Dr. Elizabeth A. Buzney (Dermatology): A newborn girl was transferred to this hospital because of a rash that had been present at birth. The infant, who weighed 3105 g, was born by spontaneous vaginal delivery at 40 weeks’ gestation to a healthy 27-year-old mother after an uncomplicated pregnancy. At birth, no meconium was present, and the Apgar score was 7 at 1 minute and 9 at 5 minutes. On examination, numerous skin lesions, described as pustules and scabs, were present on the face, trunk, arms, and legs. A Tzanck smear was reported to be positive for multinucleated giant cells. Lumbar puncture was attempted three times but was unsuccessful. Intravenous ampicillin, gentamicin, and acyclovir were administered, and the infant was transferred to this hospital and admitted to the Neonatal Intensive Care Unit 11 hours after birth.

The mother had had no exposures to infectious diseases, genital infections, or rashes during the pregnancy. Prenatal screening tests showed that her blood group was A, Rh-negative; tests for antibodies to rubella and herpes simplex virus (HSV) were positive, and tests for antibodies to syphilis and hepatitis B surface antigen were negative. A rectovaginal culture was positive for group B streptococcus. The mother had had varicella infection in childhood and had had genital ulcers. She took no medications and did not use illicit drugs, alcohol, or tobacco. The baby’s father was well, and there were no siblings. Spontaneous rupture of membranes occurred 2 hours before vaginal delivery, and antibiotics were administered intravenously during delivery.

On examination at this hospital, the temperature was 36.8°C, the pulse 135 beats per minute, the blood pressure 74/58 mm Hg, and oxygen saturation 99% while the infant was breathing ambient air; respirations were 56 breaths per minute. There were approximately 50 cutaneous erosions and papules, each 3 to 7 mm in diameter with a hard serosanguineous crust, as well as several with surrounding pink erythema, scattered over the scalp, face, trunk, arms, and legs (Fig. 1). There was no involvement of the groin area or the oral, conjunctival, or vaginal mucosae. No dysmorphic features were observed. The mucous membranes were pink and moist, and the palate was intact. The neck was supple. Auscultation of the heart and lungs disclosed no abnormalities. No enlarged lymph nodes were palpable in the cervical, axillary, or inguinal regions; however, there was a suggestion of hepatomegaly on examination.
of the abdomen. The genitalia appeared normal. Femoral pulses were present bilaterally. Results of the neurologic examination were normal.

Results of the laboratory tests are listed in Table 1. A chest radiograph was normal. Scrapings from several skin lesions were sent for bacterial staining and culture; no neutrophils or organisms were identified on the smears, and cultures were negative. Direct immunofluorescence assays for HSV and the varicella–zoster virus were negative, as were viral cultures, fungal staining, and fungal cultures. Cultures of rectal, conjunctival, and nasopharyngeal swab specimens were negative for HSV. Blood cultures, urine cytomegalovirus shell-vial culture, and rapid plasma reagin tests were negative. A lumbar puncture was performed. Examination of the cerebrospinal fluid specimen revealed no organisms (Table 1), and a Venereal Disease Research Laboratory (VDRL) test and testing for HSV amplification were negative. Magnetic resonance imaging (MRI) of the brain revealed a single punctate focus of restricted diffusion at the superior right forceps major, which was considered to be a nonspecific finding.

Abdominal ultrasonography showed borderline hepatomegaly without focal infiltration of the parenchyma. A diagnostic procedure was performed.

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**DIFFERENTIAL DIAGNOSIS**

**Dr. Matthew M. Avram:** I cared for this patient and am aware of the diagnosis. The primary lesions in this case are erosions, which are moist, depressed lesions that form after the rupture of a vesicle, vesiculopustule, or bulla. The eruptions in this case are consistent with those of vesiculobullous diseases of the newborn, which are common and range from innocuous to life-threatening conditions with both infectious and noninfectious causes (Table 2). Prompt and accurate diagnosis is essential, since there is a high potential for serious consequences and even death with misdiagnosis. It is therefore important to approach these cases in a systematic fashion. First, we need to determine whether this is a life-threatening infectious disease. The threshold for providing antibiotic coverage in a case such as this one should be low. If these diseases can be ruled out, a systematic examination for numerous other, less acute conditions can proceed.

