

Necrotizing enterocolitis in an infant with Omenn Syndrome

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ABSTRACT

Omenn syndrome (OS) is a rare disorder within the combined immunodeficiency family that is characterized by a diffuse exudative, erythematous rash, lymphadenopathy, hepatosplenomegaly, alopecia, and failure to thrive. Specific lab findings unique to OS include hypereosinophilia, elevated IgE, excess production of oligoclonal T-cells and near-to-absent B-cells. Much remains elucidated about the underlying genetic cause of OS. Until recently, it was felt that the disease was primarily caused by mutations of the RAG1 or RAG2 genes. The type of mutation of the RAG1 and RAG2 genes in patients with OS affects the degree of functioning variable (diversity) joining [V(D)J] recombination activity, which is critical to the development of lymphoid cell receptor diversity. New work has also shown that thymic tissue in OS patients demonstrates a severe defect in the expression of the autoimmune regulator element. This may contribute to the development of autoreactive T-cells that are felt to be the causative agent of a number of the clinical hallmarks unique to OS. The genetic spectrum of OS was further expanded when a patient with clinical and immunologic features consistent with OS, without RAG mutation, was found to have mutations in both alleles coding for ARTEMIS, a key V(D)J recombination/DNA repair factor. Regardless of the underlying cause, early recognition is critical because patients die at a very young age without bone marrow transplantation. We describe an infant diagnosed with OS post-mortem in which death was directly related to the development of necrotizing enterocolitis.

(Allergy Asthma Proc 27:537–543, 2006; doi: 10.2500/aap.2006.27.2893)

Omenn syndrome (OS) is a rare disorder within the combined immunodeficiency family that is characterized by a number of peculiar findings including a diffuse exudative, erythematous rash, lymphadenopathy, hepatosplenomegaly, alopecia, and failure to thrive. Specific laboratory findings unique to OS include hypereosinophilia, elevated IgE, excess production of oligoclonal T cells, and near-to-absent B cells. Much remains elucidated about the underlying genetic cause of OS. Until recently, it was felt that the disease was primarily caused by mutations of the recombinase activating gene (RAG) 1 or RAG2. The type of mutation of the RAG1 and/or RAG2 gene in patients with OS affects the degree of functioning variable (diversity) joining [V(D)J] recombination activity, which is critical to the development of lymphoid cell receptor diversity. The end result of poorly functional V(D)J recombination is the development of a severely restricted T-cell repertoire. New work also has shown that thymic tissue in patients with OS shows a severe defect in the expression of the autoimmune regulator element (AIRE). This defect contributes to the development of autoreactive T cells that are felt to be the causative agent of a number of the clinical

hallmarks unique to OS. The genetic spectrum of OS was expanded further when a recent case report of a patient with clinical and immunologic features consistent with OS, without mutation of RAG1 or RAG2, was found to have mutations in both alleles coding for ARTEMIS, a key V(D)J recombination/DNA repair factor. Regardless of the underlying cause, early recognition is critical because patients die at a very young age without bone marrow transplantation. We describe an infant diagnosed with OS post-mortem in which death was directly related to the development of necrotizing enterocolitis.

CASE PRESENTATION

This infant was born full-term to a 32-year-old G2P1001 mother with negative serologies. There was no consanguinity and both the family and the maternal history were unremarkable. The mother received regular prenatal care and both the pregnancy and the delivery were unremarkable.

In the regular newborn nursery, the baby was afebrile, vital signs were appropriate, and growth parameters were normal for gestational age. The baby appeared well overall and on exam was noted to have a diffuse, erythematous desquamating rash on the face, arms, legs, abdomen, axilla, and groin area along with scattered petechiae on the nose and ears. Like the mother, the infant's blood type was O⁺. A complete blood cell count at the time of birth was significant for a mildly elevated white blood count with a predominance of eosinophils (Table 1).

Approximately 30 hours of life, the infant developed increased work of breathing and was started on oxygen. A

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A PowerPoint presentation of this article was presented at the Illinois Society for Allergy, Asthma, and Immunology on February 4, 2005

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Table 1 Serial complete blood cell count

DOL#	1	3	6	7	10	14	16
WBC (kU/L)	35.2	15.6	16.1	19.2	18.7	16.8	9.3
Hb (gm/dL)	18.2	16.7	14.4	15.1	14.0	10.2	12.1
Hct (%)	54.6	49.9	41.9	44.1	40.8	29.5	34.5
Plt (kU/L)	212	224	164	170	166	75	69
Bands (% WBC)	0	1	6	4	5	7	30
Segs (% WBC)	62	36	8	10	14	10	3
Lymphs (% WBC)	5	11	21	19	43	42	49
Mono (% WBC)	9	13	11	9	9	15	8
Eo (% WBC)	21	39	46	39	27	21	4

Table 2 Serum IgG, IgM, IgA, and IgE levels

	Case report	Term (cord)	1 month
IgG (mg/dL)	300	1121 (636–1606)	503 (251–906)
IgM (mg/dL)	5	13 (6.3–25)	45 (20–87)
IgA (mg/dL)	7	2.3 (1.4–3.6)	13 (1.3–53)
IgE (IU/ml)	13	0.22 (0.04–1.28)	0.69 (0.08–6.12)

Bold numbers are abnormal findings in the case report. Numbers in parentheses are the 95% confidence intervals. From Refs. 65, 66, 67.

chest radiograph at the time was unremarkable, as were the results of a lumbar puncture. Blood and urine cultures were sent. On transfer to the neonatal intensive care unit, the infant was noted to have the rash as described, a positive Nikolsky sign, facial edema, a palpable axillary lymph node, and purulent drainage from the eyes, lips, and nares. Antibiotics were started for presumed staphylococcal scalded skin syndrome.

