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Case Report

Fetal Sonographic Features in an Infant with Omenn Syndrome

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Abstract

Omenn syndrome is a rare autosomal recessive disorder which is classified as a type of severe combined immunodeficiency (SCID). The syndrome presents as erythroderma, eosinophilia, hepatosplenomegaly, and recurrent serious infections during the first year of life. The only known treatments are bone marrow or umbilical cord stem cell transplantation; if these treatments are not performed early, the syndrome is uniformly fatal. In this case, a premature infant later diagnosed with Omenn syndrome was found to have a constellation of findings on fetal sonogram including scalp edema, echogenic amniotic fluid, and sloughing of the abdominal skin. The differential diagnosis in this case included congenital ichthyosis as well as other forms of SCID. In cases without a known family history of Omenn syndrome, perhaps prenatal ultrasound findings such as those noted in this case may be used to predict a need for further testing for immune deficiencies, both in utero and during the perinatal period. An early diagnosis of Omenn syndrome will allow for the prevention and early treatment of infections as well as early curative treatments such as bone marrow transplantation which may reduce morbidity and mortality.

Key words: Omenn Syndrome, SCID, Fetal sonogram, Ultrasound

Case report

A 17-year-old gravida one, para zero white female was admitted for preterm labor at 31 weeks' gestation. Maternal history included treatment for Chlamydia early in the pregnancy with oral erythromycin. The mother reported smoking ½ pack of cigarettes per day but denied any history of illicit drug use. Maternal medications included prenatal vitamins and a ten-day course of macrodantin (100 mg twice per day) which was completed on the day of admission. The mother remained hospitalized for one week prior to delivery and received two doses of steroids to improve fetal lung maturity. A fetal sonogram performed five days prior to delivery showed pronounced scalp edema (Figure 1), echogenic amniotic fluid, and sloughing of the abdominal skin (Figure 2).

Spontaneous vaginal delivery of a 1,790 gram male infant (60th percentile) occurred at 32 weeks' gestation. Membranes ruptured spontaneously on the day of delivery with thick meconium staining noted. APGARs were seven at one and eight at five minutes respectively. No meconium was noted below the vocal cords on laryngoscopy. The infant was intubated in the delivery room for acute respiratory distress and was given positive pressure ventilation.

The infant's initial examination was remarkable for significant scalp edema with very thick, scaly, peeling skin and white deposits over the scalp. An area of cutis aplasia approximately three millimeters in diameter was noted on the left frontal region. The infant demonstrated generalized desquamation of thick, scaly, dry skin and a fixed flexed posture of the extremities with very pale fingertips and toes. The liver was palpable three centimeters below the right costal margin, and the spleen was palpable two centimeters below the left costal margin. No evidence of lymphadenopathy was noted. Hair was absent from the scalp and was scarce at the eyebrows and eyelashes.

Complete blood counts performed in the infant's first week of life showed white blood cell counts ranging from 20,800 to 37,900/mm^3, normal platelet counts, and eosinophils ranging from 35 to 68%. The eosinophilia persisted throughout his hospitalization. A lymphocyte subset analysis on the ninth day of life showed a total white blood cell count of 27,800/mm^3, absolute lymphocyte count of 5,838/mm^3, a CD4/CD8 ratio 4.0 (normal range 1.1 to 1.9), a natural killer lymphocyte count of 3,970/mm^3 (normal range 150-880/mm^3), and activated T-lymphocyte count of 992/mm^3 (normal range 30-480/mm^3). Percentages for differential lymphocytes were as follows: CD 19

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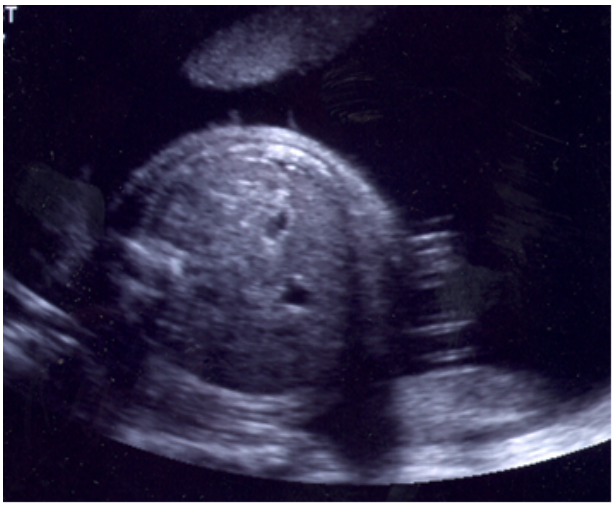

