ABSTRACT. In this article, we report the case of a 16-month-old German boy who was admitted to the Children’s Hospital of Stuttgart with a 4-week history of intermittent fever, decreased appetite, weakness, fatigue, and difficulty sleeping. He was healthy at birth and remained so for the first 15 months of his life. On admission, physical examination showed enlarged cervical, axillary, and inguinal lymph nodes, as well as hepatosplenomegaly. Laboratory data revealed pancytopenia, elevated liver function tests, and hypergammaglobulinemia. Blood, stool, and urine culture results were negative. Viral infections and rheumatologic and autoimmune disorders were ruled out, but a positive titer for Leishmania antibodies was noted. In a liver and bone marrow biopsy, the amastigote form of the parasite could not be seen in cells. The promastigote form of Leishmania was found and the diagnosis of visceral leishmaniasis was made by combining the cultures of both the liver and the bone marrow biopsy material in 5 mL 0.9% saline on brain heart infusion agar, supplemented with defibrinated rabbit blood and incubated at 25 to 26°C for 5 days. The parasite was identified by Southern blot analysis as Leishmania infantum.

Specific therapy with the antimonial compound sodium stibogluconate with a dose of 20 mg/kg body weight was begun immediately. Within 4 days, the patient became afebrile. The side effects of treatment, including erosive gastritis, cholelithiasis, worsening hepatosplenomegaly, elevation of liver enzymes, pancreatitis, and electrocardiogram abnormalities, necessitated the discontinuation of treatment after 17 days. On discharge 4 weeks later, the patient was stabilized and afebrile with a normal spleen, normal complete blood count, normal gammaglobulins, and decreasing antibody titers to Leishmania. During the next 24 months, the patient experienced intermittent episodes of abdominal pain, decreased appetite, recurrent arthralgia, and myalgia. But at his last examination in January 1998, he was well; all symptoms mentioned above had disappeared.

Because the child had never left Germany, nonvector transmission was suspected and household contacts were examined. His mother was the only one who had a positive antibody titer against Leishmania donovani complex. She had traveled several times to endemic Mediterranean areas (Portugal, Malta, and Corse) before giving birth to the boy. But she had never had an asymptomatic mother. Her bone marrow, spleen, and liver biopsy results were within normal limits. Culture results and polymerase chain reaction of this material were negative. A Montenegro skin test result was positive, indicating a previous infection with Leishmania. Western blot analysis showed specific recognition by maternal antibodies of antigens of Leishmania cultured from the boy’s tissue.

Visceral leishmaniasis is endemic to several tropical and subtropical countries, but also to the Mediterranean region. It is transmitted by the sand fly (Phlebotomus, Lutzomyia). Occasional nonvector transmissions also have been reported through blood transfusions, sexual intercourse, organ transplants, excrements of dogs, and sporadically outside endemic areas. Only 8 cases of congenital acquired disease have been described before 1995, when our case occurred.

In our patient, additional evaluation showed that the asymptomatic mother must have had a subclinical infection with Leishmania that was reactivated by pregnancy, and then congenitally transmitted to the child. Visceral leishmaniasis has to be considered in children with fever, pancytopenia, and splenomegaly, even if the child has not been to an endemic area and even if there is no evidence of the disease in his environment, because leishmaniasis can be transmitted congenitally from an asymptomatic mother to her child. Pediatrics 1999;104(5).

URL: http://www.pediatrics.org/cgi/content/full/104/5/e65; visceral leishmaniasis in infants, kala azar, congenital transmission, nonvector transmission.

ABBREVIATIONS. EIA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; CF, complement fixation test; ECG, electrocardiogram; PCR, polymerase chain reaction.

Visceral leishmaniasis is endemic to several tropical and subtropical countries but also to the Mediterranean region. It is transmitted by the sand fly (Phlebotomus, Lutzomyia). Occasional nonvector transmissions also have been reported through blood transfusions, sexual intercourse, organ transplants, excrements of dogs, and sporadically outside endemic areas. Only 8 cases of congenital acquired disease have been described before 1995. In all these case reports, the mothers were asymptomatic. In this article, we report the case of a boy who acquired the disease congenitally by transmission from his asymptomatic mother.

