A 7-week-old male Caucasian infant presented to a local emergency room on August 19, 1999, with a 1-week history of worsening cough and congestion. His birth was at term by spontaneous vaginal delivery without complications. His only immunizations were one dose each of hepatitis B and Hemophilus influenzae type b vaccines.

In the emergency room he was afibrile but was wheezing with retractions and paroxysmal cough. Respiratory rate was 60 breaths/min, and the initial oxygen saturation on room air was 94%. Because of respiratory distress, the infant was admitted. The initial workup revealed a white blood cell count of \(65.1 \times 10^9/\text{mm}^3\) with a differential count of 20% neutrophils, 4% band forms, 67% lymphocytes, 7% monocytes and 2% eosinophils. Bilateral lower lobe infiltrates were present on chest radiograph. Nasopharyngeal culture and direct fluorescent antibody test (DFA) for Bordetella pertussis were obtained. The infant was treated with ceftriaxone for pneumonia and erythromycin for possible pertussis.

During the first night of hospitalization the child’s clinical status deteriorated. He became intermittently dusky with coughing episodes, and oxygen desaturations dropped as low as 80%, despite supplemental oxygen support. A dose of nebulized racemic epinephrine was given, followed by continuous nebulized albuterol therapy.

Because of progressive respiratory distress, the patient was transferred to the Intensive Care Unit of Children’s Hospital Oakland where he was placed in an isolation room with droplet precautions. Treatment with cefotaxime and erythromycin was continued. Nasopharyngeal culture and DFA for B. pertussis were negative. However, because of the consistent clinical presentation and marked lymphocytosis, pertussis was considered the likely diagnosis. Therefore cefotaxime was stopped after 5 days, and erythromycin alone was continued for a total of 14 days (including 12 days of oral erythromycin ethylsuccinate and 2 days of intravenous erythromycin lactobionate; the latter given because of emesis). All household contacts were provided prescriptions for 14 days of erythromycin therapy, although compliance could not be confirmed. Because the patient’s father had rhinorrhea and cough, he was required to wear a mask during hospital visits.

After 5 days of erythromycin treatment, the patient was removed from isolation per infection control protocol. He had gradual clinical improvement, although paroxysmal coughing persisted. By Hospital Day 6 the patient’s condition was stable, and he was transferred to the general pediatrics ward. By Hospital Day 13 supplemental oxygen was no longer required.

Beginning on Hospital Day 14 the infant became increasingly tachypneic and had blood oxygen desaturations associated with coughing paroxysms. Despite administration of supplemental oxygen and increased frequency of nebulized albuterol, these episodes worsened markedly on Hospital Day 22, necessitating transfer back to the intensive care unit. At that time the infant’s white blood cell count was \(28.3 \times 10^9/\text{mm}^3\) with a differential count of 23% neutrophils, 11% band forms, 47% lymphocytes, 12% monocytes, 1% basophils, 5% atypical lymphocytes and 1% metamyelocytes. A chest radiograph revealed generalized hyperinflation with atelectasis and infiltrates in the right and left upper lobes. Nasopharyngeal specimens tested by enzyme immunoassay for respiratory syncytial virus as well as by DFA for parainfluenza, adenovirus and B. pertussis were negative. Sweat chloride test was normal, and an HIV antibody test was negative. T and B-cell quantitation, CH50, quantitative immunoglobulins and IgG subclasses were also normal. Another study subsequently revealed the cause of the infant’s clinical deterioration.

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For denouement see p. 492.

**Brief Reports**

**TUBERCULOSIS-ASSOCIATED HEMOPHAGOCYTIC SYNDROME IN AN INFANT**

Infection-associated hemophagocytic syndrome (IAHS) is a disease in which there is proliferation of systemic phagocytes that can lead to a rapidly fatal clinical course. Patients usually present with fever, hepatosplenomegaly, jaundice, lymphadenopathy and edema. Laboratory abnormalities include cytopenias in at least two cell lines, hypertriglyceridemia, hyperferritinemia, hypofibrinogenemia, cerebrospinal fluid pleocytosis, elevated serum liver enzyme concentrations and low or absent natural killer (NK) cell activity. This disease frequently occurs within the setting of immunodeficiency. 1-8

Diagnosis of IAHS is usually made by a bone marrow aspiration that demonstrates many histiocytes with intracytoplasmic erythrocytes and platelets. In published pediatric cases of IAHS a triggering organism was identified in 163 of 219 patients, with Epstein-Barr virus accounting for 121.9 Other associated infections include cytomegalovirus, adenovirus, human herpesvirus 6, systemic leishmaniasis, malaria and fungal infections. Tuberculosis associated with this entity in childhood has been reported only once. 10 We report the case of a young infant who rapidly succumbed to hemophagocytic syndrome in the setting of undiagnosed pulmonary tuberculosis, and we highlight this relationship. There are no previous reports of tuberculosis-associated IAHS in infants.

**Case report.** A 7-week-old Hispanic girl was admitted to Children’s Memorial Hospital in Chicago with a 2-week history of irritability, abdominal distention, fever and diarrhea. She was the full term product of a reportedly uncomplicated pregnancy, and her mother was negative for hepatitis B and HIV infection (by prenatal screening). The mother reported that she was in good health and that there were no infectious disease exposures. On physical examination the baby was jaundiced and had massive hepatosplenomegaly. She had shallow respirations with subcostal retractions and was tachypneic, although her lungs were clear to auscultation. She was hypoxic (88% by pulse oximetry) in room air.

Chest radiograph demonstrated bilateral diffuse reticulomodular opacities. Examination of a complete blood count showed anemia (7.5 g/dl), mild thrombocytopenia (125 000/μl)
and leukocytosis (24.5 × 10^9/µl) with 25% neutrophils with 40% band forms. She was hyponatremic (127 mEq/l), acidotic (CO2 = 17.8 mEq/l), hypoalbuminemic (2.2g/dl), hyperbilirubinemic (5.3 mg/dl total and 3.9 mg/dl direct), hypertriglycerideremic (171 mg/dl) and hypercholesterolemic (264 mg/dl). Alanine aminotransferase was normal at 31 IU/ml, and aspartate aminotransferase was mildly elevated at 74 IU/ml. Glutamyltransferase (666 IU/l) and ferritin (2160 ng/ml) were very elevated.

The patient was treated with humidified oxygen, and a full sepsis workup was performed, including bacterial, viral and treponemal studies of blood, urine and cerebrospinal fluid. The initial spinal tap was grossly bloody. Broad spectrum antibiotics (cefazidime, clindamycin and trimethoprim-sulfamethoxazole) were begun. All cultures remained negative. Pneumocystis carinii infection was considered because of the radiograph findings and worsening respiratory function, and on her second hospital day a bronchoscopy was performed. Bronchial washings were negative on acid-fast bacilli, fungal and Gram and silver stains. Her platelet count were 16,000/µl by Hospital Day 3, and she developed a coagulopathy.

Because the clinical picture was consistent with hemophagocytic syndrome, bilateral bone marrow aspirations and biopsies were performed. Prominent hemophagocytosis was seen on both aspirates, consistent with either IAHS or familial erythrophagocytic lymphohistiocytosis syndrome. No cultures or studies for acid-fast bacilli were sent from the bone marrow aspirates. There was no family history of hemophagocytic syndrome, opportunistic infections or neonatal death. Despite frequent platelet, packed red blood cell, plasma and cryoprecipitate transfusions, the patient's hematologic abnormalities were not corrected.

