation management regimen included nasogastric feeding, granulocyte colony-stimulating factor, systemic immunosuppressants (ciclosporin, mycophenolate mofetil), graft-versus-host disease (GvHD) prophylaxis (methylprednisolone followed by

prednisolone), anti-infective prophylaxis (aciclovir, penicillin, cotrimoxazole, itraconazole, nystatin) and intravenous IgG (Flebogamma®; Instituto Grifols, Barcelona, Spain), tapered off over a 6-month period. The post-BMT period was complicated by grade I skin GvHD that responded to an increased dose of systemic methylprednisolone followed by topical corticosteroids. As shown in Table 1, the child continued to have marked eosinophilia for several months after the BMT, which was presumed to be due to the previous OS and skin GvHD.

One year after the BMT, the patient was off all prophylactic medication and IgG. Currently, 16 months post-BMT, she is well with 100% donor engraftment, normal full blood count and lymphocyte distribution (Table 1), normal skin, no organomegaly, no infective episodes and normal stools, and she is gaining weight.

OS, originally called 'familial reticuloendotheliosis with eosinophilia', is a rare autosomal recessive form of severe combined immunodeficiency first described in 1965.¹ It presents at birth or in the neonatal period with exfoliative dermatitis, erythroderma, diffuse alopecia, lymphadenopathy, hepatosplenomegaly, recurrent infections and failure to thrive secondary to diarrhoea. Alopecia is not always present in OS, similar to our patient. Our case was also atypical in the *RAG1* mutation. Characteristic blood investigation findings include eosinophilia, normal or low lymphocyte count, poorly functional T cells, absent B cells, high IgE, hypogammaglobulinaemia with decreased/undetectable IgA, IgG, IgM and hypoalbuminaemia.

Mutations in recombinase-activating genes 1 or 2 (*RAG1* or *RAG2*) have been identified as the cause of OS in most cases, as in our patient.² The *RAG* genes are expressed in immature lymphocytes and initiate recombination of the variable (V), diversity (D) and joining (J) segments of immunoglobulins and T-cell receptors that provide the wide diversity of the human immune system. Mutations in the *RAG1* or *RAG2* genes cause impairment but not complete abolition of their function, resulting in faulty VDJ recombination, arrest in T- and B-cell development and maturation and eventually in humoral and cellular immunodeficiency. Mutations in the *ARTEMIS* gene on chromosome 10p was reported to cause OS in one patient.³ 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.⁴

OS is fatal within the first year of life due to severe infections, unless treated by BMT. Although BMT itself is associated with high morbidity and mortality, when successful it is life-saving and leads to clinical and immune recovery as in our patient.^{5–7} In addition to OS, the differential diagnosis of erythroderma, immunodeficiency and failure to thrive in neonates includes graft-versus-host disease and Netherton's syndrome.⁸ Clinical presentation in these neonates may be very similar and therefore blood investigations, skin histology and immunocytochemistry are needed to confirm the diagnosis. Other conditions to consider in the differential diagnosis of an erythrodermic neonate include infections, ichthyoses, metabolic disorders, drug reactions and other skin diseases such as inflammatory skin disorders.^{9,10} Regardless of the underlying cause, erythroderma in neonates and infants can be life-threatening, and therefore the initial management strategies apply to all cases; these include maintenance of fluid and electrolyte balance, nutrition, temperature regulation, prevention and treatment of infections, topical emollients and topical corticosteroids.

The lessons learnt from this baby are that although the combination of neonatal and infantile exfoliative dermatitis and erythroderma is rare, a high index of suspicion, appropriate investigations to confirm a life-threatening diagnosis such as OS and a bone-marrow transplant can lead to a cure.

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