METHODS

All diagnostic procedures and the treatment of the boy were conducted at the Children’s Hospital of Stuttgart in Germany. The serologic tests on Leishmania donovani species included enzyme-linked immunosorbent assay (EIA; cutoff values: weak positive ≥10 antibody units and strong positive ≥30 antibody units), immunofluorescence assay (IFA; cutoff values: weak positive titers ≥1:20 and strong positive titers ≥1:80), and complement fixation.
tests (CFs; cutoff values: weak positive titers ≥1:4 and strong positive titers ≥1:16). The cultivation of liver and bone marrow biopsy material was performed in 5 mL 0.9% saline on brain heart infusion agar, supplemented with defibrinated rabbit blood (Difco, Detroit, MI) and incubated at 25 to 26°C for 5 days. Then the promastigote form of Leishmania was detected by microscopy. The serologic tests, the cultivation, the microscopic examinations, and the Western blot analysis of the mother’s serum against Leishmania antigens from the child were performed at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany. The identification of the promastigotes was performed by Southern blot analysis, using probe pDK209 at the Royal Tropical Institute, Department of Biomedical Research in Amsterdam, the Netherlands.

CASE REPORT

In February 1995, a 16-month-old boy from a small village in southwestern Germany was admitted to the Children’s Hospital of Stuttgart with a 4-week history of intermittent fever up to 40°C, decreased appetite, weakness, fatigue, and difficulty sleeping. He was born to a 31-year-old prima gravida, prima para at 40 weeks’ gestation by vacuum extraction with a birth weight of 3720 g and a length of 53 cm. The mother’s pregnancy was complicated by a febrile gastroenteritis, but the newborn was healthy, and the child remained healthy for the first year of his life. At 15 months of age, he developed fever, enlarged cervical lymph nodes, poor appetite, and a transient icterus with elevated liver function tests. A presumptuous diagnosis of infectious mononucleosis was made. Because the symptoms persisted for >3 weeks, however, he was readmitted to the hospital for additional evaluation and treatment. Physical examination on admission showed a 16-month-old febrile male in mild distress. There were no signs of meningitis, and ear, nose, and throat examination results were normal, with normal lung and heart auscultation. The examination was remarkable for enlarged cervical, axillary, and inguinal lymph nodes (3 × 8 cm, 1 × 2 cm, and 2 × 4 cm, respectively), as well as hepatosplenomegaly (4 and 6 cm below the costal margin, respectively). Laboratory data revealed a normal erythrocyte sedimentation rate (10 mm per hour), pancytopenia (hemoglobin 7.8 g/dL, leukocytopenia with an absolute neutrophil count of 100–200/μL, platelets 40 000/μL), elevated liver function tests (serum glutamic oxaloacetic transaminase 153 U/L, serum glutamic pyruvate transaminase 184 U/L, lactic acid dehydrogenase 467 U/L), with normal bilirubin levels, and hypergammaglobulinemia (immunoglobulin G 2577 mg/dL). The results of a chest radiograph were within normal limits. Abdominal sonography verified the hepatospleno-megaly. Cardiac echography showed a mild pericardial effusion. The results of three blood cultures were negative. Urine analysis and stool and urine culture results were also negative. Serologic studies showed no evidence of brucellosis, leptospirosis, or Epstein-Barr virus infection. Human immunodeficiency virus infection, rheumatologic, and autoimmune disorders were ruled out. A bone scan was negative, and a bone marrow aspirate showed no evidence of malignancy, only a proliferation of lymphocytes and macrophages with increased hemophagocytosis. Because of the severity of the illness, an antibiotic treatment was initiated empirically, without any clinical improvement. After 7 weeks of intermittent fever, a positive titer for Leishmania antibodies (L. donovani complex, IFA 1:640, EIA 68, CF 1:32) was noted. The results were confirmed on a second specimen. In a repeat liver and bone marrow biopsy, the amastigote form of the parasite could not be seen in cells. Only by combined culture of both the liver and the second bone marrow biopsy material was the promastigote form of Leishmania found and the diagnosis of visceral leishmaniasis made. The parasite was identified as Leishmania infantum using Southern blot analysis.