Chemotherapy and stem cell transplantation were discussed with her parents, and these options were refused. Hospice options were being investigated, when on Hospital Day 6 she progressed to fulminant respiratory and renal failure. She was removed from life support at her parents' request and died soon after. The parents refused an autopsy.

No immediate cultures from any source were positive. However, 6 weeks after the patient's death, the culture of the bronchial aspirate washings yielded Mycobacterium tuberculosis. When the family was notified to discuss the results and to test the rest of the household, it was learned that the baby's mother had recently died of miliary tuberculosis. Despite frequent platelet, packed red blood cell, plasma and cryoprecipitate transfusions, her platelet count were 16,000/µl by Hospital Day 3, and she developed a coagulopathy.

Discussion. In the late 1960s and 1970s, IAHS was observed to occur in the setting of viral infections, particularly with Epstein-Barr virus.11–14 A number of adult case reports, however, have been published since then in which mycobacterial infection was identified as the causative agent of IAHS. In most of these cases the patients were immunocompromised, from AIDS,1–4 cancer chemotherapy5–7 or chronic dialysis.7, 8 One adult with aplastic anemia developed tuberculosis and a subsequent hemophagocytic syndrome (HS).9 A subset of patients, however, without apparent immunodeficiency have been reported to develop tuberculosis-associated IAHS.16–26 In several instances, as in the infant reported here, the signs and symptoms of IAHS preceded diagnosis of M. tuberculosis infection.7, 8, 15, 20, 22 Several patients with tuberculosis-associated HS who were diagnosed and treated promptly have recovered10, 24–26, but otherwise this disease is generally rapidly fatal, and the diagnosis of mycobacterial infection is often made at autopsy. The mechanism by which tuberculosis causes HS is not known, but there are several possible explanations. Phagocytosis of mycobacteria by macrophages is the initial immune response to infection. Some bacilli are killed within the macrophages, but others survive and replicate within their cellular hosts. In either case phagocytosis leads to cytokine production by the macrophages. Release of tumor necrosis factor-alpha, interleukin-12 and other chemotactic cytokines perpetuate the host's immune response and lead to recruitment of lymphocytes, neutrophils and monocytes. Tumor necrosis factor-alpha leads to the fever and tissue wasting seen with tuberculosis and hemophagocytic syndrome. This cytokine in conjunction with interleukin 12 and interleukin 5 leads to the migration of monocytes and macrophages to regional lymph nodes. This allows for the expansion of antigen-specific T cells, which in turn may lead to a secondary release of cytokines and increased proliferation and activation of phagocytes.27 This process is presumably magnified in the setting of impaired cell-mediated immunity, which explains the increased prevalence of IAHS in patients with HIV infection and other forms of immunosuppression. The role played by NK cells in the etiology of tuberculosis-associated HS is unclear, because the elimination of NK activity is well-documented in IAHS but is usually increased in tuberculosis. A hypothesized mechanism for this latter finding is target-induced NK energy.9

Based on previous publications, it appears that TB-associated IAHS is more common in adults than in children, perhaps because of a higher incidence of HIV infection and immunosuppression. We have found one pediatric report of tuberculosis-associated hemophagocytic syndrome with concurrent HIV infection and one without HIV infection,10 as in our patient. In the latter case, a 14-year-old girl with a classic presentation of miliary tuberculosis and a rapidly worsening clinical course with features of IAHS required VP-16 in conjunction with rifampin, isoniazid, ethambutol, pyrazinamide and prolonged positive pressure ventilation to survive.

The baby described here presented with the classic features of hemophagocytic syndrome (fever, hepatomegaly, cytopenias, jaundice and hypertriglyceridemia) without epidemiologic or clinical evidence of a triggering infectious agent, leading to the consideration of familial HS. Whether the baby's tuberculosis was acquired in the postnatal or prenatal period from her mother is unclear, although the latter route is less common.28 The mother denied illness and appeared well during the infant's hospitalization. Knowledge of maternal tuberculosis may have led to aggressive treatment of the infant and mother, perhaps with better outcome.

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1. Garcia C, Suntaalalla P, Gomez C, Fintor E. Hemophagocytic syndrome associated with tuberculosis in a patient infected...


LACK OF ASSOCIATION BETWEEN KAWASAKI SYNDROME AND INFECTION WITH PARVOVIRUS B19, HUMAN HERPESVIRUS 8, TT VIRUS, GB VIRUS/HEPATITIS G VIRUS OR CHLAMYDIA PNEUMONIAE

The etiology of Kawasaki syndrome (KS), an acute, self-limited multisystem vasculitis with clinical and epidemiologic features consistent with an infectious process, remains undiscovered, despite many investigations using classic as well as newly developed molecular biologic techniques. The marked restriction to young children suggests that a causative microbe may be easily contracted because it appears to result in disease or immunity early in life. Certain febrile childhood exanthematous diseases with etiologies that had been obscure have recently been found to be caused by ubiquitous rather than rare microbial pathogens. A recent example is roseola infantum, a relatively benign exanthematous disease of infancy, long thought to be an infectious disease. Roseola or exanthem subitum is now known to be caused by human herpesvirus 6 (HHV 6), which, like human herpesvirus 5 (or human cytomegalovirus), usually results in asymptomatic infection or poorly differentiated illnesses during childhood. Following this logic KS may be caused by a ubiquitous infectious agent commonly acquired during infancy or early childhood, which has not been detected by classical culture or molecular techniques.

Many groups of viruses, including retroviruses, have been excluded as a cause of KS, and no differences have been found in infection rates with cytomegalovirus, Epstein-Barr virus and HHV 6 between patients with KS and age-matched controls. Human parvovirus causes erythema infectiosum but also asymptomatic infections and undifferentiated febrile illnesses. Prompted by the controversy over the etiologic link between parvovirus B19 infection and KS and the recent discovery of two viruses with no definitive disease associations, specifically GB virus C/hepatitis G virus (GBV-C/HGV) and TT virus (TTV), along with studies implicating Chlamydia pneumoniae in the pathogenesis of atherosclerotic heart disease through molecular mimicry, as well as the possible link between C. pneumoniae infection and KS, we utilized PCR to determine whether KS could be the result of infection by these microbes. In addition we included human herpesvirus 8 (HHV 8), a gamma herpesvirus causing KapoSi's sarcoma, in our search.

Materials and methods. A total of 123 patients (55 female and 68 male; age range, 1 month to 8 years; mean and median ages, 2.4 and 1.5 years, respectively), who presented...
with KS at the Kapi‘olani Medical Center for Women and Children between 1980 and 1999, were studied. Whole blood, plasma/serum, peripheral blood mononuclear cells (PBMC) and urine were collected during the acute phase (≤7 days) of KS, after obtaining informed consent from parents or guardians. This study was approved by the research and ethics committee of Kapi‘olani Medical Center for Women and Children.