The following day, a basic metabolic panel, bilirubin panel, ammonia, lactic acid, disseminated intravascular coagulation, and coagulation studies were all found to be age appropriate. Direct fluorescent antibody of the skin lesions was found to be negative for varicella and herpes. Cultures of the facial drainage grew coagulase-negative *Staphylococcus* and group D enterococci. Blood for serum immunoglobulins was sent (Table 2) and an RAST for milk, soy, casein, a-lactalbumin, and b-lactoglobulin were all class 0. Additionally, it was discovered that the urine culture from 2nd day of life was positive for *Klebsiella pneumoniae*.

On the baby's 5th day of life, the stools were noted to be watery and one stool was positive for occult blood. HIV and hepatitis C tests were negative at the time. The baby also required occasional doses of i.v. bicarbonate for a persistent metabolic acidosis found on serial blood glasses. During the days to follow, the infant continued to have an elevated eosinophil count (Table 1). Vitamins A, D, E, and K were started because there was concern that the baby was suffering from a vitamin deficiency, specifically biotin. The genetic service was consulted and liver function

tests, serum amino acids, and urine organic acids were found to be within normal range. The state newborn screen was normal, as were chromosomes, including fluorescent *in situ* hybridization for 22q11. Because of the intermittent episodes of desaturations and lethargy, oxygen was started and a nasogastric tube was placed to assist with feedings.

On the 10th day of life, the erythematous desquamating rash from birth remained despite antibiotic coverage for presumed staphylococcal scalded skin syndrome, in addition to new eruptions of scattered erythematous papules and scalp alopecia. A skin biopsy (see Fig. 1) was performed at that time and showed the nonspecific finding of spongiotic dermatitis with few eosinophils. A hair study was performed and there was no evidence of trichorrhexis invaginata, making the diagnosis of Netherton syndrome less likely. Based on the results of the skin biopsy, in addition to the persistent erythematous desquamating rash, the diagnosis of congenital ichthyosis erythroderma was entertained. However, the infant was not found to have a mutation of the transglutaminase 1 gene, often seen in congenital ichthyosis.

At the end of the 2nd week of life, the infant was noted to have worsening edema that was felt to be the result of ongoing protein losses from persistent diarrhea and skin desquamation. An echocardiogram was performed, which was negative for any type of thrombotic or infiltrative process. The infant was given bronchodilators for wheezing and ultimately required mechanical ventilation due to worsening respiratory distress. A chest radiograph at the time of intubation was unremarkable but a tracheal aspirate grew out Gram-negative bacilli.

The next day the baby was found to have abdominal distension and worsening bilateral axillary lymphadenopathy on physical exam. An abdominal radiograph at that time showed extensive pneumatosis intestinalis and hepatobiliary air consistent with necrotizing enterocolitis. The baby was taken to the operating room where diffuse necrosis of the small intestine and air in the tissues and right colonic wall were discovered. The parents were informed of these findings and their implications for a dismal prognosis, and the decision was made to withdraw support.

After parental consent, an autopsy was performed and a number of interesting findings were discovered.

