



Perspective

Not just a rash diagnosis! The allergist's role in improving recognition of Omenn syndrome

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Omenn syndrome (OS) is an autosomal recessive subtype of severe combined immunodeficiency (SCID) with increased mortality.¹ Gilbert Omenn first reported this in 1965, describing reticuloendotheliosis with eosinophilia in several siblings from a consanguineous American family of Irish descent.² The incidence of SCID is 1:58,000 to 1:100,000, whereas OS has a frequency of 1:5,000,000.^{2,3} Omenn syndrome is most frequently caused by mutations in the *RAG* genes, but also in mutations in *ARTEMIS*, *ADA*, *ILRA2*, *ILRA7*, *CHD7*, *RMRP*, and DNA ligase 4 genes and in association with 22q11 microdeletion syndrome. The *RAG* genes encode the *RAG1* and *RAG2* enzymes, which drive a VDJ (Variable, Diversity, Joining) recombination during T and B cell development. In OS, hypomorphic *RAG* mutations may lead to a partial defect of VDJ recombination, resulting in a small number of T-cell clones which infiltrate the skin, gut, and other organs.² Clinical diagnostic criteria of OS include the triad of hepatosplenomegaly, lymphadenopathy, and erythroderma without maternofetal engraftment and either elevated immunoglobulin E or eosinophilia, with immunodeficiency.² Erythroderma is rare in infancy, making it a key diagnostic feature of OS.¹ The associated high mortality necessitates early diagnosis, because early compatible bone marrow or cord blood stem cell transplantations are lifesaving.¹ Therefore, recognition of erythroderma as a possible presentation of immunodeficiency is imperative and family members at risk should be screened. We presented a case series of 2 related individuals presenting with OS 1 year apart and discussed the importance of early recognition, screening, and management.

A midwife delivered patient 1 at home, a male of Amish heritage with known parental consanguinity (second degree cousins with

same great grandparents) and a sibling with Potter disease (deceased). Postnatally, the midwife noted a generalized, erythematous, desquamating rash (predominantly on the head, neck, and extremities) and swollen extremities (Fig 1A and 1B). Breastfeeding was initiated. The patient experienced persistent respiratory distress and required hospitalization and intubation. At day 5 of life, patient was transferred to our institution for suspected neonatal sepsis. Newborn screen indicated an undetectable T cell receptor excision circle level. Severe combined immunodeficiency was strongly suspected, breastfeeding was withheld to minimize cytomegalovirus transmission, and isolation precautions were started. Patient 1 received a diagnosis of OS (eTable 1). A homozygous *RAG-1* mutation (c.2974A>G) was confirmed. A matched, sibling donor allogeneic bone marrow transplant with a conditioning regimen of busulfan, fludarabine, and rabbit antithymocyte globulin (rATG) was done at 3 months. At day +457 after transplant, the patient had 32% total donor white blood cell chimerism with 98% donor chimerism of T-cell lineage. Given the patient's underlying disease is in lymphocytes, complete donor chimerism in T-cell lineage was likely more important than mixed chimerism status. The patient remained well after prophylactic antibiotics, intravenous immunoglobulin (IVIG), and posttransplant cyclosporine were discontinued.

The same midwife delivered patient 2, a female (first cousin of patient 1), at home. She recognized a less severe but similar generalized, desquamating rash (Fig 1C) and admitted the otherwise asymptomatic patient to our neonatal intensive care unit. Her parents are second cousins. Patient 1's mother and patient 2's father are siblings. Patient 1's father and patient 2's mother are first cousins (eFig 1). The diagnosis of OS was based on clinical presentation and laboratory results (eTable 1) with a T cell receptor excision circle count less than 25 copies per million CD3 T cells and a homozygous *RAG-1* mutation (c.2974A>G). The patient underwent a 6/6 HLA-matched unrelated allogeneic umbilical cord blood stem cell transplant with the same conditioning regimen as patient