RNA and DNA were extracted from plasma or serum using the QIAGEN Viral RNA Extraction kit (QIAGEN, Chatsworth, CA), and DNA was extracted from whole blood and PBMC, using the QIAGEN Blood Extraction kit (QIAGEN).\textsuperscript{10} DNA from urine was extracted by a conventional extraction procedure, consisting of proteinase K digestion and phenol-chloroform purification.\textsuperscript{11} Oligonucleotide primers and thermocycling conditions for the amplification of parvovirus B19,\textsuperscript{12} HHV 8,\textsuperscript{13} TTV,\textsuperscript{16} GBV-C/HGV and C. pneumoniae\textsuperscript{15} are shown in Table 1. For GBV-C/HGV amplification RNA was initially reversed transcribed into complementary DNA using the QIAGEN Blood Extraction kit (QIAGEN).\textsuperscript{10} PCR amplicons were size-fractionated by electrophoresis on 2% agarose gels and visualized by ethidium bromide staining.

In addition acute phase sera from 46 of the 123 patients were tested, in duplicate, for IgM and IgG antibodies against parvovirus B19 by enzyme immunoassay (MarDx Diagnostics, Inc., Carlsbad, CA).

**Results.** As shown in Table 2 IgG or IgM antibodies against parvovirus B19 were detected in the acute phase of 26 of 46 (57%) KS patients, whereas only 5 of 46 (11%) had both IgG and IgM antibodies. Patients in the 0- to 2-year age group had the highest age-specific seroprevalence (15 of 20 or 75%) of IgG or IgM antibodies against parvovirus B19, whereas there was a decrease in seroprevalence with increasing age. On the other hand only 2 of the 46 patients had parvovirus B19 DNA in their blood samples, as detected by PCR.

C. pneumoniae gene sequences were not detected in PBMC and urine of 26 KS patients, and HHV 8 sequences were not detected in plasma or serum from 77 KS patients. Of these 77 KS patients we amplified TTV DNA in only 2 female patients (ages, 4 and 5.4 years), who subsequently cleared the infection within 2 months. Similarly, GBV-C/HGV was detected in 2 other patients, both female, 1.5 and 2 years old. No convalescent phase samples were available to determine the persistence of GBV-C/HGV in these 2 patients.

**Discussion.** The presence of IgA-secreting plasma cells within vascular lesions of KS patients\textsuperscript{16} suggests entry of the etiologic agent by way of the gastrointestinal or respiratory tracts. In this regard the pathogens we examined are transmitted by either the fecal-oral or respiratory aerosol routes. Moreover parvovirus B19 and HHV 8 appear to target vascular endothelial cells. TTV has been found in young children and infants\textsuperscript{15} as well as shown to be transmissible by fecal-or oral routes,\textsuperscript{18} indicating possible acquisition of the virus during childhood. Our data do not support an etiologic association between KS and infection with parvovirus B19 or HHV 8 or with TTV, GBV-C/HGV and C. pneumoniae.

Although we failed to demonstrate an etiologic link between KS and infection with the above named microbes, these

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**TABLE 1.** Primer sequences and cycling conditions for amplification of microbial sequences in Kawasaki syndrome

<table>
<thead>
<tr>
<th>Microbe</th>
<th>Primer Sequence</th>
<th>Annealing Temperature (°C)</th>
<th>Cycles</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parvovirus B19</td>
<td>Outer: 5'-CTTTAGGTATAGCCAACTGG-3'</td>
<td>55</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Nested: 3'-GGCCTTCATGCAAACTGCA-5'</td>
<td>55</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>HHV 8</td>
<td>Outer: 5'-AGCGAAAAAGATCCACCT-3'</td>
<td>37, 55</td>
<td>10, 30</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Nested: 3'-GTTCTGGAATCTACCCAGATG-5'</td>
<td>55</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>TTV</td>
<td>Outer: 5'-CAGACAGAGGAGAGGAAATATGAC-3'</td>
<td>45, 50</td>
<td>10, 35</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Heminested: 3'-ATTTCACGCAAGAGGATAC-5'</td>
<td>55</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>GBV-C/HGV</td>
<td>Outer: 5'-CCGGCAGTGGTGCAGCCAC-3'</td>
<td>55</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Nested: 5'-CGGCCAAAAAGGGTGATTGCAG-3'</td>
<td>55</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3'-AAATGCTGAGGAGGACCCAGTC-5'</td>
<td>55</td>
<td>30</td>
<td>15</td>
</tr>
</tbody>
</table>

---

**TABLE 2.** Seroprevalence of parvovirus B19 infection among 46 patients with Kawasaki syndrome from Hawaii

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>No.</th>
<th>IgM</th>
<th>IgG</th>
<th>IgM &amp; IgG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>20</td>
<td>9 (45)*</td>
<td>6 (30)</td>
<td>3 (15)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>3–4</td>
<td>16</td>
<td>5 (31)</td>
<td>1 (6)</td>
<td>1 (6)</td>
<td>6 (30)</td>
</tr>
<tr>
<td>5–6</td>
<td>6</td>
<td>3 (50)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>7–8</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, percent.
data do not exclude the possibility that KS is caused by an infectious agent. A plausible explanation for the largely negative results may be that KS is caused by a previously unidentified microbial agent. Alternatively the agent may have already been cleared from the sampled compartment at the time of specimen collection. A molecular approach, with the use of representational difference analysis, to identify cryptic, nonhost, microbial genomic sequences in KS patients, currently under way, may offer further clues about an infectious etiology.

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**ACUTE DISSEMINATED HISTOPLASMOSIS WITH MULTIFOCAL CHORIOIDITIS IN A CHILD**

Ocular manifestations of histoplasmosis are rarely described at the time of initial infection. A late sequela of subclinical histoplasmal infection, called the presumed ocular histoplasmosis syndrome, is common and is characterized by bilateral, multifocal chorioretinal scarring; the disease syndrome is mainly known to ophthalmologists. Small, indolent inflammatory choroidal foci may persist for many years and can lead to subfoveal neovascularization and loss of central vision, often decades later. Substantial epidemiologic evidence suggests a causal relationship with previous histoplasmosis.

The literature suggests that ocular involvement may, however, be overlooked in cases of acute disseminated histoplasmosis. Clinically recognized disseminated histoplasmosis occurs in <1 in 2000 infected individuals, mainly in patients with impaired cellular immunity. Progressive disseminated histoplasmosis is usually fatal without treatment but responds well to amphotericin B treatment (with the notable exception of histoplasmal endocarditis). A rare occurrence in immunocompetent infants and children, acute disseminated histoplasmosis is occasionally observed in immunosuppressed children. Including young patients with HIV disease. A case with miliary multifocal choroiditis is described complicating the management of acute lymphoblastic leukemia.

**Case report.** A 6-year-old girl presented because of spiking fever for several weeks that had failed to respond to rifampin, azithromycin and trimethoprim-sulfamethoxazole therapy. The patient had been in remission from acute lymphoblastic leukemia for 18 months, maintained with weekly intramuscular methotrexate and daily oral 6-mercaptopurine. She had fevers of 102–105°F and malaise but she was otherwise asymptomatic. There was a nontender enlargement of the liver to the umbilicus with a 3- to 4-cm palpable spleen. The chest roentgenogram was normal. Pale milary
choroidal lesions scattered in both fundi (Fig. 1), without anterior segment or vitreal inflammatory signs, were detected at an ophthalmologic consultation. Her uncorrected visual acuities were 20/30 in each eye (O.U.).