**INFECTIOUS NEONATAL VESICULOPUSTULAR DERMATOSES**

The first consideration in this newborn is bacterial or nonbacterial sepsis.

**HSV**

Disseminated neonatal HSV infection was a primary concern in this patient; in the newborn, this infection can have devastating consequences if not detected and treated in a timely fashion. HSV infection can occur in utero by means of transplacental seeding or an ascending infection from the maternal genital tract. A history of recent HSV infection in the mother is helpful for this diagnosis, but there is often no such history.

Neonatal HSV infection can manifest in three forms: mucocutaneous infection, disseminated infection, and infection of the central nervous system. Lesions begin as solitary, grouped, or diffuse erythematous macules. Within 24 to 48 hours, they often develop into vesiculopustules, crusts, or erosions, similar to the lesions seen in this patient. Oral involvement is common. Skin lesions typically appear days after the onset of systemic manifestations including lethargy, fever, and poor muscle tone. There may also be jaundice, hepati-
cles, which may be sparse or numerous and be-
ules that develop into papules and “teardrop” vesi-
Cutaneous manifestations begin with pink mac-
may prolong the incubation period to 28 days.
administration of varicella–zoster immunoglobulin
after the maternal rash develops, although the ad-

Neonatal varicella infection may occur when the
mother has infection in the last 3 weeks of preg-

Varicella
Neonatal varicella infection may occur when the
mother has infection in the last 3 weeks of preg-

Cytomegalovirus
Cytomegalovirus is one of the most common in-
fections of the neonate, but only 5 to 10% of in-
ected neonates have symptoms.14 Vesicles are rare
and present only at birth. When vesicles are pres-
ent at birth, cytomegalovirus infection must be
considered. Viral cultures of blood and urine spec-
imens have the highest sensitivity when performed
within 1 week after infection. Another test with
high sensitivity in the neonate is the polymerase-
chain-reaction assay for cytomegalovirus DNA in
plasma samples. Urine culture for cytomegalovirus
in this case was negative.

Candida
Candida is the most common fungal infection of
the neonate. Congenital candidiasis usually mani-
fests on the first day of life as a result of exposure
in utero or during delivery. Risk factors include a
foreign body in the uterus (such as an intrauterine
device or a cervical suture), a maternal history of
vaginal candidiasis, and premature delivery, none
of which was present in this case.12 Most cases
are mild and confined to the skin and are charac-
terized by a generalized eruption of red macules,
pustules, vesicles, and vesiculopustules on the first
day of life.

The diagnosis can be made on the basis of
spores and pseudohyphae present in a potassium-
hydroxide preparation of skin scrapings; repeated
blood, cerebrospinal fluid, and urine cultures
should also be performed in cases of suspected
disseminated infection, because initial cultures are
often negative. This newborn was well and in no
apparent distress, and smears and cultures showed
no evidence of candidiasis.

Bacterial Infection
There are numerous bacterial infections in the
newborn that may manifest with cutaneous ero-
sions (Table 2). Symptoms of bacterial sepsis —
including lethargy, jaundice, purpura, fever, and
shock — are typical in such cases.

Group B streptococcus is the most common
cause of bacterial sepsis in the newborn. Skin findings include vesicles, bullae, crusts, and erosions, but most patients also have systemic manifestations, including bacteremia, meningitis, and pneumonia. Although the mother in this case had had a positive test for group B streptococcus, intrapartum antibiotics had been administered.

Impetigo neonatorum due to infection with Staphylococcus aureus (phage group II, type 55, with 71 subtypes) is characterized by large, flaccid bullae and moist, sometimes golden-crusted erosions from impetiginization. Typically, these eruptions are mild, but they may be severe and life-threatening, with osteomyelitis, pneumonia, and sepsis. In contrast to the timing in this case, bullae usually appear in the second week of life. Staphylococcal scalded skin syndrome begins with a scarlatiniform eruption that rapidly progresses to bullae and desquamation of large portions of skin, resembling toxic epidermolytic necrosis, with a characteristic golden crusting around the mouth and nose.

In this well-appearing infant, bacterial sepsis was unlikely, and appropriate bacterial cultures of specimens from the lesion, blood, urine, and cerebrospinal fluid were negative.