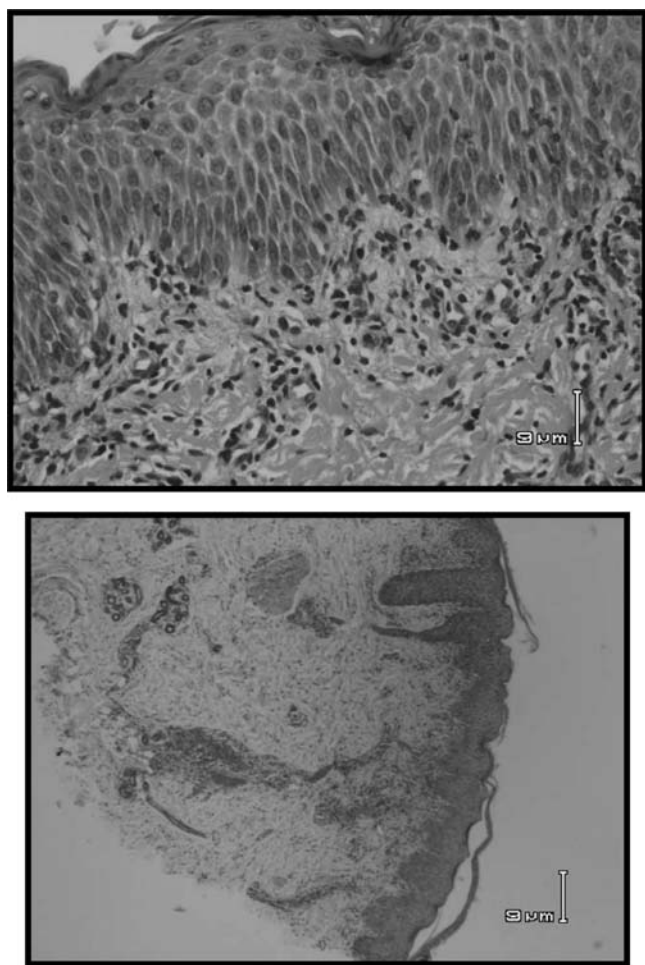


Figure 1. Skin Biopsy: Spongiotic Dermatitis with few eosinophils

Additional examination of the skin showed lichenoid interface dermatitis (a predominantly T-lymphocytic infiltrate) with basal layer vacuolar change, reduced granular layer, and scattered eosinophils. The lungs were found to have early focal bronchopneumonia with moderate-to-severe pulmonary congestion. The gastrointestinal tract showed extensive mucosal necrosis of the entire ileum and most of the jejunum, along with reduced numbers of Peyer's patches with lymphocytic depletion, and congestive hepatomegaly. Also found was splenomegaly with near absence of white pulp along with diffuse lymphadenopathy with near absence of B cells. The thymus showed hypoplasia with complete absence of Hassall's corpuscles. Most significant was the finding of a diffuse eosinophilic infiltrate (including mature and immature eosinophils) involving multiple organ systems including the skin, thymus, trachea, lungs, epicardial surface, lymph nodes, gastrointestinal tract, pancreas, and spleen thus causing a generalized organitis.

CASE DISCUSSION

The constellation of cutaneous, thymic, and hematolymphoid findings described in the aforementioned patient

are consistent with, though not in and of themselves, a diagnosis of OS. DNA analysis performed postmortem showed two mutations of the RAG1 genes, establishing the diagnosis of OS. Both parents were subsequently found to be carriers for a separate heterozygous mutation of the RAG1 gene.

OS, referred to as familial reticuloendotheliosis, was first reported by Gilbert Omenn in 1965. He described 12 infants in 6 sibships of an inbred Irish American family that all presented with severe skin eruptions, hepatosplenomegaly, generalized lymphadenopathy, hypogammaglobulinemia, and marked eosinophilia.¹ All cases eventually developed a febrile illness that progressed inexorably to a fatal outcome within 2–6 months of life.¹ Since this first report, and as of 2001, there have been ~70 cases reported in the literature.²

OS is an autosomal recessive form of severe combined immunodeficiency disease with a genetic defect mapped to chromosome 11 that often is associated with a number of specific physical exam and laboratory findings.³ Despite its rarity and peculiar findings, early recognition is critical as the majority of patients with OS die of overwhelming infections with severe metabolic disturbances within the first months of life.^{2,4}

In a recent review of the cases reported in the literature, the median age at clinical presentation was 2.5 weeks, with all cases presenting before the age of 20 weeks.² Based on this review, the clinical hallmarks of OS include an erythematous, exfoliative skin disorder, scalp alopecia, hepatosplenomegaly, and lymphadenopathy.² The majority of OS patients develop extensive diarrhea, hypoalbuminemia, failure to thrive, and overwhelming opportunistic infections.² This same review showed that more than one-half of affected infants develop an increased white blood cell count and one-quarter have an elevated lymphocyte count, thus differentiating it from most other forms of severe combined immunodeficiency (SCID).² The majority of patients with OS have markedly elevated eosinophil counts and IgE levels, making both hallmark findings of the disease.² The T cells in patients with OS have a very poor proliferative responses *in vitro*.^{5–7} *In vitro* activation leads to increased production of interleukins (IL) 4 and 5, while IL-2 and interferon (IFN) γ are hardly synthesized, thereby showing a T-helper 2 phenotype.^{7–9} The high levels of IL-5 is thought to contribute to the marked eosinophilia and the low levels of IFN- γ , which has been reported to normally inhibit IgE production, may explain the high levels of IgE.^{7,9} Another specific laboratory marker found in the majority of patients with OS is the near-to-absent B cells, along with hypogammaglobulinemia, despite elevated IgE.²

The key to making the diagnosis of OS, in addition to recognizing the clinical hallmarks as described previously, is to understand the complex immunology of the disease. Until recently, it was felt that the primary genetic defect leading to OS was due to mutations involving RAG1 and -2.^{3,10–12} These genes encode for two key lymphoid-specific proteins that are essential for the initiation of the V(D)J recombination process.^{3,13}

All of the immunoglobulin and T-cell suppressor (TCR) protein chains consist of two structural domains, the constant and the variable regions; the latter are responsible for the specific binding to antigen.¹⁴ V(D)J recombination is the process leading to the generation of variable domains through the assembly of one segment each from a set of variable (V), joining (J) and in some cases, diversity (D) subgenomic elements.^{14,15} Fully functional V(D)J recombination activity, central to the differentiation of B and T cells, allows for the development of an extensive degree of antigen receptor diversity, in turn giving the host the capacity to effectively defend against a wide array of foreign pathogens.¹⁶ Impairment in this process leads to both humoral and cellular immune deficits.^{17,18}