Investigation revealed a moderate macrocytic anemia (hemoglobin 8.0 g/dl; mean corpuscular volume 93.9 fl), low serum albumin (2.3 g/dl), normal white blood cell counts and serum biochemistry appropriate for age. Bone marrow examination showed tightly packed, noncaseating epithelioid granulomata, with rare foci of necrosis; culture and acid-fast staining for mycobacterial infections were negative. Yeastlike forms that stained with Gomori methenamine silver stain were identified within marrow granulomata. Five blood cultures and a bone marrow culture subsequently grew Histoplasma capsulatum. A urine histoplasmal antigen titer (LJ Wheat, M.D., Histoplasmosis Reference Laboratory, Indianapolis, IN) of >10 enzyme immunoassay units was detected at presentation and was still positive at 53 days. The patient received ambulatory therapy with intravenous amphotericin B 1 mg/kg daily for 4 weeks; she became afebrile on Day 7 and made an uneventful recovery. The choroidal nodules were inapparent after 3 weeks of therapy, and there was no residual scarring. The bone marrow findings reverted to normal. The patient has remained symptom-free for 22 months.

**Discussion.** Most cases of progressive disseminated histoplasmosis in children complicate the management of hematologic malignancy, particularly Hodgkin’s disease and acute and chronic lymphocytic leukemia. Usually these patients are also therapeutically immunosuppressed. Ocular complications of progressive disseminated histoplasmosis have rarely been described during life. Our patient was immunocompromised by long term maintenance chemotherapy used in the management of acute lymphoblastic leukemia.

Multifocal histoplasmic choroiditis, multifocal chorioretinitis and multifocal retinitis may occur in patients who retain sufficient immunologic capability to localize the *H. capsulatum* infection. The chorioretinal lesions are generally small (<400 μm diameter), oval and creamy white with either distinct or fluffy borders. It is assumed that these lesions are granulomatous in correspondence with the bone marrow findings. The fundal appearances must be differentiated from other causes of multifocal granulomatous posterior uveitis, such as miliary tuberculosis, sympathetic uveitis, coccidiodiomycosis, sarcoidosis, disseminated cat-scratch disease and idiopathic multifocal choroiditis. In severely immunosuppressed individuals, an immune response to the infection cannot always be generated and, as a result, histoplasmal ocular involvement may sometimes not be detectable clinically.

The diagnosis of disseminated histoplasmosis is established by biopsy of bone marrow, liver, skin or oral lesions with Gomori silver staining and culture; by blood culture (optimally using lysis centrifugation); and by Wright’s stain evaluation of peripheral blood smears. Enzyme-linked immunosorbent assay testing for urinary histoplasmal antigen provides a rapid semiquantitative diagnostic test with high sensitivity. DNA probe techniques can also be useful. A 4-fold or greater rise of complement-fixing antibody to *H. capsulatum* is generally considered diagnostic in immunocompetent individuals. Progressive disseminated histoplasmosis should be considered as an uncommon cause of multifocal choroiditis and retinitis, but one that should be specifically looked for in an immunosuppressed febrile child. There are no previous reports describing the successful treatment of histoplasmal multifocal choroiditis as part of progressive disseminated histoplasmosis.

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INTRAUTERINE STAPHYLOCOCCAL SCALDED SKIN SYNDROME: REPORT OF A CASE

Staphylococcal scalded skin syndrome (SSSS) is the clinical term used for a spectrum of blistering skin diseases induced by the exfoliative (epidermolytic) toxins (ET) of Staphylococcus aureus.1 SSSS was first described by Ritter in 1878. It occurs predominantly in neonates and infants and rarely affects children or adults.

We report the first case of intrauterine SSSS probably caused by a previous amniocentesis procedure. All the symptoms and signs associated with SSSS were found immediately after the infant's birth.

Case report. A full term female infant was born to a 25-year-old woman whose pregnancy was uncomplicated until the day before delivery when she developed fever. Labor pain and rupture of membranes occurred the next day, and the infant was delivered via cesarean section under general anesthesia. At delivery the infant suffered from asphyxia and the Apgar scores were 5 and 7 at 1 and 5 min of age, respectively. Amniocentesis had been performed twice during pregnancy for suspected fetal ascites noted since gestational age of 32 weeks. One was performed 2 days before delivery and the other on the preceding day.

The initial vital signs of the infant after delivery were normothermia, pulse of 140 and respiratory rate of 52. The birth weight was 2.5 kg. Physical examination revealed perioral crust and generalized sheetlike sloughing of the skin with a positive Nikolsky sign, especially over the flexure sites and four extremities. The involved areas beneath the sloughed skin were erythematous and moist.


Fig. 1. Generalized sheetlike sloughing of the skin is observed on the surfaces of head, neck and trunk, especially over the flexure sites and four extremities. The involved areas beneath the sloughed skin were erythematous and moist.

About 4 days of age the initial blood and amniotic fluid cultures collected at birth grew Staphylococcus aureus that was susceptible to oxacillin. The same organism was found in the maternal blood culture. Oxacillin and gentamicin were given for 10-day and 7-day courses, respectively. The patient recovered uneventfully. Two serologically distinct toxins, exfoliative toxin A (ETA) and exfoliative toxin B (ETB), were identified from S. aureus isolates by PCR.

Discussion. This is the first reported case of intrauterine SSSS and only one case of SSSS has been reported to occur within 24 h of birth.2 In our case the mother developed fever 1 day after receiving an amniocentesis procedure prompted by suspected fetal ascites, which indicates a possible infection. The dermatologic manifestations of the patient were most compatible with the diagnosis of SSSS and were noted at birth. The positive maternal blood and amniotic fluid cultures are consistent with intrauterine mode of infection.

The etiology of SSSS is usually phage group 2 staphylococci, particularly strains 71 and 55. The clinical manifestations of SSSS are mediated by hematogenous spread of staphylococcal epidermolytic or exfoliative toxins A or B (ETA or ETB). Decreased renal clearance of the toxins may account for the fact that the disease is most common in infants and young children. In western countries 80 to 85% of toxin-producing S. aureus belong to phage group II,3 and ~90% of toxin-producing strains produce ETA.4 In contrast, in Japan there is a predominance of ETB-producing strains, which are less likely to be of phage group II.5, 6 Both toxins have been identified and fully sequenced. PCR offers the advantage of a rapid, specific and inexpensive genotypic identification of strains harboring genes for ETA and ETB, with sensitivity an order of magnitude greater than that of hybridization techniques.7 Many strains of S. aureus produce both toxins simultaneously. Intact bullae are consistently sterile. Culture should be obtained from all suspected sites of localized infection and from the blood to identify the source for elaboration of the epidermolytic toxins.

The treatment regimen for SSSS should be divided into two parts: one for the underlying organism; the other for the associated symptoms. Systemic antibiotic treatment with a semisynthetic penicillinase-resistant penicillin for 7 to 10 days is indicated because the staphylococci are usually penicillin-resistant. With sepsis treatment duration should be for 10 to 14 days and possibly longer if deep-seated infections are identified.8 Topical antibiotics are unnecessary because they are frequently ineffective. Recovery is usually rapid, but complications such as excessive fluid loss, electrolyte imbalance, faulty temperature regulation, pneumonia, septicemia and cellulitis increase morbidity. Despite the dramatic clinical presentation of the syndrome, the case fatality rate is low with most infants making full recovery. A higher mortality is observed in the younger infants with sepsis.8

The purpose of this case report is to emphasize: (1) the probability of intrauterine S. aureus infection from iatrogenic origin; (2) the risk of transmission of pathogens during amniocentesis; and (3) the need of stringent disinfection between each procedure.