**Congenital Syphilis**

Congenital syphilis occurs in children of infected mothers by means of transplacental transmission. Roughly 40% of infected newborns have skin findings at delivery, including papulosquamous eruptions, condylomata lata, and desquamation; more rarely, there are vesicles and bullae, which are specific to the newborn. Hemorrhagic bullae on the palms and soles are skin findings closely associated with congenital syphilis. Serologic tests in the mother during pregnancy and in the neonate,

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**Table 1. Results of Laboratory Tests.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age-Adjusted Reference Range or Value</th>
<th>Value in Our Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>42.0–60.0</td>
<td>32.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.5–19.5</td>
<td>11.1</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>For birth to 24 hours of age, 9000–30,000 For 1–7 days of age, 9400–34,000</td>
<td>17,800</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>For birth to 24 hours of age, 66–87 For 1–7 days of age, 53–62</td>
<td>41</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>For birth to 24 hours of age, 22–37 For 1–7 days of age, 21–34</td>
<td>37</td>
</tr>
<tr>
<td>Atypical lymphocytes (%)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4–11</td>
<td>3</td>
</tr>
<tr>
<td>Band forms (%)</td>
<td>&lt;10</td>
<td>15</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>0–8</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count (per mm³)</td>
<td>150,000–450,000</td>
<td>180,000</td>
</tr>
<tr>
<td>Mean corpuscular volume (fl)</td>
<td>98–118</td>
<td>108</td>
</tr>
</tbody>
</table>

Coagulation test results

| Prothrombin time (sec)    | 10.1–15.4                            | 13.4                 |
| Partial-thromboplastin time (sec) | 25.3–48.3                    | 23.7                 |
| Sodium (mmol/liter)       | 135–145                              | 139                  |
| Potassium (mmol/liter)    | 4.0–5.6                              | 4.4                  |
| Chloride (mmol/liter)     | 98–106                               | 104                  |
| Carbon dioxide (mmol/liter) | 19.0–22.0                        | 20.6                 |
| Glucose (mg/dl)           | 60–100                               | 71                   |
| Total protein (g/dl)      | 6.0–8.3                              | 5.4                  |
as well as a VDRL test of a cerebrospinal fluid specimen, were negative; therefore, congenital syphilis was unlikely.

Although the likelihood of a serious bacterial infection or sepsis was low in this infant, it was imperative to treat her with antibiotics for bacterial and viral infections until they were conclusively ruled out. Ideally, cultures should have been performed before the broad antibiotic coverage with intravenous ampicillin, gentamicin, and acyclovir was begun.

We then investigated noninfectious causes of vesiculopustular eruptions.

### Noninfectious Conditions in the Neonate with Vesicles and Erosions

Several common, benign transient cutaneous eruptions in neonates could be considered in this case (Table 2). Erythema toxicum neonatorum, which is common in healthy infants during the first week of life, is characterized by erythematous macules, wheals, papules, and pustules that wax and wane, with new lesions persisting for several days. It usually begins on the face and migrates to the trunk, without involvement of the palms or soles. Transient neonatal pustular melanosis is characterized by superficial pustules with no erythema, as well as...
as hyperpigmented macules with or without scale. The pustules and macules can manifest anywhere on the skin, including the palms and soles. Acropustulosis of infancy consists of an extremely pruritic, vesiculopustular eruption on the hands and feet that is present at birth or within the first few weeks of life. In affected infants, it appears every 2 to 4 weeks, persisting for 5 to 10 days during each episode. It usually resolves in 1 to 2 years and is responsive to topical corticosteroids.

None of these benign transient dermatoses resembled the presentation of this newborn.

