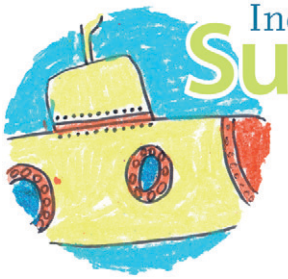

Index of Suspicion

1 Recurrent Omphalitis and Nonhealing Ulcers in a 7-month-old Girl

Shobhan Sivathanu, MD,* Sowmya Sampath, MD,* Indhumathi Sridhar, MD*

**ESIC Medical College and Post Graduate Institute of Medical Sciences and Research, Chennai, India*

PRESENTATION

A 7-month-old girl, who is the first child born to second-degree consanguineous parents, presents with a large, nonhealing ulcer (Fig 1) over the scalp of 3 weeks' duration. She has been having fever, vomiting, and loose stools for the past week. A review of the past medical history reveals 2 previous hospitalizations for the treatment of omphalitis: first as a neonate and the second time as a 2-month-old infant. The repeated episodes of omphalitis were attributed to a patent urachus (Fig 2) detected at that time. The infant had also developed skin lesions on 3 occasions between ages 2 and 5 months, diagnosed as atopic dermatitis, seborrheic dermatitis, and irritant contact dermatitis, at 3 different medical centers. She was also treated for acute suppurative otitis media at age 5 months.

On physical examination, the infant is febrile and pale. She weighs 5.7 kg (<3rd percentile), her length is 64 cm (between 3rd and 15th percentiles), and her head circumference is 45 cm (between 75th and 97th percentiles). She has a large ulcer in the left frontoparietal region (Fig 1) and an area of perianal ulceration with necrotic tissue. Also present are multiple scaly, hypopigmented skin lesions over the body, especially in the flexural areas. She has a small umbilical hernia with hepatosplenomegaly. There is no significant lymphadenopathy.

Preliminary laboratory evaluation reveals a white blood cell count of 71,000/μL (71 $\times$ 10^9/L) (79.4% neutrophils, 12.9% lymphocytes, 5.8% monocytes, 1.5% basophils, and 0.4% eosinophils), hemoglobin of 7.5 g/dL (75 g/L), and platelet count of 490 $\times$ 10^3/μL (490 $\times$ 10^9/L).

A detailed review of the patient's old records and the family history lead to the diagnosis.

DISCUSSION

A review of the previous laboratory reports revealed striking leukocytosis with polymorphonuclear preponderance (approximately 40,000/μL [40 $\times$ 10^9/L]) during the previous hospitalizations. There was absence of pus, and umbilical cultures grew unusual organisms such as *Citrobacter* and *Enterobacter* as well as *Staphylococcus aureus* during both hospitalizations for omphalitis.

Review of the family history showed that the infant's deceased stepsister also had multiple episodes of omphalitis. The mother had remarried her husband's younger brother after her first husband died in a road traffic crash. The setting of consanguinity with a sibling death due to a similar illness raised the possibility of

EDITOR'S NOTE

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AUTHOR DISCLOSURE Drs Sivathanu, Sampath, and Sridhar have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

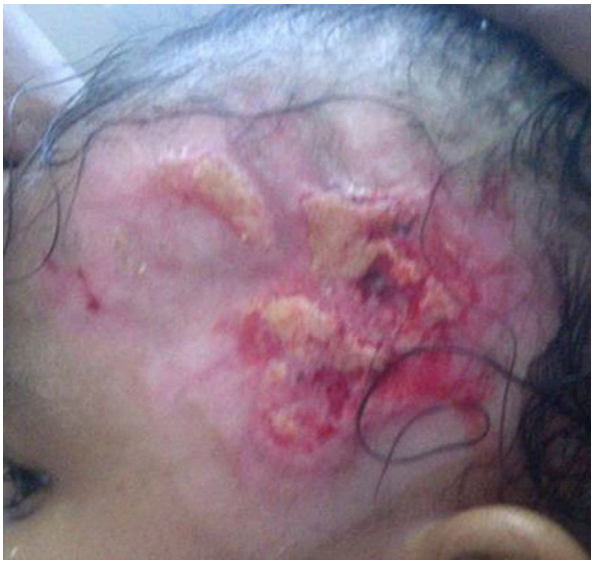

Figure 1. Nonhealing ulcer on the scalp.

a recessively inherited primary immunodeficiency disorder. The most probable diagnosis was leukocyte adhesion deficiency (LAD) because of the history of recurrent omphalitis caused by unusual organisms, absence of pus formation with infections, and high leukocyte counts. Flow cytometry confirmed the diagnosis of a severe form of LAD1 characterized by complete absence of CD11a, CD11b, and CD18 markers on leucocytes.