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PRIMARY CUTANEOUS ASPERGILLOSIS IN VENTILATED NEONATES

Primary cutaneous aspergillosis (PCA) is being reported with increased frequency and, in the overwhelming majority, in premature neonates. Of the 16 described cases 15 have been reported in the last decade, and all but 1 were premature babies.1–6 Association with the use of adhesive tape has been reported in 2 cases: one in relation to a chest tube; and the other in an area macerated by adhesive tape.5, 6 We report the first 2 cases of primary cutaneous aspergillosis occurring on the face after the use of adhesive strapping to secure endotracheal tubes.

Case reports. Case 1. A 900-g male, preterm second twin was admitted to the neonatal intensive care unit (NICU) in respiratory distress requiring ventilation. Chest roentgenogram showed bilateral pulmonary infiltrates. The differential diagnoses of hyaline membrane disease and acute bacterial sepsis were considered. Therapy was commenced empirically with penicillin and gentamicin. The hemoglobin was 15.7 g/dl, white blood cells 15.5 x 10^3/mm^3 and platelets 182 x 10^3/mm^3. Blood and cerebrospinal fluid cultures were sterile. He remained ill and pyrexial and developed sclerema and a progressive pneumonia. The antibiotics were changed to ceftazidime and subsequently to imipenem because nosocomial sepsis was suspected. On Day 5 of imipenem treatment (Day17 in the nursery), the infant’s overall condition was unchanged despite the use of broad spectrum antibiotics. It was also noted that he had developed ulcerated lesions with black eschars on the left cheek, side of nose and ear, beneath the adhesive tape used to secure the endotracheal tube. The diagnosis of disseminated candidiasis with emolic skin lesions was considered, and fluconazole (5 mg orally) was added. A swab of the lesion was taken and Aspergillus niger was isolated in pure culture. Therapy was amended to amphotericin B deoxycholate in an initial dose of 0.25 mg/kg/day and increased at daily increments of 0.125 mg with the aim of reaching 1 mg/kg/day. Further investigations to exclude disseminated disease (endotracheal aspirates and blood cultures, processed via a lysis-centrifugation method) were negative. The patient remained ventilator-dependent and scleremic with a nonresolving pneumonia. He died 6 days after commencement of amphotericin B. The parents refused an autopsy.

Case 2. A term, female newborn with Apgar scores of 3, 4 and 5 at 1, 5 and 10 min, respectively, required ventilatory and inotropic support soon after birth. Hypoxic ischemic encephalopathy and neonatal sepsis were suspected. Therapy was empirically commenced with penicillin and gentamicin. Specimens of gastric aspirate, blood culture, cerebrospinal fluid and ear swab sent for bacterial culture were negative. By Day 3 the infant had developed pancytopenia (hemoglobin 5.6 g/dl, platelets 10 x 10^3/mm^3, leukocyte count 2.4 x 10^3/mm^3 with 56% neutrophils) with an abnormal coagulation profile (INR 8.7, platelet count 180 x 10^3/mm^3, fibrin degradation products >2000 ng/ml) consistent with worsening sepsis. Therapy was changed to cefotaxime. On Day 10 in the NICU the neonate developed three distinct lesions on the left neck, right cheek and lip beneath the adhesive tape securing the endotracheal tube. These began as hemorrhagic bullae that rapidly evolved into ulcers with indurated edges and central necrotic bases. A clinical diagnosis of ethylma gangrenosum was made. Swab of the cheek lesion yielded a pure culture of A. flavus. Histology of the subsequent biopsy revealed ulceration with necrotizing acute inflammation. No specific pathogens were demonstrated and the periodic acid-Schiff stain for fungal elements was negative. Culture of the biopsy, however, grew A. flavus. The chest roentgenogram showed a progressive bilateral bronchopneumonia, the possible etiology of which included bacteria, viruses or systemic dissemination of PCA. Further investigations (endotracheal tube aspirates, blood) of cultures to exclude these were negative. Fontanel ultrasonography revealed a frontal fossa hemorrhage presumed to be related to the bleeding diathesis and/or severe birth asphyxia. Owing to the overall poor prognosis antifungal therapy was not commenced, and antibiotics were discontinued. She died 4 days after the onset of PCA. The infant’s parents did not consent to an autopsy.

In both patients the HIV antibody tests were negative. Glucocorticoid therapy had not been administered antenatally or during the course of their illness. Both infants appeared to have inflammatory conditions, possibly caused by infection, that progressively worsened from the time of birth. PCA in this context most likely represents an epiphenomenon. The cases were temporally unrelated and occurred in NICUs in two hospitals. Culture of samples of the tapes used in the NICUs at the respective times did not yield Aspergillus, and the environmental sources were not established.

Discussion. Cutaneous aspergillosis can be a site-specific entity or the initial focus for fatal disseminated disease.2, 69 In our cases we failed to retrieve the organism from extracutaneous sites (lung, blood). The yield of blood cultures in disseminated disease, however, is low,1 even with blind terminal subculture and lysis-centrifugation. Thus invasive biopsies are ultimately required to establish the diagnosis. In the absence of these and autopsy findings we were unable to reliably exclude the possibility of disseminated invasive disease.

Preterm infants have an almost unique predisposition to neonatal PCA. This may be ascribed to the increased vulnerability of their skin to minor trauma associated with intensive care as well as immaturity of host defenses.
Of the 16 reported cases, 15 have been described in premature neonates. The first patient in this report was preterm but the second was a term baby. To our knowledge this is the second reported case of PCA occurring in a term baby.

Other recognized risk factors for primary cutaneous aspergillosis include neutropenia, glucocorticoid administration and prior use of antibiotics. Although neutropenia appears to be an important risk factor in certain immunocompromised groups, including bone marrow transplant patients and those with hematologic malignancies, our patients were not neutropenic. This observation is in keeping with that of Groll et al. who noted neutropenia to be an infrequent occurrence in neonatal aspergillosis. Instead a qualitative defect in neutrophil chemotaxis and phagocytosis is thought to predispose this group of patients to aspergillosis. Glucocorticoids, on the other hand, have been shown to impair macrophage and neutrophil killing of Aspergillus spores and hyphae, respectively. We have not been aware of our patients having previously received glucocorticoids during the course of their illness. The role of antibiotics in the pathogenesis of PCA is unclear. Of the 16 cases of neonatal PCA reported thus far, 13 had previously received antibiotics. Likewise our patients received prolonged broad spectrum antibiotics (>10 days). It may be that systemic antibiotics contribute to the disturbance in the ecology of the skin flora.

Mechanical disruption of the barrier function of the skin is involved in all cases of PCA. In one-half of all reported cases of neonatal PCA, the source was not determined. In the remaining eight cases, these included a contaminated hand splint (one), macerated skin associated with an oxymeter sensor (one), contaminated latex finger stalls (four) and adhesive tape (two). The skin of newborns is exceedingly fragile, especially on the face, and minor friction can thereby predispose to a breach in the epithelium allowing Aspergillus conidia to enter. Fragility of skin in the newborn might explain the lack of reports of PCA localized to the face in high risk adult populations requiring prolonged intubation. We, however, cannot explain why cases similar to ours have not been reported previously, given the large number of premature neonates who have endotracheal tubes secured by adhesive tape. It is likely that more such cases will be described in the future.

