Clinical allergy–immunology rounds
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An erythematous rash, diarrhea, failure to thrive, and lymphadenopathy in a 3-month-old girl

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CHIEF COMPLAINT

The patient is a 3½-month-old Caucasian girl with a history of an erythrodermic skin rash appearing shortly after birth. She was admitted with diarrhea, hypothermia, and adenopathy.

HISTORY OF PRESENT ILLNESS

The patient was a 3300 g product of a 37-week gestation. The pregnancy was complicated by pre-eclampsia. The newborn infant was noted to regurgitate much of her feeding. A barium swallow showed pyloric stenosis, pyloromyotomy was performed at 2 weeks of age and the problem resolved. At 3 weeks of age, she developed an erythematous, exfoliative rash that began on the cheeks and spread over the entire body. The rash would scale, flake, and sometimes weep a serous fluid, but there were no vesicles or bullae. Treatment with lubrication was ineffective.

The infant was noted to have poor weight gain and at age 2 months was admitted to another institution with fever and diarrhea. She was treated for a presumed skin super-infection with antibiotics. She was readmitted 1 week later with the same symptoms. Blood, urine, and cerebrospinal fluid cultures revealed no bacterial pathogens and she was discharged. At 3 months of age, she developed high spiking fevers and was admitted to our institution for further evaluation.

Past medical history was otherwise notable only for frequent diarrhea. She had achieved appropriate developmental milestones. The parents were nonconsanguineous and this was the first pregnancy. The mother received prenatal care, was rubella immune, and had a negative serologic test for syphilis. There was no family history of early infant deaths, skin diseases, atopic disorders, immune deficiency or collagen vascular disease. The patient was immunized only with one dose of hepatitis B vaccine.

PHYSICAL EXAMINATION

The infant was lethargic but arousable. Weight and length were less than the 5th percentile for age. Temperature was 34.7 °C rectally, pulse was 148 beats per minute, respirations were 46 per minute, and blood pressure was 90/55 mmHg. There were multiple patches of white exudate on the buccal mucosa and posterior pharynx consistent with thrush. There was generalized adenopathy in the cervical, supraclavicular, axillary, and inguinal regions with some lymph nodes as large as 2 cm in diameter. There was a diffuse exfoliative erythroderma accentuated on the extremities and total alopecia. Heart and lungs were normal. The liver was palpable 1.5 cm below the right costal margin; the spleen was not palpable. There was mild edema of the hands and feet. Genitalia were normal.

LABORATORY EVALUATION

Upon admission to the hospital, white blood cell count was 21,000/mm^3 with 19% bands, 53% neutrophils, 24% lymphocytes, 3% monocytes, and 1% eosinophils. Platelet count was 343,000/mm^3. Hematocrit was 35%. Uric acid was normal. Serum transaminases were elevated with aspartate aminotransferase 160 IU/L (0 to 35) and alanine aminotransferase 155 IU/L (0 to 31). Total and direct bilirubin were normal. Serum immunoglobulins were very low with IgG 36 mg/dL (165 to 780), IgA $<$7 mg/dL (4 to 80) and IgM 18 mg/dL (25 to 100). Total protein was 4.4 mg/dL (6.0 to 8.2) and albumin was 3.5 mg/dL (3.5 to 5.3). Urinalysis was normal. Cerebrospinal fluid was acellular with normal protein and glucose. Stool, blood, spinal fluid and urine were sent for bacterial, fungal, and viral cultures. Serum zinc level was normal. Serologic tests for human immunodeficiency virus, hepatitis B surface antigen, and syphilis were negative in both the child and her mother.

QUESTIONS

(1) Based on the initial history, physical examination, and screening laboratory results, what should you include in your differential diagnosis? (2) What etiologic factors should you consider?

DIFFERENTIAL DIAGNOSIS

The salient features of this infant's illness include an erythrodermic, exfoliative rash with alopecia, diarrhea, recurrent fevers, adenopathy, and failure

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to thrive in the setting of hypogammaglobulinemia. In constructing a differential diagnosis, primary skin disorders (some of which may be associated with the other symptoms noted in this case), systemic illnesses with prominent skin manifestations as well as primary and secondary immunodeficiency disorders should be considered. Various aspects of the clinical presentation may also be caused or modified by infection.