Specific therapy with the antimonial compound sodium stibogluconate (Pentostam; Wellcome Foundation, London, UK) at a dose of 20 mg/kg body weight was begun immediately after the biopsies were taken, given once daily intravenously (Fig 1). Within 4 days, the patient became afebrile but developed hematemesis, elevation of liver enzymes, and electrocardiogram (ECG) abnormalities, necessitating discontinuation of treatment. After the status of the patient improved, treatment was restarted. The side effects of the treatment, including erosive gastritis, cholelithiasis, worsening hepatosplenomegaly, and pancreatitis necessi-

Fig 1. Clinical, biochemical, and therapeutic course of visceral leishmaniasis in our patient
tated the discontinuation of treatment after 17 days. The patient stabilized and was discharged from the hospital 4 weeks after treatment with Pentostam. On discharge, he was afebrile with a normal spleen, normal complete blood count and gammaglobulins, and decreasing antibody titers to *Leishmania*. During the next 24 months, the patient experienced intermittent episodes of abdominal pain, decreased appetite, recurrent arthralgia, and myalgia. His hepaticomegaly slowly resolved, however, and there was no recurrence of splenomegaly or fever. His physical examination remained unremarkable and the antibody titers to *Leishmania* were low (in November 1996, IFA 1:20, EIA negative, CF negative). No objective signs of rheumatologic, immunologic, or neurological diseases were found during detailed investigations in March 1997 at the University Children's Hospital of Tübingen. Antibody titers remained low, polymerase chain reaction (PCR) was negative, and bone marrow aspirate was normal. At his last examination in January 1998, the boy was well and all of the symptoms that were mentioned above had disappeared.

Because the child had never left Germany, transmission by the sand fly could be excluded. Household contacts (including the family's dog) were examined. His mother was the only one who had a positive antibody titer against *L. donovani* complex (IFA 1:40, EIA 16, CF 1:4). The mother had traveled to several endemic Mediterranean countries 2, 5, and 6 years before giving birth to the boy (Table 1). She had never had any symptoms compatible with visceral leishmaniasis. Her bone marrow, spleen, and liver biopsies were within normal limits. Culture and PCR of this material were negative. A Montenegro skin test result (test for cutaneous delayed hypersensitivity response to a killed promastigote preparation called leishmanin) was positive, indicating a previous infection with *Leishmania*. Western blot analysis showed specific recognition by maternal antibodies of antigens of *Leishmania* cultured from the boy's tissue. Neither the mother nor the child had ever received a blood transfusion.

### DISCUSSION

Infections with the protozoan parasite *Leishmania* can lead to three different forms of disease: cutaneous, mucocutaneous, and visceral leishmaniasis. Visceral leishmaniasis, also called kala azar, is usually caused by *L. donovani*, *L. infantum*, or *L. chagasi* and rarely by *L. tropica* or *L. mexicana*. These are protozoan parasites that are generally transmitted by sand flies and then disseminate in the body of their host by infecting macrophages in multiple organs, but particularly in the spleen, liver, bone marrow, and lymph nodes. The clinical incubation period ranges typically from 6 weeks to 6 months but can vary from 10 days to >10 years. The course of the disease is identical in children and adults. It may begin either suddenly with high fevers, vomiting, diarrhea, and coughing, or insidiously with irregular daily increasing fever, poor appetite, weight loss, lassitude, and pallor. Later characteristic findings are splenomegally, fever up to 41°C with a pattern of double daily spikes (however, this pattern is seen rarely), recurrent respiratory and intestinal infections, pancytopenia, and hyperglobulinemia. Hepatomegaly, lymphadenopathy, and general bleeding diathesis may follow. Untreated, the disease is fatal in 90% of cases after 1 to 3 years. Diagnosis should be confirmed either by microscopic identification of the amastigote or promastigote form of the parasite in liver, spleen, or bone marrow biopsies, or by detection of the desoxyribonucleic acid of *Leishmania* by PCR in blood or biopsy material. The mainstay treatment is with pentavalent antimony (20 mg/kg intravenously in the form of sodium stibogluconate once daily for 28 days), which reduces mortality from 90% to 1 to 15%. Side effects may occur, including nausea, vomiting, jaundice, ECG abnormalities, elevation of liver enzymes, pancreatitis, worsening of hepatomegaly, bleeding diathesis, and thrombocytopenia. Other accepted drug regimens include meglumine antimonate (Glucantime, 60–100 mg/kg intramuscularly once daily for 14–28 days). The daily intramuscular injection may cause painful local inflammation. Toxicity is similar to sodium stibogluconate but side effects include renal failure and sudden death. Allopurinol (15 mg/kg per day) in combination with antimonials may reduce the rate of relapse. Pentamidine (2–4 mg/kg daily intramuscularly or intravenously for 15 days or every second day for 30 days) and amphotericin B (1 mg/kg intravenously on alternate days giving a total dose of 30–35 mg/kg) show much more toxicity and are used only as second-line regimens. Liposomal amphotericin B (Ambisome) is more expensive but less toxic and more efficient than conventional amphotericin B. Recent studies in children suggest that even in comparison with pentavalent antimonials, it may provide better results, shorter courses of treatment, lower costs of hospitalization, and fewer side effects. Two alternative regimens are recommended: a daily dose of 3 mg/kg for 10 days or a daily dose of 3 mg/kg only on days 0, 1, 2, 3, 4, and 10.11,12

