Recurrent *Achromobacter xylosoxidans* Bacteremia Associated with Persistent Lymph Node Infection in a Patient with Hyper-IgM Syndrome

Jörn-Hendrik Weitkamp, Yi-Wei Tang, David W. Haas, Narinder K. Midha, and James E. Crowe, Jr.

*Departments of 1Pediatrics, 2Medicine, 3Pathology, and 4Microbiology and Immunology, Vanderbilt University Medical Center, Nashville, Tennessee*

*Achromobacter xylosoxidans* (formerly *Alcaligenes xylosoxidans*) is a rare but important cause of bacteremia in immunocompromised patients, and strains are usually multiply resistant to antimicrobial therapy. We report an immunocompromised patient with hyper-IgM syndrome who suffered from 14 documented episodes of *A. xylosoxidans* bacteremia. Each episode was treated and resulted in rapid clinical improvement, with blood cultures testing negative for bacteria. Between episodes, *A. xylosoxidans* was isolated from an excised right axillary lymph node, whereas the culture of the central venous catheter, removed at the same time, was negative. Multiple cultures from sputum, stool, and urine samples, as well as from gastrointestinal biopsies or environmental sources, were negative. Results from antibiotic sensitivity testing and pulsed-field gel electrophoresis suggested that a single strain of *A. xylosoxidans* caused the recurrent bacteremias in this patient; this strain originated from persistently infected lymph nodes. Lymphoid hyperplasia is a prominent characteristic of hyper-IgM syndrome and may serve as a source of bacteremia with low-pathogenicity organisms.

*Achromobacter xylosoxidans* is an aerobic, motile, oxidase and catalase-positive, non-lactose-fermenting, gram-negative bacillus. This organism was briefly classified as genus *Alcaligenes* but was recently reclassified as *Achromobacter* [1]. *A. xylosoxidans* has been isolated from blood, CSF, stool, urine, sputum, peritoneal fluid, skin, ear discharge, wounds, abscesses, bone, joints, endocardium, and central venous catheters [2–5]. Most published clinical reports about *A. xylosoxidans* describe nosocomial infections in immunocompromised patients [2, 3, 5–19]. Reported case-fatality rates have varied from 3% for primary or catheter-associated bacteremia to 80% for neonatal infection [6]. *Achromobacter* strains are frequently resistant to aminoglycosides, ampicillin, first- and second-generation cephalosporins, chloramphenicol, and fluoroquinolones but are usually susceptible to anti-*Pseudomonas* third-generation cephalosporins, imipenem, and trimethoprim-sulfamethoxazole [3, 10, 20–22].

Hyper-IgM syndrome (HIM) is characterized by low levels of circulating IgG and IgA, normal to increased IgM serum levels [23], and susceptibility to unusual infections. The most common form of HIM is X-linked and is caused by mutations in the gene encoding CD40 ligand (CD40L) located at Xq26 [24, 25]. Approximately 20% of male patients with HIM do not have mutations in the CD40L gene but instead have defects in CD40-mediated B cell activation [26]. This report describes a patient with the latter form of HIM. This patient suffered from recurrent episodes of bacteremia with *A. xylosoxidans* due to persistent infection of lymphoid tissues.

**Case Report**

A 1-month-old boy developed chronic otitis media and frequent upper respiratory infections. At 9 months of age, he had culture-negative meningitis, bilateral pneumonia, and persistent neutropenia. There was no family history of immunodeficiency. Quantitative serum immunoglobulin assays showed an IgM level of 100 mg/dL (normal range [NR], 33–126 mg/dL) [27], an IgD level of 0 mg/dL (NR, 0–8 mg/dL), an IgA level of <5 mg/dL (NR, 11–106 mg/dL), an IgG level of 26 mg/dL (NR, 172–1069 mg/dL), and an IgE level of <10 IU/mL (NR, 0–230 IU/mL). There were normal numbers of B and T cells, but peripheral blood and bone marrow B cells lacked membrane-associated IgG and IgA. The CD4– CD8+ T cell ratio and the T cell proliferative response to mitogens were normal. The WBC count was 7000 cells/mm<sup>3</sup> without segmented cells; however, the boy’s neutropenia resolved after the first year of life. The patient’s T cells had previously been shown to have normal binding to CD40 and lacked mutations in the CD40L gene, but the B cells had defective responses to activation mediated by CD40 stimulation [26]. Therefore, he was considered to have CD40L– positive HIM.

