Suspected Brazilian Purpuric Fever in a Toddler with Overwhelming Epstein-Barr Virus Infection


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We describe a toddler from Connecticut who developed purulent conjunctivitis, fever, and a morbilliform rash. Blood cultures were positive for Haemophilus influenzae biogroup aegyptius; further investigation was performed to assess the possibility that the illness was consistent with Brazilian purpuric fever, which, to our knowledge, has not been reported in the United States. This isolate shared morphological and some biochemical characteristics with previously studied H. influenzae biogroup aegyptius strains but differed according to slide agglutination testing, plasmid characterization, and ribotyping. Blood and tissue samples obtained during his hospitalization were also positive for Epstein-Barr virus. The child died 8 days after hospitalization. Fifty other cases of invasive H. influenzae infection were identified by active surveillance studies. Of the 49 viable surveillance isolates, 10 were biotype III (two of which had the same ribotype as the strain from our case).

Brazilian purpuric fever (BPF) is a fulminant childhood septicemia preceded by conjunctivitis and caused by Haemophilus influenzae biogroup aegyptius [1]. BPF has been recognized only in Brazil and Australia; no cases have been reported in the United States [1–4]. We describe a previously healthy child from Connecticut who developed a fatal illness consistent with BPF.

Case Report

A 17-month-old male toddler was in good health until 1 month before admission when he presented with a 10-day history of purulent conjunctivitis accompanied by symptoms of an upper respiratory tract infection. Despite empirical antimicrobial therapy with amoxicillin/clavulanate, cefaclor, and clarithromycin, his symptoms did not abate, but the conjunctivitis resolved. Twenty-four days after the onset of conjunctivitis, he was brought to the emergency department of hospital A because of fever and lethargy; a diagnosis of otitis media was made, and he was discharged with instructions to continue clarithromycin therapy. Five days later, he was brought back to hospital A because of continuation of his fever and rigors and was subsequently transferred to hospital B for admission. Blood specimens for culture were obtained before transfer.

The child lived at home with his parents and two siblings in southeastern Connecticut. There was no history of recent travel outside the state. He did not attend day care. The eldest sibling (5 years old) and one cousin (4 years old) who lived in a different household both had conjunctivitis that was diagnosed in the 2 weeks before conjunctivitis was diagnosed for the patient. The other sibling (3 years old) had an episode of fever and vomiting without conjunctivitis during the 2 weeks before the patient’s hospitalization. There was no history of familial illness.

Physical examination at the time of admission to hospital B revealed a boy with fever (temperature, 102.4°F), tachycardia, tachypnea, and normotension. He was pale and icteric with labored breathing, rhonchi, a soft systolic murmur, and hepatosplenomegaly. There was no documentation of conjunctivitis. A morbilliform rash was noted over his lower extremities. He was lethargic with no meningeal signs and had no focal deficits.

Laboratory studies revealed pancytopenia, an absolute neutrophil count of 660/mL (with a few atypical lymphocytes evident on a peripheral blood smear), abnormal liver function, elevated prothrombin and partial thromboplastin times, and an abnormal D-dimer level (0.5–1.0 g/mL). A chest roentgenogram showed bilateral pleural effusions and interstitial infiltrates. Urinalysis demonstrated hematuria and mild proteinuria. Immunofluorescence revealed that titers of IgG antibody and IgM antibody to Epstein-Barr virus (EBV), early antigen, and Epstein-Barr nuclear antigen were positive (1:1,280 and 1:640, respectively), negative, and positive, respectively. The test for heterophile antibody was negative. EIA was positive for antibody to cytomegalovirus. Tests for antibodies to hepatitis A, B, and C viruses were all negative. A bone marrow biopsy showed severe hypocellularity, increased reticulin deposition, and a marked histiocytic infiltrate.
Blood cultures from hospital A yielded a nontypeable strain of *H. influenzae*. Cultures of blood obtained at the time of admission to hospital B were positive within 24 hours for small gram-negative bacilli. There was growth on chocolate agar alone. On the haemophilus identification quad plate (Remel, Lenexa, KS), there were nonhemolytic colonies that grew only in the presence of both factors X and V. Biochemical analysis showed that this isolate was *O*-nitropheryl-β-d-galactoside–negative, ornithine decarboxylase–negative, and urease-positive. It was identified as unencapsulated *H. influenzae* biotype III and was sent to the Connecticut Department of Public Health (Hartford) for further testing.