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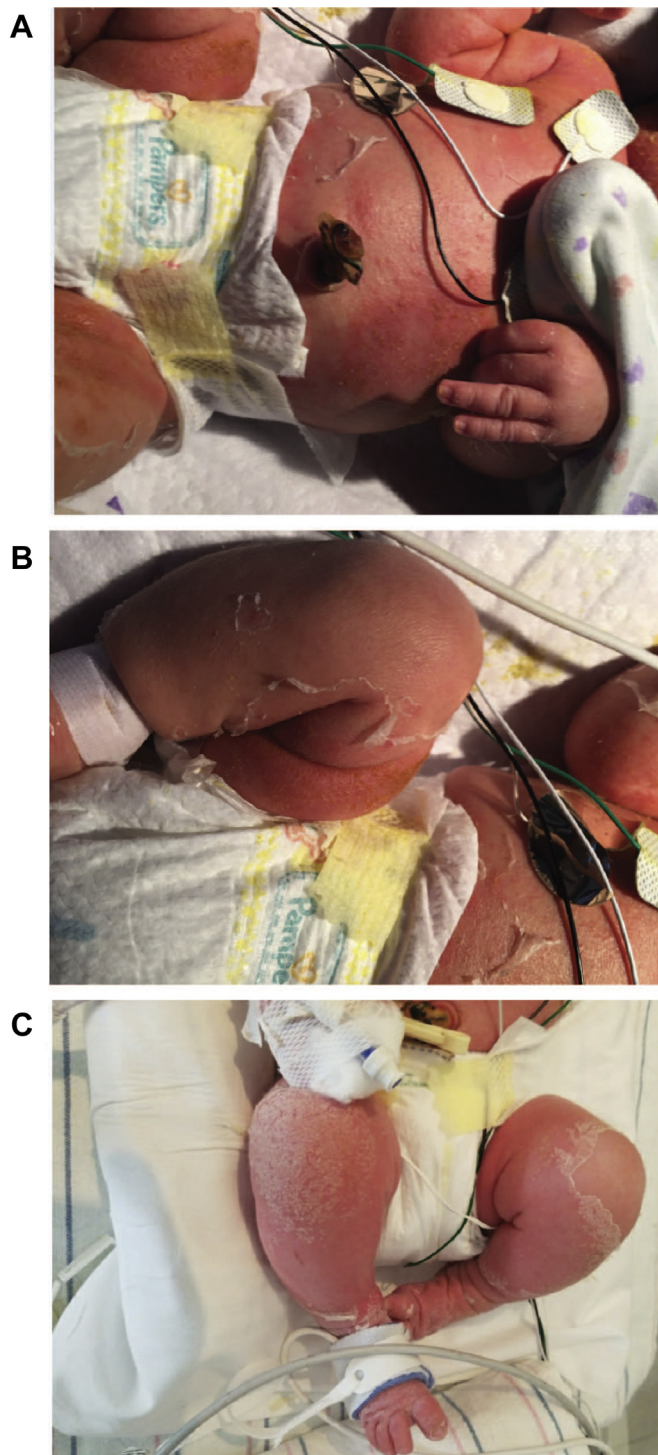


Figure 1. A and B, Desquamating, generalized, erythematous rash seen on the trunk and extremities in patient 1. C, Desquamating, generalized, erythematous rash seen on the extremities in Patient 2.

1. At day +124, total donor chimerism reached 90% with 97% T cell lineage chimerism. Her graft-versus-host disease gradually improved on cyclosporine and tapering steroids.

The rapid progression of SCID requires a prompt diagnosis and recognition that neonatal rashes may be an initial presentation of immunodeficiency. An extensive discussion of the differential diagnoses of OS was beyond the scope of this manuscript,^{1,4} but it included severe atopic dermatitis, graft-versus-host disease, histiocytosis X, infections (including Staphylococcal scalded skin syndrome or congenital candidiasis), ichthyoses, Netherton syndrome, metabolic disorders, or medication-related adverse effects. Allergists or immunologists are in close interaction with the primary care providers and therefore in a prime position to provide education on immunodeficiency. Populations at risk for OS include neonates born at home (lack of standard newborn screening) and with family history of consanguinity or immunodeficiency. Being allergists/immunologists, we have the opportunity and responsibility to translate complex immunologic diseases into understandable concepts and practical strategies when working with primary care providers and families. As highlighted in this case, based on experience with patient 1, the midwife recognized the characteristic rash in patient 2, resulting in earlier referral to a tertiary care center with immunology consult service. In addition, the parents of patient 2 showed increased understanding of the disease and its management. Newborn screening for all infants is crucial because patients with SCID often present with severe infections and no early physical signs. Treating newborns of at-risk populations requires increased communication between immunologists, midwives, and primary providers. Awareness of OS in at-risk communities often increases with new cases and should lead to additional education for all parties involved.

Genetic screening of high-risk families, particularly with multiple and complex layers of consanguinity or a family history of immunodeficiency, improves early detection and diagnosis. Health care providers should preemptively discuss genetic screening with high-risk families.

In patients with suspected immunodeficiency, treatment and management should be initiated while awaiting confirmation. Infection prevention through use of isolation precautions, IVIG, palivizumab during RSV season, and antibiotic prophylaxis is key. Of particular importance is avoidance of breastfeeding to minimize cytomegalovirus transmission. Live vaccines should be avoided in patients with suspected SCID. Early matched hematopoietic stem cell transplantation (HSCT) is potentially lifesaving, and therefore prompt hematology and/or oncology consultation is required. Patients should be monitored for infectious and autoimmune complications and provided psychosocial and nutritional support.^{1,5}

A multidisciplinary approach is required for successful OS management. The recognition that neonatal rashes are not always benign is imperative in addition to newborn screening and appropriate and timely intervention. Ultimately, allergists and/or immunologists should promote the maxim that OS is not just a rash diagnosis!

Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2020.04.019>.