Figure 1: Edema and sloughing of abdominal skin

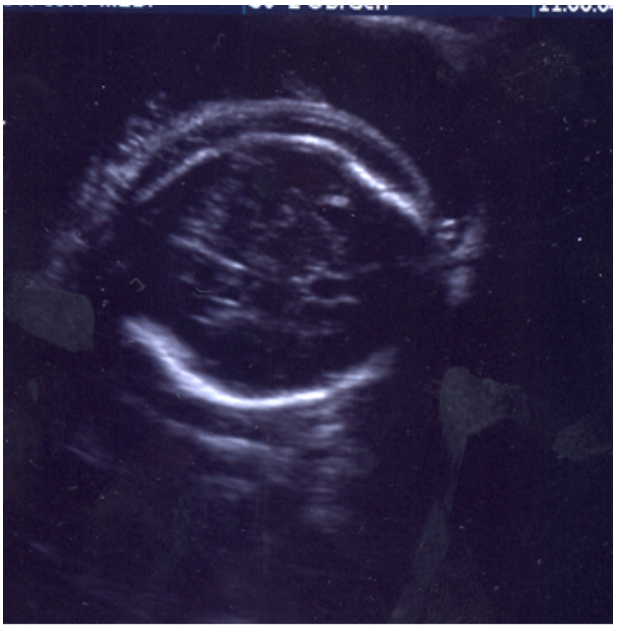

Figure 2: Scalp edema with sloughing of skin

PAN B 2% (normal 7-17%), CD3 PAN T 23% (normal 65-79%), CD4 helper 17% (normal 33-37%), CD8 suppressor 5% (normal 23-37%), natural killer cells 68% (normal 10-22%), and activated T-cells 17% (normal 7-15%). A diagnosis of Omenn syndrome was made based on the infant's phenotypic presentation of skin manifestations, hepatosplenomegaly, and alopecia as well as his laboratory findings of eosinophilia, decreased B-cells, and mildly elevated activated T-cells. In order to reduce the infant's risk for developing iatrogenic sepsis, appropriate gowning and gloving procedures were followed for all patient contact.

In addition to his immunodeficiency, the infant was also diagnosed with acute respiratory distress secondary to hyaline membrane disease. He initially required conventional mechanical ventilation and surfactant therapy; the ventilatory support was subsequently changed to high-frequency ventilation on his second day of life. The infant's hospital course was complicated by coagulase-negative *Staphylococcus* sepsis, cholestasis, and renal failure. He expired on his seventeenth day of life.

Discussion

Omenn syndrome, which was first described by Gilbert Omenn in 1965 [1], is classified as one type of severe combined immune deficiency (SCID) [2,3]. In all forms of SCID, the adaptive immune system is absent. The adaptive immune system is responsible for the formation of antigen-specific immune cell receptors [2]. More than eleven distinct phenotypes of SCID have been described; multiple causative gene mutations have been discovered, and the specific mutation determines which phenotypic presentation is seen [3]. In Omenn syndrome, the defect occurs in the T-cell receptor assembly and regulator genes known as recombinase-activating genes 1 and 2 (RAG1 and RAG2) which are located on chromosome 11. The RAG genes control V(D)J recombination which is necessary for both the development of immunoglobulins reactive to specific antigens and for the maturation of lymphocytes [2]. RAG1 and RAG2 mutations have been found to result in several phenotypes of SCID, including the Omenn syndrome phenotype [3]. Another hypothesized mutation in Omenn syndrome patients is reduced expression of the *AIRE* gene. This gene allows for the expression of self-antigens in the thymus and is required for T-cells to develop without autoreactivity [4].