### Nontransient Bullous Dermatoses of the Neonate

Several inherited disorders can manifest with bullous dermatosis in neonates. Epidermolysis bullosa consists of a group of rare, inherited vesiculobullous disorders of varying clinical manifestations and severity; the subtypes are classified according to the depth of the blisters, the inheritance pattern, and the genetic defect. Most affected patients present at birth with vesicles, bullae, and denuded skin and mucous membranes. Incontinentia pigmenti is a very rare, X-linked dominant vesiculobullous disorder associated with mutations in the gene encoding the NEMO protein. Manifestation occurs at birth in about half of all cases, with linearly arranged vesicles following the lines of Blaschko. Epidermolytic hyperkeratosis is a very rare, autosomal dominant disorder caused by defects in the genes encoding keratins 1 and 10; it is characterized by the appearance of widespread bullae, erythroderma, and desquamation at birth. The hyper-IgE syndrome (Job’s syndrome) may be associated with solitary or numerous vesicles that are tense, with surrounding erythema on the head and shoulders. None of these disorders appeared likely in this patient with no family history of skin disorders.

Two autoimmune diseases of the mother can affect neonates. Herpes gestationis is an autoimmune disorder that most commonly manifests in the mother in the second trimester of pregnancy and can produce blistering in the infant. In pemphigus vulgaris, maternal autoantibodies can be passed transplacentally to the newborn. This mother had no history of either of these disorders.

### Langerhans’-Cell Histiocytosis

Congenital Langerhans’-cell histiocytosis is a clonal proliferative disorder of Langerhans’ cells, which are antigen-presenting cells derived from bone marrow. The disease may be manifested as single-organ—system or multiorgan-system involvement at birth. The disorder known as Hashimoto–Pritzker’s disease, or congenital self-healing reticulohistiocytosis, is now thought to represent one end of the spectrum of single-organ—system Langerhans’-cell histiocytosis, with a high likelihood of complete, spontaneous resolution. Skin lesions in neonatal Langerhans’-cell histiocytosis may include solitary or multiple vesicles, bullae, erosions, papules, nodules, crusts, petechiae, milia, and atrophy. The erosions, like the

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**Table 2. Differential Diagnosis of Cutaneous Vesicles, Bullae, and Erosions in the Neonate.**

<table>
<thead>
<tr>
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<td>Transient neonatal pustular melanosis</td>
<td>Incontinentia pigmenti</td>
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<td>Cytomegalovirus</td>
<td>Milia</td>
<td>Epidermolytic hyperkeratosis</td>
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<tr>
<td>Candida infection</td>
<td>Neonatal acne</td>
<td>Hyper-IgE syndrome</td>
</tr>
<tr>
<td>Scabies</td>
<td>Eosinophilic pustular folliculitis</td>
<td>Herpes gestationis</td>
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<tr>
<td>Aspergilus infection</td>
<td>Acropustulosis of infancy</td>
<td>Pemphigus vulgaris</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>Sucking blister</td>
<td>Langerhans’-cell histiocytosis</td>
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<tr>
<td></td>
<td>Trauma</td>
<td>Mastocytosis</td>
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lesions in this patient, tend to have more poorly defined borders than those of neonatal herpes lesions. Rapid diagnosis of Langerhans’-cell histiocytosis can be made with the use of a Tzanck preparation, which in positive cases shows cells with characteristic reniform nuclei and abundant cytoplasm. However, this appearance may be confused with the multinucleated giant cells of herpesvirus infections, as occurred in this case. Skin biopsy is required for a definitive diagnosis.

In summary, the morphologic characteristics of the skin lesions in this newborn are consistent with either neonatal HSV infection or neonatal Langerhans’-cell histiocytosis. Since an extensive evaluation failed to disclose evidence of infection, and since she remained clinically well, I felt that single-organ–system Langerhans’-cell histiocytosis was the most likely diagnosis in this case. The diagnostic procedure was a biopsy of a lesion on the flank, with care taken to include both normal and lesional skin in the specimen.

**DR. MATHEW M. AVRAM’S DIAGNOSIS**

Langerhans’-cell histiocytosis.

**PATHOLOGICAL DISCUSSION**

*Dr. Alireza Sepehr:* There was epidermal ulceration and crust formation (Fig. 2A) and an infiltrate of medium-sized to large mononuclear cells with indented or grooved nuclei, typical of Langerhans’ cells (Fig. 2B). Clusters of these cells were present in the papillae and scattered in the upper dermis. Eosinophils were also present. Immunohistochemical analysis showed that the cells were positive for CD1a (Fig. 2C) and S-100 protein (Fig. 2D), both characteristic of Langerhans’ cells. The histologic differential diagnosis of Langerhans’-cell histiocytosis may include dendritic-cell sarcoma (indeterminate-cell histiocytosis), xanthogranuloma, xanthoma disseminatum, benign cephalic histiocytosis, and occasionally mycosis fungoides (in cases of mycosis fungoides with numerous eosinophils and histiocytes; these cells are always present in Langerhans’-cell histiocytosis). Recognition of the characteristic morphologic features of Langerhans’ cells and, most important, positive staining for CD1a are essential for establishing the diagnosis of Langerhans’-cell histiocytosis. The diagnosis in this case is cutaneous Langerhans’-cell histiocytosis.