The RAG1/2 complex plays a critical role in the V(D)J rearrangement process by recognizing recombination signal sequences (RSSs) that flank all V, D, and J segments and causing a DNA double-strand break in these RSSs.^{19–24} Ultimately, through a complex process of “cut-and-paste” involving the RAG1/2 proteins and several other molecules that act in concert together, different combinations of V(D)J gene segments are brought together creating a diverse repertoire of antigen receptors.^{14,20,21}

Complete absence of the recombination activity of RAG1 and/or RAG2 proteins, because of null mutations, leads to an absence of antigen receptors and, ultimately, a T-/B-SCID.^{13,14,25} Patients with the clinical phenotype consistent with OS have been found to have mutations that lead to partial or impaired, but not eliminated, activity of the RAG1 and RAG2 proteins.^{2,3} This partial RAG activity, often referred to as “leaky mutations,” leads to a markedly decreased degree of V(D)J recombination, which does allow for T-cell receptor gene rearrangement to occur but with reduced efficiency.^{2,3,26} This limited T-cell receptor gene rearrangement contributes to the finding that the peripheral and thymic T cells in patients with OS are of oligoclonal origin with a highly restricted T-cell receptor repertoire.^{16,26,27} It remains unclear why partial V(D)J recombination activity in OS leads to strongly reduced numbers and functionally deficient B lymphocytes.^{2,13} It is felt that for yet unknown reasons, B-cell differentiation relies more strictly on intact V(D)J recombination machinery.

Recent work by Villa *et al.* analyzed the RAG mutations of 45 affected patients and concluded that the clinical and immunologic phenotypes of patients with RAG mutations are much more diverse than once thought and that the clinical and immunologic phenotype is determined in part by the specific type and site of RAG mutation.¹⁴ The nine patients that presented with classic T-/B-SCID did in fact carry null mutations caused by either nonsense or missense mutations that all resulted in a lack of RAG1 or RAG2 protein expression.¹⁴ The 17 patients considered to have a phenotype consistent with classic OS (erythroderma, lymphadenopathy, and hepatosplenomegaly) were all found to carry at least one missense mutation of either RAG1 or RAG2, with the majority having missense substitutions on both alleles.¹⁴ The group's work also discovered an intermediate class of patients with some T (and occasionally B) cells but without the frank stigmata of

OS.¹⁴ This group of 11 patients was referred to as having atypical SCID/OS.¹⁴ These atypical patients also carried missense mutations of RAG1 and/or RAG2 and, interestingly enough, this group of patients even shared some of the same mutations as those with a classic OS phenotype.¹⁴

Work by Corneo and colleagues recently reported on nine patients in which three of the patients' mutations should have, in theory, not been compatible with RAG activity and in turn should have led to a phenotype consistent with a complete T-/B-SCID.¹⁹ For unknown reasons, these patients instead presented with a phenotype consistent with OS.¹⁹ Additionally, other RAG mutations, specifically RAG2-R229Q, RAG1-ΔT631, and RAG1-R561H, have been reported in patients with T-/B-SCID and OS alike.^{3,19,25,26} The reason why residual V(D)J recombinase activity, in the context of mutated RAG proteins, does not always cause the classic OS phenotype has raised the possibility of additional factors, still to be determined, that are required for the development of classic OS.¹⁹ One hypothesis questions the possibility of a particular antigen, either a genetically encoded antigen or an environmental antigen, that when present in patients with OS but not in those with SCID, triggers surviving T cells to expand and autoactivate out in the periphery, especially within the gut and in the skin.^{9,14,19,26}

The patient described previously was found to be a compound heterozygote carrying two different mutations on both of her RAG1 alleles. She inherited the missense mutation R396c from her father and the C256 mutation from her mother. R396 is within the homeodomain of RAG1 and mutation of it reduces binding of the RAG protein to the RSS, while it has no effect on the RAG1/RAG2 interaction.^{3,14} Villa *et al.* described a family in which two siblings were homozygous for the R396c mutation of the RAG1 alleles in which one brother presented with classic OS and the other was classified as having atypical SCID/OS.¹⁴

Patients with a phenotype consistent with OS but without RAG mutations also have been reported and still no other genetic defects other than RAG mutations have been reported as the molecular cause of OS.² Ege *et al.* reported on such a case in which a 5-month-old male baby, free of RAG1 or RAG2 gene mutations, presented with failure to thrive, septicemia, lymphadenopathy, hepatosplenomegaly, erythrodermatitis, alopecia, numerous eosinophils, marked proliferation of histocompatibility antigen (HLA)-DR⁺ CD45R0⁺ T cells, and absent B cells.²⁸ Maternofetal transfusion was excluded and the patient's T-cell receptor repertoire was noted to be severely restricted despite normal V(D)J recombination coding joints.²⁸ Genetic, biochemical, and functional analyses pinpointed hypomorphic ARTEMIS mutations as the molecular cause of the patient's OS phenotype.²⁸