Primary Skin Disorders

The differential diagnosis of diffuse erythroderma (Fig 1) is presented in Table 1 and includes both illnesses with erythroderma as a primary component and those in which another skin disorder (eczema, seborrheic dermatitis) progresses to an erythroderma. Several of the more common skin disorders in infancy will be considered first. Rash, eosinophilia, adenopathy, and diarrhea could be consistent with a drug eruption, but the infant was not taking any medications at the time of onset. Atopic dermatitis usually occurs on the face and extensor surfaces in infancy, but can progress to a generalized erythroderma and increases susceptibility to staphylococcal superinfection. The diagnosis of atopic dermatitis, however, seems unlikely because this patient had no family history of atopy, the onset of skin rash at 3 weeks of age would be highly unusual (typical onset is after 6 to 8 weeks of age), the lesions did not have the papulovesicular quality of early lesions of atopic dermatitis, and, finally, many of the associated findings in this patient (eg, generalized lymphadenopathy and hypogammaglobulinemia) would be difficult to explain on the basis of primary atopic dermatitis.[1] The rash has some qualities of seborrheic dermatitis, but that rash occurs primarily on the scalp and intertriginous areas and it does not cause alopecia or the systemic symptoms observed in this infant.

Other rare, primary skin disorders may be considered. Non-bullous, congenital ichthyosiform erythroderma is an autosomal recessive exfoliative erythroderma which begins at birth.[2] This disorder does not usually include alopecia and does not cause systemic symptoms. Exfoliative erythroderma (erythrodermic psoriasis) presents with diffuse erythema and scaling that includes alopecia but is extremely rare in childhood.[3] In adults with this disorder, associated findings include adenopathy, hepatomegaly, peripheral edema, cardiomegaly, protein loss from the skin, eosinophilia, and polyclonal increases in immunoglobulins.[4] Lastly, Netherton's syndrome is an autosomal recessive disorder of skin cornification that leads to generalized erythroderma at birth and alopecia. It is sometimes associated with failure to thrive, lymphadenopathy, eosinophilia, and increased total IgE.[5,6] However, these patients have characteristic abnormal hair with nodular swelling of the hair shaft and some have hypergammaglobulinemia.

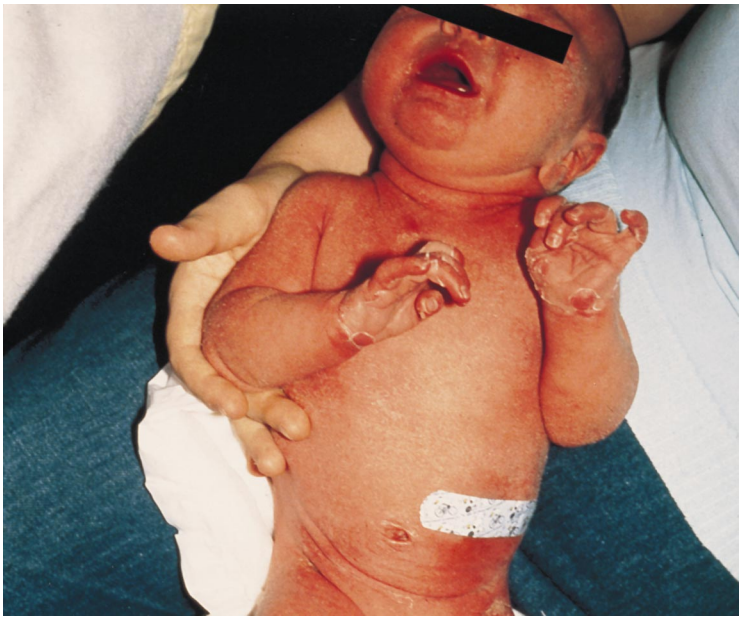

Figure 1. An example of an erythrodermic rash identical to that of the patient.