The lesions of PCA may be nonspecific, ranging from induration to pustules, hemorrhagic bullae, ulcers, small abscesses and eschars. Thus any new skin lesion in a neonate at risk should raise the suspicion of PCA. Confirmation requires histology and culture of a biopsy taken from the center of the lesion. Because neonates tend not to tolerate skin surgery well, treatment entails antifungal therapy often without surgical excision. Amphotericin B is the recommended choice with the adjunctive use of flucytosine being controversial but widely practiced. Limited reports exist on the use of itraconazole in neonates, but it may have a place in localized PCA, not related to catheter exit sites. In contrast to disseminated invasive aspergillosis, the prognosis for PCA is favorable probably owing to easier and earlier diagnosis and treatment.

These are the first two reported cases of PCA occurring on the face after the use of adhesive tape to secure endotracheal tubes. Although neonatal PCA is relatively uncommon, early recognition and treatment require a high index of suspicion in patients at risk.

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__MYCOBACTERIUM FORTUITUM OSTEOMYELITIS OF THE CUBOID AFTER NAIL PUNCTURE WOUND__

Puncture wounds to the feet are common injuries in children. It is estimated that 3 to 18% of these wounds become infected, resulting in cellulitis or a localized deep tissue abscess. Osteomyelitis, with or without pyoarthritis, is the next most common complication and occurs in ~0.65 to 1.8% of cases. Pseudomonas aeruginosa is the infecting organism in >90% of such cases. Nontuberculous mycobacteria infections other than lymphadenitis are uncommon in children, especially in those with no underlying immunodeficiency. We describe a child who had osteomyelitis of the cuboid bone caused by Mycobacterium fortuitum after nail puncture wound of his left foot.

Case report. An 11-year-old child was admitted to the emergency room because of a 1-week history of swelling, tenderness and redness of his left foot. He was well until 1 month before admission, when he stepped on a nail while wearing sneakers and sustained a puncture wound to the sole of his left foot. Local care was given to the wound, and no systemic antibiotic therapy was initiated. Therapy with 50 mg/kg/day cephalixin was started but without any clinical response.

On admission to the hospital physical examination revealed a healthy-looking and afebrile child. A swollen, red and tender area was noted on the dorsum of his left foot. The erythrocyte sedimentation rate was 20 mm/h, and the leukocyte count was 9200/mm³ with a normal differential. Radiography (Fig. 1) and computed tomographic scan of the left foot revealed a round lytic lesion in the lateral aspect of the cuboid bone with swelling of the surrounding soft tissues. ⁹⁹ᵐTc-methylenediphosphonic acid bone scan demonstrated increased uptake in the cuboid bone at the blood pool and late
phases, which was compatible with osteomyelitis. The cuboid bone was surgically drained and the lesion was debrided. Histopathologic examination of the bone revealed acute and chronic inflammation with no malignancy.

Based on the history of a nail puncture wound, therapy with intravenous piperacillin 300 mg/kg/day, gentamicin 5 mg/kg/day and cloxacillin 100 mg/kg/day was started. The Gram-stained smear of the pus was negative, but the culture yielded Gram-positive filamentous branched organisms after 3 days of incubation at 35°C. These organisms were partially acid fast and were identified as *Nocardia* sp. Because the organism was susceptible only to amikacin and meropenem by the disk diffusion method, the patient’s antibiotic therapy was changed to intravenous amikacin 20 mg/kg/day for 3 weeks.

Complete bone healing was demonstrated by repeat x-ray of the foot 3 months after the admission.

Because of the unusual susceptibility pattern of the organism, the isolate was sent to the Actinomycete Reference Laboratory at the CDC for further identification. On preliminary studies at CDC, the Gram-stained smear of the patient’s isolate had Gram-positive pleomorphic coccobacilli, with longer filaments frequently observed. Identification of the isolate as *Nocardia* sp. was ruled out based on lack of aerial hyphae, a positive arylsulfatase reaction in 3 days and 100% acid fastness with the modified Kinyoun’s acid-fast test in subcultures. Biochemical tests routinely used in the Actinomycete Reference Laboratory were performed. By these tests the isolate was identified as a strain of *M. fortuitum* complex. Antibacterial susceptibility testing for the patient’s isolate was performed by disk diffusion and broth microdilution methods. The isolate was susceptible only to amikacin, amoxicillin/clavulanic acid, ciprofloxacin and gentamicin.

The isolate was referred to CDC’s Mycobacteriology Laboratory, where it was identified as *M. fortuitum/Mycobacterium peregrinum* group based on its mycolic acid analysis patterns by high performance liquid chromatography. Ribotype DNA analysis showed identical hybridization bands between the patient’s isolate and the type and reference strains of *M. fortuitum*; this pattern of bands differed from those for the type strains of *Mycobacterium senegalense* and *M. peregrinum*. Thus the isolate was definitively identified only by ribotyping.

**Discussion.** To our knowledge this patient is the second described case of *M. fortuitum* osteomyelitis secondary to a nail puncture wound to the foot. The first case was in a 14-year-old girl who developed osteomyelitis of the calcaneus 3 weeks after she had a nail puncture wound to her right foot. Members of the *M. fortuitum* complex are rapidly growing acid-fast bacteria that include *M. fortuitum, M. peregrinum* and *M. fortuitum* third biovariant complex (D-sorbitol negative and D-sorbitol positive). They are opportunistic pathogens of humans that can be isolated from environmental sources such as water, soil, dust, fish and raw or unpasteurized milk. Although rare, disseminated infections have been described in immunocompromised patients. *M. fortuitum* has been associated with pulmonary, central nervous system and catheter-related infections; however, skin and soft tissue infections account for the majority of diseases caused by the *M. fortuitum* complex.

Preceding penetrating trauma and subsequent tissue devitalization are well-defined epidemiologic risk factors for the development of soft tissue and bone infections with nontuberculous mycobacteria. It is hypothesized that these bacteria colonize the skin and cause infection when the integrity of the skin is interrupted. This was most probably the preceding event in our case. The typical cutaneous lesion is a nodular indolent, recurring lesion with scant serous drainage caused by fistula formation.

The organism that was isolated from our patient was initially identified as *Nocardia* sp. As with *M. fortuitum*, soft tissue and bone infection with *Nocardia* sp. after penetrating trauma have been described. Staneck et al. described a patient who developed osteomyelitis of his left ankle after a compound dislocating fracture. The organism that was isolated from the bone was initially identified as *Nocardia asteroides*, based on the Gram stain and the gross morphology of the culture. The infection failed to respond to the therapy directed to *N. asteroides*, and subsequent laboratory investigation revealed that the organism was *M. fortuitum*. It may be difficult to make a distinction between *Nocardia* and *Mycobacterium* on morphology alone. Further, even routine biochemical and cultural characteristics may not provide a definitive identification. In 1998 von Graevenitz and Punter-Streit reported on the extent of the misidentification of *M. fortuitum* in a Swiss External Quality Control study. Of the 50 participating laboratories only 26% of the participants identified “rapidly growing mycobacteria” or “*M. fortuitum*” in the proficiency testing sample; 46% of the participants identified the *M. fortuitum* as *Nocardia* sp. Because antibiotic therapy for the 2 organisms is different, a definitive identification should be made if acid-fast, rudimentary branched bacteria grow from specimens obtained from skin, soft tissues or bone lesions. The arylsulfatase (3-day) is a relatively simple procedure that can provide this differentiation.