After recognition of the RSSs flanking the V, D, and J subgenomic elements, the RAG proteins introduce a nick in the DNA double strand between the coding V, (D), or J element and the heptamer of its flanking RSS.^{20,21,28–30} Once cut, the resulting 3'-OH DNA end attacks the opposite end, which leads to the formation of a coding end

hairpin at the ends of the V, (D), and J segments.²⁸ The corresponding coding end hairpins are reopened and joined by ubiquitously expressed factors of the nonhomologous end joining DNA repair pathway that works to ensue resolution of the RAG1/2-induced DNA, thus allowing for V(D)J recombination to continue.^{28,31} Recent work showed that lack of ARTEMIS in humans, a protein responsible for opening up such coding end hairpins, leads to the phenotype of T-/B-SCID.^{28,31–33} Fibroblasts and hematopoietic stem cells in bone marrow, deficient in ARTEMIS, have been shown to establish increased sensitivity to ionizing radiation and, therefore, the resulting SCID often is referred to as “radiosensitive SCID.”³⁴ The patient described by Ege and colleagues, while having clinical and laboratory findings consistent with OS without RAG mutations, was indeed found to have increased fibroblast irradiation sensitivity.²⁸ Further evaluation of the ARTEMIS gene showed mutations on both the maternal and the paternal alleles, which did not allow for hairpin opening activity *in vitro* and it was not functional with *in vivo* V(D)J recombination assay.²⁸ It is felt that the hypomorphic mutations of this important nonhomologous end joining factor was, indeed, the cause of the patient’s OS phenotype.²⁸

The limited T-cell receptor gene rearrangement caused by leaky RAG mutations contributes to the finding that T cells in patients with OS are of oligoclonal origin with a highly restricted T-cell receptor repertoire.^{9,16,26,27,35} The anomaly of a high number of T cells in a form of SCID can be explained in part by the oligoclonal nature of the T-cell repertoire because of continuous antigenic stimulation out in the periphery that in combination with intrathymic restriction, leads to poorly functional, autoreactive T lymphocytes.^{9,16,27} Negative selection of thymocytes is dependent on expression of trace amounts of tissue-specific antigens presented by medullary epithelial cells. AIRE is a transcriptional activator expressed by these medullary thymic epithelial cells that regulates the ectopic expression within the thymus of a set of tissue-specific proteins that are normally expressed in the periphery.^{11,36} This suggests that proper AIRE expression is critical to the development of central tolerance.^{11,36,37} Expression of AIRE within the thymus is dependent on normal T-cell development, normal thymic structure, and a well-organized corticomedullary structure, all of which are missing in OS.¹¹ Recently, a deficiency AIRE has been found in the thymi of two patients with OS.¹¹ It has been hypothesized that these cytotoxic, autoimmune clones, which may have escaped negative selection within the thymus, are directed against self-antigens and in turn precipitate the desquamating rash and gastrointestinal involvement seen in OS that so closely resembles graft vs. host disease (GVHD).^{11,38}

OS can be difficult to differentiate from maternal graft versus host disease because of significant overlap of both physical exam, histological, and laboratory findings.² Maternal GVHD, seen in up to 25–40% of infants with SCID, occurs when immunocompetent maternal T cells cross the placenta of an immunodeficient fetus, who is in turn unable to reject these foreign cells.³⁹ In maternal GVHD,

~40% of affected infants become symptomatic in which skin manifestations have been reported to occur in up to 40–83% of affected infants.^{6,7} As a result of infiltration of tissues by abnormal lymphocyte clones in OS, it has been considered to be an atypical variant of GVHD.^{35,41} A skin biopsy showing a psoriaform-lichenoid spongiotic pattern with dyskeratotic degeneration of epidermal cells reflecting the status of basal epidermal cells as the target for GVH effector cells¹⁰ is suggestive of SCID-associated maternal engraftment.^{41,42} In turn, skin biopsy specimens in patients with OS also show cellular dyskeratosis and a dense dermal and epidermal infiltration of histiocytes, T lymphocytes, and eosinophils, in addition to parakeratosis.^{10,38,43–45} In addition to the histological findings, the pathological findings in patients with OS are similar to those found in graft-versus-host disease.^{35,43} In OS, the thymus, lymph nodes, spleen, lamina propria, and Peyer patches of the intestinal mucosa are profoundly depleted of T cells.² Autopsy of patients with OS typically reveals thymic atrophy with absence of Hassall’s corpuscle.² Lymph nodes typically are enlarged with both histiocytes and eosinophils while organs are infiltrated by T-cells, histiocytes, and eosinophils leading to a generalized organitis.^{43,44,46} In OS, the degree of eosinophilia, erythroderma, lymphadenopathy, and hepatosplenomegaly are felt to be usually more pronounced.^{14,47} Villa *et al.* recently described seven patients with various degrees of mutated RAG proteins all with documented maternal–fetal T-cell engraftment.¹⁴ Although all seven patients had failure to thrive, the five patients that had higher proportions of circulating T cells more often manifested signs resembling OS (erythroderma, lymphadenopathy, and hepatosplenomegaly).¹⁴ The diagnosis of OS in the patient described was made based on finding RAG mutations known to cause classic OS. However, HLA typing or molecular analysis to evaluate for maternal T lymphocytes, which often is used to discriminate between maternal engraftment and classic OS, was not performed. Therefore, it is possible that the patient could have had RAG mutations with maternal GVHD that mimicked OS.