Dermatologic Manifestations of Systemic Illness

There are a number of systemic illnesses in which skin disease is prominent. Acrodermatitis enteropathica caused by nutritional zinc deficiency or an inherited disorder of zinc metabolism leads to a syndrome of failure to thrive, diarrhea, and alopecia. The skin rash occurs in a periorifacial, diaper and acral distribution and consists of psoriasiform plaques. The patient's normal serum zinc level rules out this syndrome. Lastly, Letterer-Siwe disease, an acute disseminated form of histiocytosis X that occurs in infancy, can result in hepatomegaly, lymphadenopathy, and increased susceptibility to infection. There may be an exfoliative erythroderma, but the skin is typically characterized by small papules on the trunk and scalp, unlike the rash observed in this patient.[7]

Dermatologic Manifestations of Infection

Manifestations of congenital syphilis include hepatomegaly, diffuse adenopathy, and a mucocutaneous rash presenting with erythematous maculopapular or bullous lesions, followed by desquamation. The diagnosis is unlikely in our patient because several other characteristic findings of congenital syphilis (condylomatous lesions and rhinitis) did not occur, there is no association of syphilis with hypogam-

Table 1. Differential Diagnosis of Erythroderma with References

Diagnosis	Associated Features
Drug eruption	Eosinophilia, adenopathy, fever (4)
Atopic dermatitis	Atopy, pruritus, facial/extensor surface involvement in infants, xerosis (1)
Seborrheic dermatitis	Scalp and intertriginous distribution (4)
Mycosis fungoides	Late involvement of lymph nodes, liver, spleen, usually in adults (4)
Non-bullous, congenital ichthyosiform erythroderma	Autosomal recessive, onset in infancy, occasional ectropion (2)
Erythrodermic psoriasis	Alopecia, scaly plaques, nail pitting, fever, arthralgia, myalgia (3,4)
Netherton's syndrome	Autosomal recessive, rash at birth, alopecia, characteristic hair, eosinophilia, adenopathy (5,6)
Letterer-Siwe disease	Adenopathy, bone lesions, hepatomegaly, papular skin lesions (7)
Immunodeficiency	Failure to thrive, chronic/recurrent infections (8)
Infection	Staphylococcal, may be secondary to many of the above disorders

maglobulinemia, and there was a negative test for syphilis in the mother.

Colonization or infection with toxin-producing strains of *Staphylococcus aureus* can cause a desquamating macular erythroderma, fever, diarrhea and multi-organ involvement. By itself, staphylococcal infection does not cause diffuse adenopathy or hypogammaglobulinemia and is thus unlikely to explain the complex combination of findings in this child.

Primary or Secondary Immune Diseases

Immunodeficiency should be considered in the setting of rash, diarrhea, and failure to thrive.[8] Secondary immune deficiency may be due to compromise of immune system components through loss or destruction. At 3 months of age, the patient may be expected to have a normal level of immunoglobulins acquired, in part, through placental transfer from the mother. A low level in this patient could be explained by protein loss through skin or gastrointestinal tract with or without failure of endogenous immunoglobulin production. In severe protein losing enteropathy, even lymphopenia can result.[9] These diagnoses are unlikely because they do not cause selective loss of immunoglobulin while sparing other serum proteins such as albumin, which was within the normal range.

Viral infections can also compromise the immune system. Congenital rubella can cause hypogammaglobulinemia,[10] but the rash is more typically petechial, and there often are associated features such as microcephaly and cataracts. Infection with human immunodeficiency virus must be considered as a cause of diffuse adenopathy and failure to thrive. HIV infection usually causes hypergammaglobulinemia, but severe hypogammaglobulinemia has been reported in a small number of cases.[11] This diagnosis is unlikely since the mother was seronegative and the baby had no other risk factors. Polymerase chain reaction tests in the baby could be used for a definitive diagnosis.

In considering primary immunodeficiency, the finding of hypogammaglobulinemia is a key feature prompting a consideration of common variable immunodeficiency. Most patients with this disorder have hypogammaglobulinemia with a normal or moderately decreased number of circulating B lymphocytes and normal cell-mediated immunity. There may be associated chronic inflammatory or autoimmune disorders leading to adenopathy, hepatosplenomegaly, dermatitis, and hepatitis. Presentation in infancy is unusual, however, and most patients develop the disorder after puberty.[12] Symptoms in X-linked agammaglobulinemia usually do not occur until after 6 months of age. These patients lack mature B cells due to an arrest in B cell development, and have resulting severe hypogammaglobulinemia.[13] They are particularly susceptible to enteroviral infections which can cause chronic dermatitis, hepatitis, and diarrhea.[14] Of course, since this is an X-linked disorder, it would be unlikely to occur in a girl unless she had Turner's syndrome (XO genotype), maternal isodysomy, or an XY genotype with androgen insensitivity. Furthermore, lymphadenopathy would be very unusual in such patients since the absence of B cells prevents the formation of germinal centers.