The optimal antibiotic therapy for osteomyelitis with *M. fortuitum* complex consists of a combination of two or more of the following agents: amikacin, imipenem, meropenem, ciprofloxacin and clarithromycin. The optimal duration of antimicrobial therapy is unknown but should probably be for 4 to 6 weeks. Because the final identification of the culture was obtained after the child’s foot had completely healed, no additional antimicrobial therapy was given. However, because clinical isolates of the *M. fortuitum* complex may vary in their antimicrobial susceptibility pattern, it is important to identify the species of these microorganisms as well as to perform susceptibility studies.

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TUNGIASTIS IN A YOUNG CHILD ADOPTED FROM SOUTH AMERICA

Tungiasis is an inflammatory infestation caused by burrowing of the female flea, Tunga penetrans, into the skin. Although tungiasis is rarely diagnosed in the United States, it is likely to be seen more frequently than in the past among those entering the United States from endemic areas because of increases in the volume and speed of international travel and migration. We present the first report of tungiasis diagnosed in a child in the United States.

Case report. A 15-month-old girl was seen in hospital with a 1-month history of a red, swollen, asymptomatic distal right fifth toe. One month before her presentation the patient was adopted from a foster home in Paraguay. When the child arrived in the United States, her adoptive parents noted redness and swelling of the right fifth toe. The swelling increased during the next 2 weeks, and the lesion appeared to blister, prompting a visit to a community physician who prescribed cephalaxin. When no improvement was noted 1 week later and purulent-appearing material was expressed from the edge of the lesion, she was referred to us for evaluation.

She had no fever or other constitutional symptoms, has had no other skin problems and had a normal gait. The right fifth toe was swollen and erythematous distal to the metatarsophalangeal joint. On the distal dorsal surface, extending under the distal nail plate, was a 7-mm pale, firm, hyperkeratotic papule with a black central core. A roentgenogram of the toe showed no foreign body, no gas in the tissue and no periosteal elevation.

The distal nail was clipped back and the papule was unroofed under sterile conditions with a scalpel. Whitish material with a pasty consistency and the appearance of fine tapioca was expressed. The wound was debrided of all devitalized tissue, irrigated with normal saline and dressed with bacitracin ointment. The wound healed uneventfully.

Microscopic examination of the exudate in the microbiology laboratory revealed numerous eggs (Fig. 1) and insect parts which were consistent with T. penetrans.

Fig. 1. Eggs of the flea T. penetrans recovered from a pale papule with a black central core on the right fifth toe of a 15-month-old girl adopted from Paraguay.
19 Risk factors for contracting tungiasis include walking barefoot in an endemic area and contact with the sand ballast of an English ship. The first reported case in the United States was in 1930 in a man who had lived his entire life in New Orleans but had probably contracted the infestation from a hemp pile which had come from Mexico. The first imported case in the United States occurred in 1966 in a traveler returning from Gabon, Africa. Only 22 reported cases of tungiasis, including our patient, have been diagnosed in the United States; all except the first case occurred in individuals who had been in Africa or South America a few days to weeks before presentation. Ours is the first report of tungiasis diagnosed in a pediatric patient in the United States and the first in an international adoptee, expanding the list of potential illnesses in these children.

Prevalence. Tungiasis is now prevalent in Central and South America, the Caribbean Islands, tropical Africa, the Seychelles, Pakistan and the west coast of India. Reappearance of the infestation was reported recently in Mexico, where no cases had been seen since 1948. Prevalence of tungiasis was 15 to 40% among children in Nigeria and Trinidad. All ages are affected although boys 5 to 9 years old have the highest prevalence of infestation because they frequently walk barefoot. Risk factors for contracting tungiasis include walking barefoot in an endemic area and contact with animal reservoirs.

The flea. T. penetrans is a wingless, reddish-brown flea of the order Siphonaptera. It is among the smallest of fleas, measuring ~1 mm long when unfed. It has a more angular head and triangular-shaped thorax than the common flea, *Pulex irritans*. Other names for the flea include sand flea, chigoe flea, chigo, chica, jigger, chique, nigua, pico and bicho de pe (bug of the foot). It should not be confused with the mite *Trombicula alfreddugesi*, which causes “chiggers” in North America. The flea lives in warm, dry, sandy soil on beaches and around houses and farms, particularly in cattle stables or pigsties, or in dust or ashes in poorly kept human dwellings. The flea’s proliferation depends on a warm temperature, sandy soil and the presence of a suitable host.

Both sexes of flea feed on the blood of mammals, particularly cows, pigs, dogs, cats, mice, rats, occasionally on some birds and humans, but only the pregnant female burrows into human skin. After being impregnated the female flea jumps repeatedly up to 35 cm off the ground until she dies or is able to attach to the skin by her mouth parts and insinuate into the stratum corneum by clawing. Because the flea is a poor jumper, she is able to attach most readily to the toes and feet. Individuals who frequently squat may develop lesions on the perineum or buttocks. The pregnant female flea burrows until her head reaches the dermis, where she feeds on blood, and her terminal thoracic segment is flush with the outer skin surface, allowing her to obtain air through the last pair of gills. In myiasis a blood-sucking fly drops ova from the abdomen into the bite lesion. Only the larvae of the fly penetrate the skin, producing a furunculoid lesion. In myiasis the fly and its larva are usually solitary, but multiple lesions occur. Those with impaired sensation because of leprosy or diabetes mellitus are particularly prone to multiple, widespread infestation that can produce a honeycombed appearance to the affected areas such as the hands and feet. Complications of tungiasis include severe pruritus, pain, impetigo, lymphangitis, erysipelas, cellulitis, gangrene, sepsis, inflammation leading to autoamputation of the infested digit (ainhum), tetanus and death.

Diagnosis. Definitive diagnosis rests on demonstration of the flea within a lesion on a patient with an appropriate travel history. Under magnification the ovipositor of the flea on the posterior abdominal segment is visible within the central punctum of the lesion: this is diagnostic of tungiasis. Histopathologically the epidermis is hyperkeratotic and is often buttressed next to the flea. In the subadjacent dermis there is an inflammatory infiltrate of lymphocytes, plasma cells and eosinophils. Histopathologic sections through the flea reveal an intraepidermal cystic cavity lined by a thick, eosinophilic cuticle and rings of structures representing the trachea, digestive tract and ovaries containing numerous eggs. When the nodule is excised a whitish substance exudes from the lesion. Direct smear of the contents and examination under low power magnification reveals the presence of numerous whitish eggs.

Differential diagnosis includes foreign body, acute paronychia, ingrown nail, arthropod bite, folliculitis, wart, creeping eruption (*Anycyclostoma* spp.), cercarial dermatitis, dracunculiasis, cutaneous leishmaniasis and cutaneous myiasis. In myiasis a blood-sucking fly drops ova from the abdomen into the bite lesion. Only the larvae of the fly penetrate the skin, producing a furunculoid lesion.