At the time of admission, the patient was treated with penicillin G, imipenem, corticosteroids, and intravenous immunoglobulin. After the identification of *H. influenzae* G, imipenem, and was sent to the Connecticut Department of Public Health (Hartford) for further testing. Of the 49 viable surveillance strains received from Connecticut, 29 were nontypeable (10 of which were biotype III). Two of the biotype III strains had the same ribotype as that of the strain from our case. Review of the medical records of the two patients from whom these strains were isolated revealed that both were elderly patients for whom pneumonia was diagnosed who lived in counties not adjacent to the one our patient lived in.

Postmortem blood cultures were positive for *Enterobacter cloacae* and *Enterococcus faecalis*. An autopsy revealed massive hepatic necrosis, bone marrow necrosis with hemophagocytosis, generalized lymphoid necrosis with multifocal bronchopneumonia, and disseminated intravascular coagulopathy, findings compatible with sepsis and fulminant infectious mononucleosis. By using a PCR assay for the quantitative determination of EBV genomes [5], it was shown that a premortem peripheral blood sample contained >50,000 EBV genomes per 100,000 WBCs. In situ hybridization [6] of postmortem tissue samples from the liver, spleen, lymph nodes, and lung revealed EBV RNA.

Cultures of conjunctival specimens from the patient’s siblings and the cousin with a history of conjunctivitis failed to yield *H. influenzae*. Family members received rifampin as prophylaxis [7], and no one developed illness consistent with BPF.

Analysis of the patient’s isolate at the Centers for Disease Control and Prevention (CDC) confirmed that it was nontypeable *H. influenzae*. The isolate required factors X and V for growth and was negative for indole, porphyrin, ornithine decarboxylase, and acidification of D-xylose. The isolate was resistant to troleandomycin and was positive for urease and alkaline phosphatase. The isolate was susceptible to trimethoprim-sulfamethoxazole and was β-lactamase-positive, a characteristic differing from most previously described isolates causing BPF [8]. The isolate differed from the specific strains found to cause BPF in Brazil and Australia because it was negative according to slide agglutination testing with the polyclonal antiserum prepared at the CDC, had a ribotype other than 3 or 4, and did not harbor the typical 3031 plasmid (a 24-MD plasmid present in all strains causing BPF in Brazil, except the isolates obtained from the cases occurring in Valparaiso) [9].

The Connecticut Emerging Infections Program (Hartford) conducts active population and laboratory-based surveillance studies, by using methods previously reported [10], for a variety of organisms (including invasive *H. influenzae*). Between 1 March 1995 and 31 January 1996, 50 additional cases of invasive *H. influenzae* infection were described in Connecticut residents. None of these infections were associated with clinical illnesses consistent with BPF. The isolates were sent to the CDC for further testing. Of the 49 viable surveillance strains received from Connecticut, 29 were nontypeable (10 of which were biotype III). Two of the biotype III strains had the same ribotype as that of the strain from our case. Review of the medical records of the two patients from whom these strains were isolated revealed that both were elderly patients for whom pneumonia was diagnosed who lived in counties not adjacent to the one our patient lived in.

**Discussion**

BPF was first recognized in 1984 when 10 children died of an acute febrile illness associated with purpura and hypotension in a rural town in São Paulo State, Brazil [1]. Attack rates during outbreaks of BPF have reached 2.3 cases per 1,000 children younger than 10 years of age, and case-fatality rates can be 70% [11]. Although clinically similar to meningococcemia, this illness is distinguished by the absence of meningitis and by a strong statistical association between illness and a history of conjunctivitis. Characteristically, the conjunctivitis is resolving or has resolved by the time that more severe symptoms occur. During the initial outbreaks in 1984, multiple cultures (including viral), serologies, and necropsy examinations did not reveal a cause [1]. In 1986, *H. influenzae* biogroup aegyptius was isolated from samples from both conjunctivae and normally sterile sites in patients with BPF, thus suggesting a direct role for this agent in the pathogenesis of the illness [1].