The clinical findings are most suggestive of severe combined immunodeficiency (SCID). This heterogeneous group of disorders is characterized by severe impairment of cell-mediated and humoral immunity. There are X-linked (due to a defect in the gamma chain of the IL-2 receptor)[15] and autosomal recessive forms of this disorder. The etiology of the recessive forms are numerous and include molecular defects in proteins responsible for T cell signal transduction and deficiencies of the purine pathway enzymes, adenosine deaminase, and purine nucleoside phosphorylase.[16] Early in infancy, patients with SCID develop infections caused by a wide variety of viruses, bacteria, and fungi. They may have rashes caused by staphylococci, fungi, and viruses such as coxsackie and varicella.[17] Eczematous, psoriasiform and sebhorreic rashes are also quite common, although the reasons are not understood. Graft versus host disease

may be a complication of severe combined immunodeficiency disease because maternal lymphocytes can be transferred to the fetus in utero or at the time of delivery.[18] Transfusions with unirradiated blood can also result in graft versus host disease, but this patient was never transfused. The rash of graft versus host disease may be morbilliform, exfoliative, lichenoid, or sclerodermoid. Associated findings may include diarrhea, adenopathy and hepatitis.

Two other combined immunodeficiencies are associated with rashes, though the rashes are not erythrodermas and thus do not explain this patient's illness. Wiskott-Aldrich syndrome is an X-linked disorder defined by the triad of eczema, combined T and B cell immunodeficiency, and thrombocytopenia with small platelets.[19] Hyper-IgE syndrome can present with recurrent staphylococcal infections (usually abscesses), a pruritic dermatitis, markedly elevated IgE, and normal levels of IgG with abnormal specific antibody responses.[20] Clearly, this patient does not exhibit the associated features of either of these diseases.

CLINICAL COURSE AND FURTHER EVALUATION

The patient was treated with intravenous immune globulin, broad spectrum antibiotics, and fluconazole. Staphylococcus aureus grew from a blood culture. Erythema of the skin faded with antibiotic therapy; however, she developed congestive heart failure, requiring ventilator and vasopressor support. Echocardiogram showed a dilated heart with ejection fraction of 19%.

Because of the hypogammaglobulinemia and possibility of severe combined immunodeficiency disease, further laboratory evaluation of the immune system was performed. Lymphocyte enumeration by flow cytometry showed normal numbers of CD4+ and CD8+ T cells and natural killer (CD56+) cells, but complete absence of CD19+ B cells. She had severely diminished in vitro proliferative responses to phytohemagglutinin, pokeweed mitogen, and concanavalin A. Lymph node biopsy (Fig 2) showed architectural effacement, proliferation of T cells and histiocytic cells, numerous eosinophils and absence of B lymphocytes. HLA typing of the patient showed no evidence of graft versus host disease caused by maternal engraftment.

The patient continued to deteriorate. Eye examination revealed retinitis, and cytomegalovirus was isolated from the urine. Despite treatment with gancyclovir and intensive care support, cardiac function declined and she died. Autopsy revealed viral inclusion bodies in the heart and liver and confirmed that she had normal female internal genitalia.