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Supplementary Data

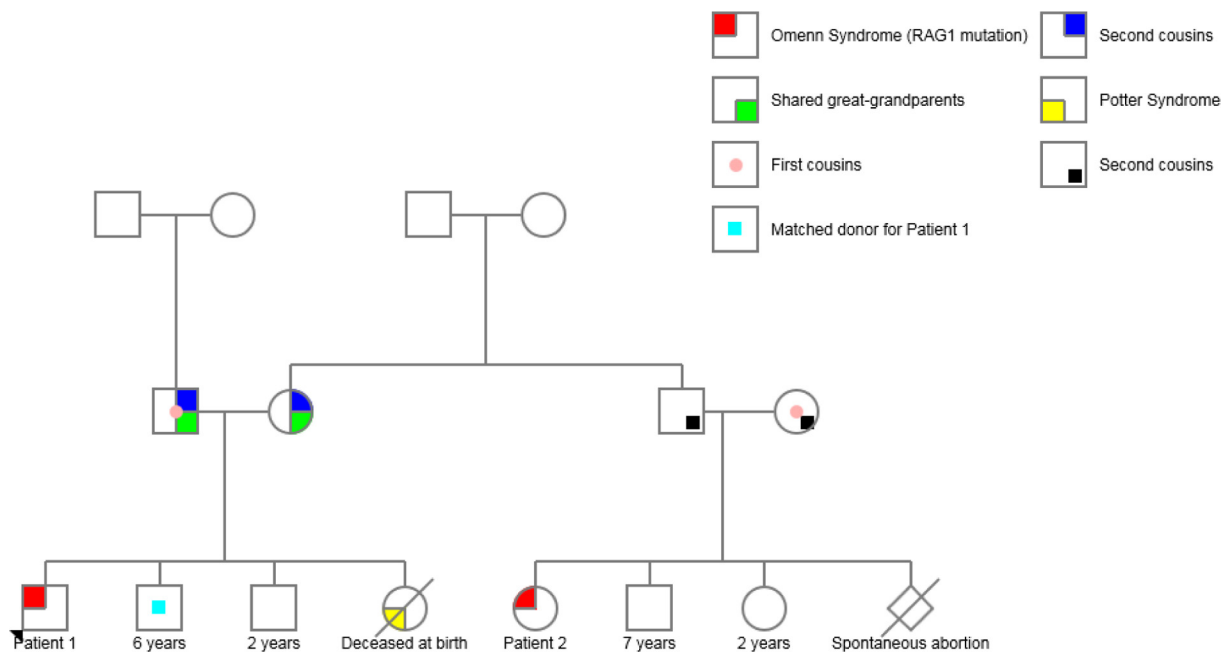
eTable 1

Laboratory Data

Laboratory results	Patient 1	Patient 2	Reference range
T cells			
CD3-Pan T (abs count)	337 cells/mm ³ L	671 cells/mm ³ L	2500-5500 cells/mm ³
CD4 Helper (abs count)	234 cells/mm ³ L	641 cells/mm ³ L	1600-4000 cells/mm ³
CD8 suppressor (abs count)	81 cells/mm ³ L	24 cells/mm ³ L	560-1700 cells/mm ³
B cells			
CD19 (abs count)	71 cells/mm ³ L	6 cells/mm ³ L	300-2000 cells/mm ³
NK cells			
CD16 + CD56 (abs count)	67 cells/mm ³ L	153 cells/mm ³ L	170-1100 cells/mm ³
CD4:CD8 ratio	2.87	26.53	
CD4: Naïve (RA)	0%	Not done	82-90
Memory (RO)	99.9%		8-19
CD8: Naïve (RA)	0.5%	Not done	71-100
Memory (RO)	98.6%		0-26
Lymphocyte mitogen proliferation responses (SI)¹			
PHA (phytohemagglutinin) 1:20	6 (1495)	36 (1396)	
PHA 1:50	3 (1540)	10 (762)	
Con A (concanavalin A) 1:40	2 (545)	8 (1164)	
Con A 1:200	3 (105)	5 (350)	
Pokeweed mitogen (PWM) 1:40	19 (1179)	7 (239)	
PWM 1:200	12 (934)	6 (270)	
IgE	4358 IU/mL H	1944 IU/mL H	0.04-1.28 IU/mL
IgG	568 mg/dL	723 mg/dL	636-1606 mg/dL
IgM	23 mg/dL	Less than 5 mg/dL L	6.3-25 mg/dL
IgA	9 mg/dL	Less than 5 mg/dL L	1.4-3.6 mg/dL
Eosinophils	10.5 K/uL H	2.70 K/uL H	Mean 0.5 K/uL (12 hours to 1week old)

Abbreviations: CD, cluster of differentiation; Con A, concanavalin A; Ig, immunoglobulin; NK, natural killer cells; PHA, phytohemagglutinin; SI, stimulation indices.

¹Values in table are the stimulation indices (SI) of patient with lab control SI in parenthesis.



eFigure 1. Pedigree for patients 1 and 2.