The reported incidence of SCID is approximately 1 case per 100,000 live births; however, SCID is likely underreported as many patients die before the diagnosis is made [5]. Patients with Omenn syndrome present in the newborn or infant period with an erythematous desquamating rash, alopecia, hepatosplenomegaly, diarrhea, lymphadenopathy, failure to thrive, and recurrent infections. Laboratory findings include leukocytosis with eosinophilia and elevated levels of IgE with all other immunoglobulin isotypes absent [2,4].

Omenn syndrome may be difficult to differentiate from classical SCID. In classical SCID, both B-cells and T-cells are lacking, and no immunoglobulin synthesis occurs. Due to the lack of T-cell activation, findings such as desquamation and gastrointestinal losses are absent. In Omenn syndrome, B-cells are absent, but T-cells are found in large numbers due to a massive oligoclonal expansion; IgE is also usually elevated in the absence of other isotypes [2]. The poorly-regulated T-cells lack an ability to recognize self antigens; as a result, these T-cells enter the periphery and attack the tissues of the skin and gut to produce a clinical picture of autoimmune disease. The activated T-cells also produce increased amounts of the cytokines interleukin-4 and interleukin 5 [4]. Management of Omenn syndrome includes infection prevention and treatment as well as corticosteroids and other immunomodulators to suppress the autoimmune disease; the definitive treatment is hematopoietic stem cell transplant. Without early definitive treatment, most patients succumb to overwhelming opportunistic infections early in life [3].

A review of the literature about SCID treatment in May 2010 found three studies which showed that earlier treatment with hematopoietic stem cell transplant is associated with improved survival [5]. Therefore, the earliest possible diagnosis is necessary. Currently, no safe and accurate method of prenatal diagnosis for SCID exists. In 2004 Tabori, et al. demonstrated that prenatal diagnosis of

both classical SCID and Omenn syndrome can be accomplished in families with a known history of immunodeficiency via chorionic villus sampling and DNA analysis for RAG1/RAG2 mutations [6]. However, chorionic villus sampling is associated with a significant risk of fetal loss. Several methods for generalized newborn screening have also been attempted without consensus on a best method [5]. In one 2010 case report, Adeli, et al. recommended obtaining white blood cell counts on all newborns; a WBC count less than 2500 at this time would support a diagnosis of SCID. While this method of screening would allow for early detection for some forms of SCID, Omenn syndrome may be missed because the oligoclonal T-cell expansion results in elevated white blood cell counts rather than lymphopenia [7].

The phenotypic presentation of Omenn syndrome, including skin edema and desquamation, is similar to the phenotypic presentation of congenital ichthyosis. Congenital ichthyosis is a rare, likely autosomal recessive, disorder in which hyperkeratosis results in the entire body becoming encased in a rigid sheath of thick, armor-like skin. Recently, three-dimensional sonography has allowed for the diagnosis of congenital ichthyosis to be made without the performance of a fetal skin biopsy. Ultrasonographic findings include facial dysmorphism with abnormal ears and open mouth with large lips, thick skin, and decreased fetal movement, stiff limbs in a semiflexed position, limb anomalies, and echogenic amniotic fluid [8].

We hypothesize that because Omenn syndrome shares several phenotypic characteristics with congenital ichthyosis, prenatal ultrasound may be used to increase the index of suspicion for an Omenn syndrome diagnosis. In our case, prenatal ultrasound demonstrated pronounced scalp edema, echogenic amniotic fluid, and sloughing of the abdominal skin. These findings are consistent with the phenotypic abnormalities produced by the T-cell expansion seen in Omenn syndrome. Similar findings on prenatal ultrasound should raise suspicion for both congenital ichthyosis and Omenn syndrome and may allow for earlier immunologic testing to confirm the diagnosis.

Conclusion

Fetal sonographic features consistent with congenital ichthyosis may be seen with Omenn syndrome. With family history of Omenn syndrome or congenital icthyosis ultrasound findings may necessitate amniocentesis or additional work-up after birth for immune deficiency. An early diagnosis of Omenn syndrome will allow for the prevention and early treatment of infections as well as early bone marrow transplantation which may reduce morbidity and mortality.

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