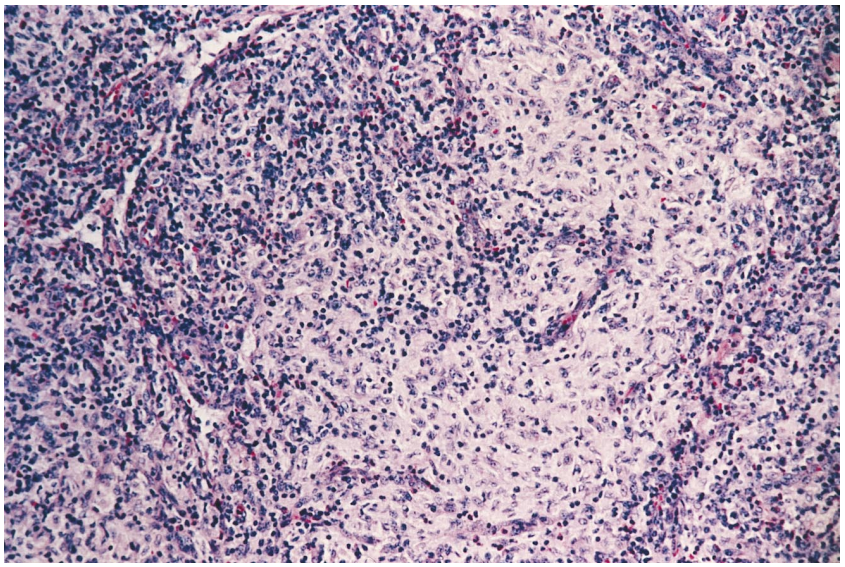

Figure 2. Lymph node biopsy (hematoxylin and eosin) showing architectural effacement, no germinal centers, and proliferation of histiocytoid cells and numerous eosinophils. Immunostain showed absence of B cells and a mixed population of T cells. (original magnification × 210).

QUESTIONS

(1) What is the most likely diagnosis? (2) What are the therapeutic options for such a patient? (3) What counseling advice can be given to the parents?

DISCUSSION

The additional findings of absent B cells and dysfunctional T cells confirms the suspicion of a primary immunodeficiency, specifically some form of a combined immunodeficiency syndrome. The finding of diffuse adenopathy, however, is distinctly unusual in this setting and prompted further investigation. The lymph node biopsy showing prominent proliferation of histiocytes and eosinophils without germinal centers is pathognomonic for Omenn's syndrome. In 1965, Omenn[21] reported a large family in which many individuals had a generalized exfoliative erythrodermic eruption in early infancy, alopecia, lymphadenopathy, hepatosplenomegaly, eosinophilia, and histiocytic infiltration of lymph nodes. Subsequently, it has been noted that these patients have an increased susceptibility to bacterial, fungal, and viral infections[22–27] and that the syndrome is transmitted as an autosomal recessive disorder.[21,22,24]

Immunologic defects in Omenn's syndrome are heterogeneous. Patients are not lymphopenic but usually have low or absent B cells with hypogammaglobulinemia,[22–27] and deficiency of cell mediated immunity.[25,26] Pathologic examination of lymphoid tissue shows obliteration of the normal architecture by cells that have the histochemical

characteristics of Langerhans' cells but do not contain their specific granules (Birbeck's granules). These cells also infiltrate the skin and liver.[23] Germinal centers are absent in lymph nodes; the thymus is hypoplastic and lacks Hassall's corpuscles.

The etiology of Omenn's syndrome is unknown, but recent studies show increased radiosensitivity of granulocyte-macrophage colony forming units in this syndrome, in patients with severe combined immunodeficiency without T and B cells, and in mice with severe combined immunodeficiency caused by a defect in DNA break repair function.[28] Patients with Omenn's syndrome also show a restricted T cell repertoire which suggests that this syndrome is a "leaky" form of a severe combined immunodeficiency disease.[28]

Omenn's syndrome is uniformly fatal without bone marrow transplantation.[21–26] There are three cases of bone marrow transplant all of which were successful with resolution of clinical symptoms and evidence of improved immune function 2 years after transplant.[29,30] Support with protective isolation from infection and prophylaxis with intravenous immune globulin should therefore be implemented until bone marrow transplantation can be performed. Since Ommen's syndrome is a genetically determined disorder inherited as an autosomal recessive trait,[21–26] the parents need to be counseled about the risk of recurrence, which is 25% for each pregnancy. There is no definitive prenatal diagnostic test.

CONCLUSION

The presentation of skin rash, diarrhea, and failure to thrive should prompt a thorough evaluation for immunodeficiency. Early diagnosis is important so that appropriate therapy can be instituted before there has been end organ damage. Furthermore, because some primary immunodeficiency diseases are inheritable, early diagnosis is essential for making genetic information available to the families of affected individuals.

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