There are no histologic or immunophenotypic features that permit distinction between the two clinical forms of Langerhans’-cell histiocytosis involving the skin.\(^{17-23}\) Thus, the differential diagnosis in this case still includes both single-organ–system cutaneous Langerhans’-cell histiocytosis, also known as cutaneous self-healing Langerhans’-cell histiocytosis, and multisystem Langerhans’-cell histiocytosis, also known as Letterer–Siwe disease.

**DISCUSSION OF MANAGEMENT**

*Dr. Verena Gobel:* The prognosis and treatment of a patient such as ours with cutaneous Langerhans’-cell histiocytosis vary markedly depending on whether the disease is confined to the skin or involves other organs. The prognosis of truly isolated cutaneous single-organ–system Langerhans’-cell histiocytosis is excellent, and observation without treatment is justified. However, multiorgan-system Langerhans’-cell histiocytosis, particularly in neonates, with involvement of the liver, spleen, lung, the hematopoietic system, or a combination of these is a potentially fatal disease. In addition, congenital cutaneous single-organ–system Langerhans’-cell histiocytosis not infrequently evolves into multiorgan-system Langerhans’-cell histiocytosis.\(^{24}\) If this patient had evidence of multiorgan-system disease, current therapy would be combined treatment with prednisone and vinblastine, with or without methotrexate, for 6 months to 1 year. Unfortunately, neonatal multiorgan-system Langerhans’-cell histiocytosis is particularly poorly amenable to treatment. In a 2005 European retrospective analysis,\(^{25}\) the 5-year survival rate of neonates with single-organ–system Langerhans’-cell histiocytosis (most of whom did not receive treatment) was 94%, whereas that of neonates with multiorgan-system Langerhans’-cell histiocytosis (all of whom were treated) was only 57%.

For this reason, after the diagnosis of Langerhans’-cell histiocytosis was made, on the basis of the biopsy in this case, evaluation for the presence of disease in locations other than the skin was initiated. A skeletal survey was negative. CT and MRJ of the abdomen confirmed that the size of the liver was at the upper limit of normal and that there was no splenomegaly or intrasplenic lesions. The initial anemia, which resolved, was not pronounced enough to suggest involvement of the hematopoietic system. There was no evidence of...
lung involvement. Thus, the disease appeared to be confined to the skin, and the diagnosis was cutaneous single-organ–system Langerhans’-cell histiocytosis.

All of the skin lesions had spontaneously resolved by 1 month of age. The very rapid spontaneous regression suggested a favorable outcome; the median time to regression in retrospective studies\(^\text{25}\) of only small numbers of patients is about 4 months. However, relapse with subsequent dissemination to multiorgan-system Langerhans’-cell histiocytosis has been described.\(^\text{24,26}\) In addition, isolated lesions of the pituitary, including diabetes insipidus — a classic manifestation of Langerhans’-cell histiocytosis — and other neurodegenerative lesions have been detected in such patients many years after the initial diagnosis.\(^\text{24–26}\)

We elected not to treat this infant, but because of the risks of development of multiorgan-system Langerhans’-cell histiocytosis in infancy and later complications, we followed her closely during the first year of life and will continue long-term follow-up at longer intervals. At 1 year of age, she is thriving and has no evidence of either cutaneous or systemic disease.

**ANATOMICAL DIAGNOSIS**

Cutaneous Langerhans’-cell histiocytosis, with single-organ–system involvement.

No potential conflict of interest relevant to this article was reported.

We thank Dr. Martin C. Mihm, Jr., for his supervision of Dr. Sepehr’s preparation of the Pathological Discussion section.
REFERENCES