Congenital visceral leishmaniasis was described first in 1926 by Low and Cooke.1 Seven more case reports had been published until 1995, when our case occurred.2–8 One more case report has been published since13 (Table 2). The course of the disease seems to be identical in congenital transmitted and otherwise acquired kala azar. Most of the children developed the disease in the first year of life. However, in congenital cases the route of transmission remains unclear. Most likely the infection occurs during labor via blood exchange from the mother to the child. Transplacental transmission during pregnancy before birth is rather unlikely, because no parasites were found in the organs of an aborted fetus of 5 months' gestational age who was born to a 30-year-old infected mother in Sudan while the placenta showed large numbers of amastigotes.7

### TABLE 1. Mother’s Travel History to Endemic Mediterranean Countries

<table>
<thead>
<tr>
<th>Date</th>
<th>Country</th>
<th>Area</th>
<th>Mosquito Bites</th>
</tr>
</thead>
<tbody>
<tr>
<td>September 1988</td>
<td>Portugal</td>
<td>West coast, south of Porto (2 d)</td>
<td>20 to 30 severe bites, 2 resulting in permanent scarring</td>
</tr>
<tr>
<td>August 1989</td>
<td>Malta</td>
<td>Nazaré (10 d) South coast, near Marsaxlokk (18 d)</td>
<td>Bad big bite on left foot; needed 6 mo to heal</td>
</tr>
<tr>
<td>July through August 1992</td>
<td>France</td>
<td>Corse, north part (10 d); south west part (5 d)</td>
<td></td>
</tr>
</tbody>
</table>

http://www.pediatrics.org/cgi/content/full/104/5/e65
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A RARE CASE OF CONGENITAL LEISHMANIASIS

Each year 500,000 new infections with visceral leishmaniasis occur. According to the World Health Organization, the ratio of subclinical to clinical infections is 5:1. A study from Kenya suggested that asymptomatic persons can be a reservoir of Leishmania parasites for expended periods. Patients can develop leishmaniasis years and even decades after traveling to an endemic area, if they become immunosuppressed. During pregnancy, a shift from cell-mediated to humoral immunity has been described in mice as well as in humans. Therefore, females may have a higher susceptibility to leishmaniasis during pregnancy, as has been shown recently in mice. This also may suggest that pregnancy can trigger (re)activation of leishmaniasis.

In our patient, visceral leishmaniasis started insidiously. On hospital admission, the patient presented with intermittent fever, lymphadenopathy, hepatosplenomegaly, and pancytopenia. Bacterial infections, autoimmune disorders, and malignancies were ruled out. An unusual infection was suspected. Although the patient had no travel history to any endemic country, a laboratory diagnosis of visceral leishmaniasis was made. The diagnosis was confirmed by culture. The promastigote parasite could be identified as L. infantum. (PCR was not available at our hospital and institute at that time).

Additional evaluation showed that the asymptomatic mother was the only potential carrier in the environment of the child who showed antibody titers against Leishmania. Therefore, she must have had a subclinical infection that could have been reactivated by pregnancy, which was then transmitted congenitally to the child. The flu-like symptoms that the mother described in early pregnancy might represent nonspecific signs of reactivation. The mother’s positive Montenegro skin test result and the negative culture result for Leishmania suggest that the parasites persisted after infection and eventually reappeared during pregnancy to induce parasitemia but after pregnancy were suppressed in the mother by cellular immunity. She most likely contracted the disease years before this pregnancy during her journeys to several endemic Mediterranean areas: Portugal, Malta, and Corse. The prevalence of visceral leishmaniasis in this area is not known, but the latest available reports show 70, 8, and 3 new cases each year, respectively. Leishmania infantum is endemic to the whole Mediterranean region.