Treatment. Treatment of an early lesion consists of peeling back the keratin around the punctum with a sterile needle and extracting the flea with the needle. This was such a common practice in the Caribbean that some women would pierce their lip with a needle to provide a place to carry it. Nodular lesions are best treated by unroofing the nodule and removing the contents completely by sterile curettage. Alternatively the nodule can be excised. Chemical means of treatment that have been advocated, but are not now recommended, include immersion of the affected limb in 4% formalin solution or spraying it with chlorophenothane. Systemic niridazole (Ambilhar) 30 mg/kg as a single dose was effective in a double blind placebo-controlled trial in Nigeria: this may be the best treatment if multiple sites of infestation are present. Treated lesions generally heal within 2 to 3 weeks. Given the potential for *Clostridium tetani* secondary infection, up-to-date tetanus vaccination is required. Secondary infection, reported in 6% of cases in a large series of patients in Trinidad, also should be treated with appropriate antibiotics. Prophylaxis consists of wearing shoes, sweeping floors in dwellings or spraying the floors with malathion. Control measures in endemic areas consist of encouraging
residents to wear shoes; treatment of infested areas with insecticides; treatment of infected human hosts, including education on extraction of fleas using sterile instruments, use of wound dressings and tetanus immunization; and improved animal husbandry practices to reduce transmission to humans. Application of malathion to infested sandy areas in Trinidad reduced the incidence of tungiasis by 80%. Methoprene is an insect growth regulator that is being used successfully in some endemic areas such as Brazil to prevent immature fleas from developing into adults.

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BACILLUS ANTHRACIS SEPSIS IN A NEWBORN

Bacillus anthracis, the etiologic agent for anthrax, is a zoonotic illness recognized since antiquity. In industrialized countries anthrax has been virtually eradicated because of effective public health measures including animal vaccination and quality control of animal products. In developing parts of the world, however, anthrax continues to be an occupational hazard of people who have direct contact with infected animals or who process animal hides, hair, bone, bone products and wool. The disease is uncommon in children especially in neonates and is not described in recent pediatric textbooks. Our review of the literature since 1982 did not reveal any report of B. anthracis as a cause of neonatal sepsis. In this article we describe the first case of neonatal sepsis caused by B. anthracis in a Turkish newborn. The clinical findings, diagnosis and management of this uncommon entity are discussed in this report.

Case report. A 2-day-old male baby was admitted to our neonatal intensive care unit of the Children’s Medical Center Hospital in Van, Turkey, because of refusal to suckle, cyanosis, fever and hypotonia. This baby was born at home by spontaneous vaginal delivery, after an estimated gestation of 39 weeks, to a 20-year-old gravida 1, para 1 woman in a rural area outside of the city. No medically trained person was in attendance at the time of delivery. The mother had no complications during pregnancy. There was no history of premature rupture of membranes. The delivery was prolonged, and the baby did not cry for 3 or 4 min. Parents of the patient were healthy. The family was involved with sheep-herding.

On admission the patient was restless, had mild cyanosis with a weight of 2900 g, head circumference of 34 cm, pulse rate of 148/min and rectal temperature of 38.7°C. The skin was slightly icteric. The umbilicus was dirty and tied with a dirty thread. The area of surrounding umbilicus was hyperemic.

Laboratory data on admission revealed a white blood cell count of 21 000/mm³ with 5% band forms and 80% neutrophils. The hematocrit was 34%, and the platelet count was 245 × 10⁶/ml. Coagulation studies were normal. Total serum bilirubin was 10.2 mg/ml, and biochemical profile and liver transaminase values were normal. The cerebrospinal fluid (CSF) examination and Gram-stained smear were negative. Ultrasound of the head revealed a hemorrhage 9 by 10 mm in area in the right cortex. On the day of admission blood, urine, umbilical discharge and CSF cultures were obtained, and ampicillin and gentamicin therapy was started. Although CSF culture was negative, blood, urine and umbilical cultures yielded B. anthracis, as identified by the Microbiology Laboratory of the Medical Faculty using sheep blood brain-heart infusion agar. It was identified as B. anthracis and confirmed with a BBL Crystal Gram-Positive 10 system panel (Becton-Dickinson). The organism was susceptible to penicillin and netilmicin. Therapy was changed to penicillin G 300 000
units/kg/day and netilmicin 5 mg/kg/day. All cultures obtained from the mother's blood, urine, throat and vagina were negative for *B. anthracis*. Repeated blood, urine and umbilical cultures were negative for *B. anthracis* 2 weeks after starting penicillin and netilmicin therapy. During the hospital course the patient's clinical and laboratory findings gradually improved, and the therapy was continued for 4 weeks. The patient was discharged home in stable condition and remained well at his follow-up examination. Investigation in the home revealed that wool hides from which the threads for tying the patient's umbilicus were positive for *B. anthracis*.

**Discussion.** Anthrax is rarely seen in developed countries as a result of strict and careful control of raising live stock and related industrial products. However, 2000 to 100 000 anthrax cases are reported worldwide every year. Areas of high prevalence include the Middle East, Africa, Australia, South America and New Zealand. The incidence probably correlates with the enzootic status of the disease in the livestock of these countries. Familiar clustering has occurred in association with exposure to diseased animals. Domestic animals, cattle, horses, sheep, goats and swine are most commonly infected. All domestic and many wild animals may serve as hosts.

Anthrax is endemic in our country's rural areas especially at the East Anatolia, where raising livestock is one of the major income source.

*B. anthracis* is a Gram-positive, encapsulated microorganism that can cause a zoonotic infection in human by the transfer of organisms from sick animals or their products. The disease in humans is acquired by butchering, skinning or dissecting contaminated hides, wool, hair or other materials. The disease usually follows inoculation of bacilli or spores into skin, often through a wound or abrasion. Several clinical forms are seen in childhood. Cutaneous infection is the most common (90%), followed by pulmonary and gastrointestinal infections (5% each). As a result of lymphohematogenous spread, sepsis and meningitis can occasionally occur. This condition is associated with high mortality. When it occurs without cutaneous lesions, it is called primary anthrax sepsis. Although fatal meningitis cases secondary to untreated skin forms were reported, our patient's CSF findings were completely normal despite septicemia.

A review of the literature from 1976 to 1998 revealed no neonatal cases of *B. anthracis* sepsis. Systemic forms of anthrax in children are rare. To our knowledge only one case a child ≤3 years old has been reported, but no cases have been in the neonatal period. If the typical cutaneous lesion is present diagnosis is not difficult. Without a cutaneous lesion or a history of occupational exposure, the diagnosis can be difficult to establish. Detecting the agent in the simple smear or a history of occupational exposure, the diagnosis can be difficult to establish. Detecting the agent in the simple smear or the hemagglutination test supports the diagnosis. We did not perform a direct specimen smear or the hemagglutination test. We diagnosed our case by means of blood and other tissue cultures, and we assumed our case had primary *B. anthracis* sepsis.

Successful management and therapy in newborn patients depends not only on early diagnosis but also on vigorous antibiotic and other supportive therapy. Large intravenous doses of penicillin G are recommended. Treatment should be continued for at least 3 or 4 weeks. Ciprofloxacin, erythromycin, tetracycline and chloramphenicol are effective alternative drugs in penicillin-allergic patients. Corticosteroids are beneficial in treatment of cutaneous anthrax, especially in severe toxic cases with edema and meningitis. Control of the disease in humans depends on control of the disease in animals. Effective animal vaccines are available. A human anthrax vaccine is also available. Penicillin prophylaxis for 7 days may prevent infection after known exposure.

Our patient represents the first documented case of neonatal *B. anthracis* sepsis. Neonatal anthrax sepsis should be considered in the differential diagnosis of newborn sepsis in areas where it is prevalent, especially when there is a history of occupational exposure. Our case illustrates the need for awareness of this rare clinical entity of neonatal anthrax as a possible cause of newborn septicemia in such a setting.

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