Despite intensive supportive care, 69% of patients with OS die within the 1st year.^{2,4} Corticosteroids, cyclosporine, and IFN- γ have shown transient symptomatic efficacy.^{1,35,48} Complete correction of both clinical and immunologic manifestations have been achieved by means of bone marrow transplantation, although fewer patients have survived than those transplanted for other types of SCID.^{4,10,49–54} Gomez *et al.* reported the results of nine patients with OS that received an allogeneic bone marrow transplantation between 1980 and 1989.⁴ Engraftment occurred in four of five recipients of HLA-identical marrow and in three of four recipients of HLA-haploidentical marrow.⁴ Of these seven patients that engrafted, five survivors had fully restored immune function.⁴ Another promising report described the results of hematopoietic stem cell transplantations performed on 11 patients with OS between 1991 and 2000. Of the 11 patients, 9 were noted to be alive with full immunoreconstitution at 2.5–12 years post-transplant.⁵⁵ The overall mortality in this recent group was

18.2%, much lower than the 46% previously reported in transplanted OS patients.^{2,55} The patient described in this case report would not have been a candidate for transplantation because of the rapid development of such extensive and ultimately fatal necrotizing enterocolitis.

In review of the literature, it is believed that this is the first reported case of an infant with OS who developed extensive pneumatosis intestinalis preceding her death. Pneumatosis intestinalis, a radiographic finding, is caused by cystic or linear collections of gas within the intestinal wall and is felt to be the result of gastrointestinal bacterial fermentation.⁵⁶ In neonates, the number one cause of such a finding is necrotizing enterocolitis, a syndrome of intestinal necrosis that like pneumatosis intestinalis, the etiology is unknown but is felt to be due to multiple factors in a susceptible host.^{57–59} Pneumatosis intestinalis is rare beyond the 1st year of life, with most cases being documented in immunosuppressed children.^{60,61} Recently, a small series of case reports revealed an overall incidence of 5% of benign courses of pneumatosis intestinalis in children with combined immunodeficiency states.⁶⁰ Unfortunately, our patient, despite having a combined immunodeficiency state, did not have a benign course of pneumatosis intestinalis and, in fact, it was the extensive degree of intestinal necrosis that contributed most to her death. Patients with OS should be considered at risk for the development of necrotizing enterocolitis because of their poorly functional T cells and lack of B cells, leading to impaired antibody response, both of which are known risk factors for necrotizing enterocolitis.^{2,62} The autoreactive T cells in OS are targeted to infiltrate specific organs, especially the skin and the gut, and constant activation at these sites leads to a GVHD-like reaction, which in this particular patient presented as necrotizing enterocolitis.¹⁹ Additionally, we also feel that the marked degree of intestinal eosinophilic infiltration seen on autopsy and also characteristic of OS, contributed to significant mucosal injury, which is considered to be the culminating factor in the development of necrotizing enterocolitis. *In vitro* studies have shown that eosinophilic granule constituents are toxic to a variety of tissues, including intestinal epithelium.⁶³ Taken together, it can be assumed that it was the infant's underlying disease process that caused her to develop intestinal necrosis, which ultimately led to her death.