Harrison et al. [11] developed the following case definition for BPF: a febrile illness in a child along with isolation of *H. influenzae* biogroup aegyptius from a normally sterile body site or an acute febrile illness in a child 3 months to 10 years old that is characterized by fever (temperature, ≥101.3°F), abdominal pain and/or vomiting, development of petechiae or purpura, and no evidence of meningitis; a history of conjunctivitis within the 30 days preceding the onset of fever; and absence of *Neisseria meningitidis* infection as determined by cultures of blood specimens obtained before antibiotic administration or by detection of antigen in serum or urine. In addition, if samples are obtained, CSF should have ≤100 leukocytes/L and be negative by culture or antigen detection for pathogenic bacteria other than *H. influenzae* biogroup aegyptius, and serological studies should be negative for known pathogens other than *H. influenzae* biogroup aegyptius.

*H. influenzae* biogroup aegyptius has long been recognized as a common cause of seasonal epidemics of conjunctivitis in the southern United States and other parts of the world [12–15]. Previously known as *Haemophilus aegyptius* or the Koch-Weeks bacillus, this organism was shown by phenotypic and genetic studies to be highly related to *H. influenzae* and was
designated *H. influenzae* biogroup aegyptius in 1988 [8, 16]. It remains difficult to distinguish *H. influenzae* biogroup aegyptius from other unencapsulated *H. influenzae* strains, especially biotype III, by routine laboratory methods. Cellular morphology, susceptibility to troleandomycin, ability to grow on tryptic soy agar with factors X (protoheme) and V (nicotinamide adenine dinucleotide), ability to agglutinate human erythrocytes, and inability to produce acid from D-xylose have been described as differential characteristics; however, none of these characteristics have proved to be absolutely discriminatory [8].

EBV, the causative agent of infectious mononucleosis, is a ubiquitous B cell tropic virus that normally infects children at an early age [17, 18]. Infectious mononucleosis is typically a self-limited illness characterized by fever, pharyngitis, and adenopathy. Primary EBV infections, with or without the features of infectious mononucleosis, have many nonfatal complications, including hemolytic anemia, thrombocytopenia, encephalitis, hepatitis, splenic rupture, and glomerulonephritis. However, primary progressive and ultimately fatal EBV infections can arise in presumed healthy patients who have undetected deficiencies of cellular immunity, either congenital or acquired [19].

In the absence of *H. influenzae* biogroup aegyptius bacteremia and the isolate’s characteristics, most of patient’s symptoms and hospital course could be attributed to fulminating infectious mononucleosis. Although the medical history did not indicate that the child was immunosuppressed before the onset of this illness and there was no indication for a genetic predisposition, the clinical course, high number of EBV genomes, bone marrow necrosis with hemophagocytosis, and tissue necrosis suggest the possibility of an X-linked lymphoproliferative disorder (i.e., Duncan’s disease).

The syndrome of purulent conjunctivitis preceding an acute febrile illness in a child younger than 10 years of age along with isolation of *H. influenzae* biogroup aegyptius from a normally sterile body site is consistent with BPF. In addition, the resolution of conjunctivitis before the onset of systemic disease is consistent with the usual clinical course of BPF. This phenomenon raises the possibility that the bacterium may be eliciting antibodies that block its killing [20, 21]. The contribution of *H. influenzae* biogroup aegyptius bacteremia to the patient’s illness and subsequent death is unclear. Although not identical to the organisms that caused outbreaks in Brazil, this organism demonstrated its potential to cause invasive disease. This case emphasizes the need to gain better understanding of the virulence factors associated with *H. influenzae* biogroup aegyptius and their possible interactions with host factors.

**Acknowledgments**

The authors thank Ms. Patricia Mshar (Epidemiology Service) and Dr. Dale Vance (Biological Sciences Service) of the Connecticut Department of Public Health (Hartford) for their assistance.

**References**