The Disorder

LAD is a rare (incidence of 1 in 1 million) autosomal recessive disorder of leukocyte function. Hallmark features are recurrent infections of skin and mucosal surfaces along with marked leukocytosis. The disease manifestations result from a defect in the inflammatory process, namely, the adhesion of leukocytes to the endothelium. Of the 3 types of LAD, LAD1 is the most severe and has the worst prognosis. It may present in the newborn period with delayed separation of the umbilical cord. Such delayed separation was not reported in this patient. Recurrent omphalitis with absence of pus formation is a clue to the diagnosis. Mutation in the *ITGB2* gene located on chromosome 21 that encodes for CD18, the β subunit of the integrin molecule, causes LAD1. Defects in CD18 expression result in either absence or very low surface membrane expression of CD11a and CD11b molecules. The defective CD18 expression on the leukocyte surface membrane causes a substantial defect in the adhesion of leukocytes to the endothelial cells and migration of neutrophils to the site of infection, thereby predisposing them to infection.

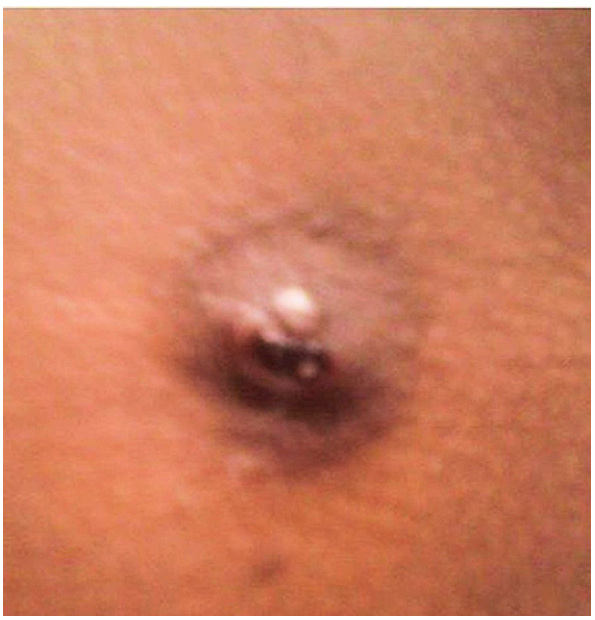

Figure 2. Omphalitis.

Diagnosis

The confirmatory test for LAD1 is a flow cytometry study demonstrating deficiency of CD11 and CD18 expression on leukocytes. The severity of infectious manifestations directly correlates with the degree of CD18 deficiency. Patients with moderate-to-mild CD18 deficiency (2.5%-10%) have fewer infections and are known to have long-term survival. Severe defects, as in the child reported, have less than 1% of the normal CD18 surface expression and are fatal without curative treatment.

Management

Treatment is targeted at preventing and treating infections in conjunction with supportive care. Most patients who have LAD succumb to the disorder because of delayed/missed diagnosis and infections by unusual organisms that are not identified and treated appropriately. The curative treatment for LAD is allogeneic hematopoietic stem cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched donor.

This patient required multiple courses of parenteral broad-spectrum antibiotics to treat infections. She also received irradiated leukocyte transfusions to combat infection and packed red blood cell transfusions to treat anemia. Because severe LAD1 is incompatible with survival beyond infancy, HSCT was planned. Fortunately, she had a sibling donor with a 10/10 HLA match and received HSCT.

At the time of this writing, the infant is 3 months post-transplant, doing well, and has just celebrated her first birthday. Although there are about 200 to 300 cases of LAD reported worldwide, stem cell transplant has been performed in fewer

than 50 cases, including the infant mentioned in this case. The reason for such a small number of successful HSCTs is delayed diagnosis, with infants succumbing to sepsis by the time the diagnosis is established.

Lessons for the Clinician

- Recurrent omphalitis caused by unusual organisms, absence of pus, and onset in the neonatal period should prompt clinicians to consider leukocyte adhesion deficiency (LAD).
- The diagnosis of an immunodeficiency such as LAD may be delayed due to recurrent indolent infections and presentation to different physicians at varying points in time, with each episode probably being treated in isolation. The whole picture frequently is missed. A timeline constructed from a meticulous record of events facilitates early diagnosis.
- Severe immunodeficiency disorders such as LAD can have good outcomes if diagnosed early and treated appropriately.

Suggested Readings for this article are at http://pedsinreview.aappublications.org/content/37/11/491.

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