During therapy with pentavalent antimony (Pentostam), our patient developed hematemesis and gastrointestinal bleeding, which may be part of the disease. There is evidence about a toxic effect of Pentostam on the platelets that could have aggravated the bleeding. Most likely, the elevation of liver enzymes and ECG changes were also side effects. Temporary discontinuation of treatment is necessary when these side effects occur. We do not know whether treatment with liposomal amphotericin B might have minimized the complications in our case. Future studies are needed to evaluate the advantages of this medication.

Three years after discharge from the hospital, our patient is a normally developed 4-year-old boy. He has a younger brother who is now 2 years old. The brother never showed any signs of leishmaniasis and is seronegative for the disease.

### TABLE 2. Reported Cases of Congenital Kala Azar

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Mother</th>
<th>Age and Symptoms of Child</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/Cooke</td>
<td>1926</td>
<td>England</td>
<td>Yes</td>
<td>2 wk: convulsion, bad feeding</td>
<td>Antimone as Stibosan (75 mg/d)</td>
<td>Cured</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(India)</td>
<td></td>
<td>7 wk: diarrhoea, pain, failure to thrive</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mo: weight loss, fever, splenomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Banerji</td>
<td>1955</td>
<td>India</td>
<td>Yes</td>
<td>6 mo: fever, hepatosplenomegaly</td>
<td>Antimone as Stibanin (glucamine antimonate) 500 mg/d</td>
<td>Cured (after 1 recurrence) Cured</td>
</tr>
<tr>
<td>Blanc</td>
<td>1984</td>
<td>France</td>
<td>Yes</td>
<td>7 mo: weight loss, fever, icterus, hepatosplenomegaly, adenopathy</td>
<td>Glucantime 100 mg/kg/d for 12 d</td>
<td>Cured</td>
</tr>
<tr>
<td>Mittal</td>
<td>1987</td>
<td>India</td>
<td>Yes</td>
<td>8 mo: fever, cough, hepatosplenomegaly</td>
<td>Glucantime 100 mg/kg/d for 12 d</td>
<td>Cured</td>
</tr>
<tr>
<td>Nyakundi</td>
<td>1988</td>
<td>Kenya</td>
<td>Yes</td>
<td>Premature, born after 6 months’ GA 6 d: poor feeding</td>
<td>Pentostam (sodium stibogluconate) 20 mg/kg/d</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 mo: pneumonia, urinary tract infection (specific symptoms not reported)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yadav</td>
<td>1989</td>
<td>India</td>
<td>Yes</td>
<td>6 wk: 3 mo: fever and diarrhoea</td>
<td>Glucantime 100 mg/kg/d for 2 wk</td>
<td>Parasite free bone marrow 2 wk after therapy Died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10 mo: fever, hepatosplenomegaly, dystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>El-Toum</td>
<td>1992</td>
<td>Sudan</td>
<td>Yes</td>
<td>Birth: small for gestation age 7 mo: fever, cough, hepatosplenomegaly</td>
<td>Pentostam</td>
<td>Died</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dystrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elamin</td>
<td>1992</td>
<td>Sudan</td>
<td>Yes</td>
<td>4 wk: fever, hepatosplenomegaly</td>
<td>Pentostam</td>
<td>Died</td>
</tr>
<tr>
<td>Our case</td>
<td>1995</td>
<td>Germany (Mediterranean)</td>
<td>No</td>
<td>12 mo: poor appetite, weight loss, recurrent infections</td>
<td>Pentostam 20 mg/kg/d for 17 d</td>
<td>Cured, no recurrence until now</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15 mo: fever, cough, lymph-adenopathy, icterus, hepatosplenomegaly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sharma</td>
<td>1996</td>
<td>India</td>
<td>No</td>
<td>18 mo: failure to thrive, anemia, splenomegaly</td>
<td>Not reported</td>
<td>Cured</td>
</tr>
</tbody>
</table>

GA indicates gestational age.
CONCLUSION

If an infant presents with fever, pancytopenia, and splenomegaly, leishmaniasis has to be considered if the child is in an endemic area. Our report shows that visceral leishmaniasis has to be considered even if the child has not been to an endemic area and even if there is no evidence of the disease in his environment, because leishmaniasis can be transmitted congenitally from an asymptomatic mother to her child. Beyond this, in endemic areas, congenital transmission may occur much more often than is known. Therefore, more detailed investigations on this question may be warranted in endemic areas.

REFERENCES

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Congenital Transmission of Visceral Leishmaniasis (Kala Azar) From an Asymptomatic Mother to Her Child
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