REFERENCES

- Omenn G. Familial reticuloendotheliosis with eosinophilia. *New Engl J Med* 273:427–432, 1965.
- Aleman K, Noordzij J, De Groot R, et al. Reviewing Omenn syndrome. *Eur J Pediatr* 160:718–7253, 2001.
- Villa A, Santagata S, Bozzi F, et al. Partial V(D)J recombination activity leads to Omenn syndrome. *Cell* 93:885–896, 1998.
- Gomez L, Le Deist F, Blanche S, et al. Treatment of Omenn syndrome by bone marrow transplantation. *J Pediatr* 127:76–78, 1995.
- Businco L, Di Fazio A, Ziruolo M, et al. Clinical and immunological findings in four infants with Omenn's syndrome: A form of severe combined immunodeficiency with phenotypically normal T cells, elevated IgE, and eosinophilia. *Clin Immunol Immunopathol* 44:123–133, 1987.
- Brooks EG, Filipovich AH, Padgett JW, et al. T-cell receptor analysis in Omenn's syndrome: Evidence for defects in gene rearrangement and assembly. *Blood* 93:242–250, 1999.
- Melamed I, Cohen A, and Roifman CM. Expansion of CD3+CD4-CD8- T-cell population expressing high levels of IL-5 in Omenn's syndrome. *Clin Exp Immunol* 95:14–21, 1994.
- Appleton AL, Curtis A, Wilkes J, et al. Differentiation of maternal-fetal GVHD from Omenn's syndrome in pre-BMT patients with severe combined immunodeficiency. *Bone Marrow Transplant* 14:157–159, 1994.
- Rieux-Laucat F, Bahadoran P, Brousse N, et al. Highly restricted human T-cell repertoire in peripheral blood and tissue-infiltrating lymphocytes in Omenn's syndrome. *J Clin Invest* 102:312–321, 1998.
- Barth RF, Vergera GG, Khurana Sk, et al. Rapidly fatal familial histiocytosis associated with eosinophilia and primary immunological deficiency. *Lancet* 2:503–506, 1971.
- Cavadini P, Vermi W, Facchetti F, et al. AIRE deficiency in thymus of 2 patients with Omenn Syndrome. *J Clin Invest* 115:728–732, 2005.
- Wada T, Takei K, Kudo M, et al. Characterization of immune function and analysis of RAG gene mutations in Omenn syndrome and related disorders. *Clin Exp Immunol* 119:148–1555, 2000.
- Notarangelo L, Villa A, and Schwarz A. RAG and RAG defects. *Curr Opin Immunol* 11:435–442, 1999.
- Villa A, Sobacchi L, Notarangelo FB, et al. V(D)J recombination defects in lymphocytes due to RAG mutations: Severe immunodeficiency syndrome with a spectrum of clinical presentations. *Blood* 97:81–88, 2001.
- Tonegawa S. Somatic generation of antibody diversity. *Nature* 302:575–581, 1983.
- Santagata S, Villa A, Sobacchi C, et al. The genetic and biochemical basis of Omenn syndrome. *Immunol Rev* 178:64–7411, 2000.
- Pupo R, Tyring S, Raimer S, et al. Omenn's syndrome and related combined immunodeficiency syndromes: Diagnostic considerations in infants with persistent erythroderma and failure to thrive. *J Am Acad Dermatol* 25:442–44618, 1991.
- Ochs H, Starkey D, Mickelson E, et al. Combined immunodeficiency and reticuloendotheliosis with eosinophilia. *J Pediatr* 85:463–465, 1974.
- Corneo B, Moshous D, Gungor T, et al. Identical mutations in RAG1 or RAG2 genes leading to defective V(D)J recombinase activity can cause either T-B-severe combined immune deficiency or Omenn Syndrome. *Blood* 97:2772–2776, 2001.
- Shatz DG, Oettinger MA, and Baltimore D. The V(D)J recombination activating gene, RAG-1. *Cell* 59:1035, 1989.
- Oettinger MA, Shatz DG, Gorka C, et al. RAG-1 and RAG-2, adjacent genes that synergistically activate V(D)J recombination. *Science* 248:1517, 1990.
- McBlane JF, van Gent DC, Ramsden DA, et al. Cleavage at a V(D)J recombination signal requires only RAG1 and RAG2 proteins and occurs in two steps. *Cell* 85:107, 1995.
- van Gent DC, Ramsden DA, and Gellert M. The RAG1 and RAG2 proteins establish the 12/23 rule. *Nature* 380:85, 1996.
- Eastman QM, Leu TMJ, and Schatz DG. Initiation of V(D)J recombination in vitro obeying the 12/2 rule. *Nature* 380:85, 1996.
- Schwarz K, Gauss GH, Ludwig L, et al. RAG mutations in human B cell-negative SCID. *Science* 274:97–99, 1996.
- Signorini S, Imberti L, and Pirovano S. Intrathymic restriction and peripheral expansion of the T-cell repertoire in Omenn syndrome. *Blood* 94:3468–3478, 1999.
- Saint-Basile G, Le Deist F, Villartay JP, et al. Restricted heterogeneity of T lymphocytes in combined immunodeficiency with hypereosinophilia (Omenn's syndrome). *J Clin Invest* 87:1352–1359, 1991.

28. Ege M, Ma Y, Manfras B, et al. Omenn syndrome due to ARTEMIS mutations. *Blood* 105:4179–4186, 2005.
29. Fugmann SD, Lee AI, Shockett PE, et al. The RAG proteins and V(D)J recombination: Complexes, ends and transposition. *Ann Rev Immunol* 18:495–527, 2000.
30. Gellert M. V(D)J recombination: RAG proteins, repair factors, and regulation. *Annu Rev Biochem* 71:101–132, 2002.
31. Le Diest F, Poincignon C, Moshous D, et al. Artemis sheds new light on V(D)J recombination. *Immunol Rev* 200:142–155, 2004.
32. Ma Y, Pannicke U, Schwarz K, et al. DNA-dependent protein kinase complex in non-homologous end joining and V(D)J recombination. *Cell* 108:781–794, 2002.
33. Noordzij JG, Verkaik NS, van der Burg M, et al. Radiosensitive SCID patients with ARTEMIS gene mutations show a complete B-cell differentiation arrest at the pre-B-cell receptor checkpoint in bone marrow. *Blood* 101:1446–1452, 2003.
34. Moshous D, Callebaut I, de Chasseval R, et al. Artemis, a novel DNA double-strand break repair/V(D)J recombination protein, is mutated in human severe combined immunodeficiency. *Cell* 105:177–186, 2001.
35. Wirt DP, Brooks EG, Vaidya S, et al. Novel T-lymphocyte population in combined immunodeficiency with features of graft-versus-host disease. *New Engl J Med* 321:370–374, 1989.
36. Anderson MS, Venzani ES, Klein L, et al. Projection of an immunological self shadow within the thymus by the aire protein. *Science* 298:139–140, 2002.
37. Liston A, Lesage S, Wilson J, et al. Aire regulates negative selection of organ-specific T cells. *Nat Immunol* 4:350–354, 2003.
38. Nazzari G, Drago F, and Crovato F. Omenn's syndrome. *Int J Dermatol* 36:141–144, 1997.
39. Thompson LF, O'Connor RD, and Bastian JF. Phenotype and function of engrafted maternal T cells in patients with severe immunodeficiency. *J Immunol* 133:2513–2517, 1984.
40. Muller SM, Ege M, Pottharst A, et al. Transplacentally acquired maternal T lymphocytes in severe combined immunodeficiency: A study of 121 patients. *Blood* 98:1847–1851, 2001.
41. Denianke KS, Freiden IJ, Cowan MJ, et al. Severe combined immunodeficiency cutaneous manifestations of maternal engraftment in patients with severe combined immunodeficiency: A clinicopathologic study. *Bone Marrow Transplant* 28:227–233, 2001.
42. Appleton AL, and Sviland L. Current thought on the pathogenesis of graft-versus-host disease. *J Clin Pathol* 46:785–789, 1993.
43. Jouan H, Deist F, and Nezelof C. Omenn's syndrome—pathologic arguments in favor of a graft-versus pathogenesis: A case report. *Hum Pathol* 18:1101–1108, 1987.
44. Chilosi M, Facchetti F, Notarengelo LD, et al. CD30 cell expression and abnormal soluble CD30 serum accumulation in Omenn's syndrome: Evidence for a T helper 2-mediated condition. 26:329–334, 1996.
45. Wyss M, von Flidner V, Jacot-Des-Combes E, et al. A lymphoproliferative syndrome, "cutaneous dystrophy" and combined immune deficiency with lack of helper T-cell factor. *Clin Immunol Immunopathol* 23:34–49, 1992.
46. Martin JV, Willoughby PB, Giusti V, et al. The lymph node pathology of Omenn's syndrome. 19:1082–1087, 1995.
47. Hoeger P, and Harper J. Neonatal erythroderma: Differential diagnosis and management of the "red baby." *Arch Dis Child* 79:186–191, 1998.
48. Shandene L, Ferster A, Mascart-Lemone F, et al. T-helper type 2-like cells and therapeutic effects of interferon-gamma in combined immunodeficiency with hypereosinophilia (Omenn's syndrome). *Eur J Immunol* 23:56–60, 1993.
49. Shofer O, Blaha I, Mannhardt W, et al. Omenn phenotype with short-limbed dwarfism. *J Pediatr* 118:86–89, 1991.
50. Junker AK, Chan KW, and Massing BG. Clinical and immune recovery from Omenn syndrome after bone marrow transplantation. *J Pediatr* 114:496–500, 1988.
51. Bruckmann C, Lindner W, Roos R, et al. Severe pulmonary vascular occlusive disease following bone marrow transplantation in Omenn Syndrome. *J Pediatr* 150:242–245, 1991.
52. Heyderman RS, Morgan G, Levinsky RJ, et al. Successful bone marrow transplantation and treatment of BCG infection in two patients with severe combined immunodeficiency. *Eur J Pediatr* 150:477–480, 1991.
53. Fischer A, Landais P, Friedrich W, et al. European experience of bone marrow transplantation for severe combined immunodeficiency. *Lancet* 336:850–854, 1990.
54. Fischer A, Landais P, Friedrich W, et al. BMT in Europe for primary immunodeficiencies other than severe combined immunodeficiency: A report from the European Group for BMT and the European Group for Immunodeficiency. *Blood* 83:1149–1154, 1994.
55. Mazzolari E, Moshous D, Forino C, et al. Hematopoietic stem cell transplantation in Omenn syndrome: A single-center experience. *Bone Marrow Transplant* 36:107–114, 2005.
56. Feczko PJ, Mezwa DG, Farah MC, et al. Clinical significance of pneumatosis of the bowel wall. *Radiographics* 12:1069–1078, 1992.
57. Berdon WE, Grossman H, Baker DH, et al. Necrotizing enterocolitis in the premature infant. *Radiology* 83:879–887, 1964.
58. Heng Y, Schuffler M, Haggitt R, et al. Pneumatosis intestinalis: A review. *Am J Gastroenterol* 90:1747–1758, 1995.
59. Engel R, Virnig N, Hunt C, et al. Origin of mural gas in necrotizing enterocolitis. *Pediatr Res* 7:292, 1973.
60. Tang M, and Williams L. Pneumatosis intestinale in children with primary combined immunodeficiency. *J Pediatr* 132:546–549, 1998.
61. Kleinman P, Brill P, and Winchester P. Pneumatosis intestinalis. *Am J Dis Child* 134:1149–1151, 1980.
62. Neu J. Necrotizing enterocolitis: The search for a unifying pathogenic theory leading to prevention. *Pediatr Clin North Am* 43:409–432, 1996.
63. Gleich GJ, Frigas E, Leogering DA, et al. Cytotoxic properties of the eosinophil major basic protein. *J Immunol* 123:2925–2927, 1979.
64. Kjellman NM, Johansson SG, Roth A. Serum IgE levels in healthy children quantified by a sandwich technique (PRIST). *Clin Allergy* 6(1):51–59, 1976.
65. Joliff CR, Cost KM, Stivins PC. Reference intervals for serum IgG, IgM, C3 and C4 as determined by rate nephelometry. *Clin Chem* 28:126–128, 1982.
66. Zetterstrom O, Johansson SGO. IgE Concentrations measured by Phadebas IgE PRIST in serum of adults and patients with respiratory allergy. *Clin Allergy* 36:537–547, 1981. □