The boy was treated with iv immunoglobulin and glucocor-
ticoid therapy for marked lymphoproliferation. Other medical problems included protein-losing enteropathy with parenteral nutrition–dependent malabsorption, recurrent bilateral otitis media, recurrent pneumonia requiring right middle lobectomy, hypersplenism requiring splenectomy, and recurrent axillary lymphadenitis.

At age 12 years, *A. xylosoxidans* was first isolated from the patient in blood obtained through a central venous catheter. He subsequently experienced 13 other documented episodes of *A. xylosoxidans* bacteremia. These episodes were each associated with multiple symptoms, including low-grade fever, headache, nausea, diarrhea, hematochezia, abdominal distension, and dizziness. The patient exhibited generalized lymph node enlargement due to lymphoid hyperplasia associated with HIM but often also had further enlargement and inflammation of specific lymph nodes during bacteremic episodes. Each episode of *A. xylosoxidans* infection was treated either with iv imipenem plus tobramycin or with imipenem alone. Each course of therapy was continued for 7–14 days and resulted in rapid clinical improvement of the symptoms associated with the infection and sterilization of blood.

**Methods**

**Bacterial isolates.** Blood specimens were inoculated into Bactec Peds Plus/F bottles (enriched soybean-casein digest broth with CO₂) and processed by a nonradiometric system for blood culture (Bactec 9240; Becton Dickinson Microbiology Systems, Sparks, MD). Isolates were identified by the RapID NF Plus System (RE-MEL, Norcross, GA), which assigned biotype numbers that characterized the isolates as *A. xylosoxidans*. Classical culture methods and biochemical tests supported this identification: the organism produced nonpigmented colonies on MacConkey agar and was oxidase positive and indole negative on spot biochemical tests. Isolates were frozen at −70°C until subcultured for susceptibility testing and pulsed-field gel electrophoresis (PFGE).

**Microdilution susceptibility tests.** Antimicrobial MICs were determined in cation-adjusted Mueller-Hinton broth (BBL; Becton Dickinson Microbiology Systems) on Sensititre microdilution plates (Trek Diagnostic Systems, Westlake, OH) by use of an inoculum density of 3.8 × 10⁷ cfu/mL in each 50-μL well. Plates were incubated in ambient air at 35°C for 24 h. Susceptibility reporting was performed according to the National Committee for Clinical Laboratory Standards [28].

**Genomic DNA analysis by PFGE.** Genomic DNA was extracted from logarithmic-phase cultures of *A. xylosoxidans* isolates grown in brain-heart infusion broth (BBL; Becton Dickinson Microbiology Systems), prepared in low–melting-point agarose plugs, and digested with *Xba*I enzyme (New England Biolabs, Beverly, MA) for 24 h [29]. A bacteriophage lambda standard DNA size ladder was used (Bio-Rad Laboratories, Hercules, CA). Electrophoresis was performed with a GenePath system (Bio-Rad); we used the manufacturer’s dedicated program 2 for 20 h. Gels were stained with ethidium bromide and photographed under ultraviolet light with the Gel Doc 2000 computerized documentation system (Bio-Rad). Isolates were considered clonally related if there were fewer than 3 fragment differences, according to criteria described elsewhere [30]. PFGE of *Xba*I enzyme digested genomic DNA is an established method for reproducibly performing epidemiologic typing of *A. xylosoxidans* [31]. *Achromobacter* field strains exhibit a wide diversity of restriction fragment–length polymorphisms [29, 31, 32].

**Results**

Blood cultures were drawn through a Port-A-Cath central venous catheter (SIMS Deltec, St. Paul, MN) or from sites that were not indicated in the medical records (table 1). Over a 3.5-year period, 12 blood cultures obtained during 10 symptomatic episodes were positive for *A. xylosoxidans*. Isolates were not available for this study from 3 bacteremic episodes that occurred before this period. Cultures of environmental water sources, such as home drinking, tap, refrigerator, and air conditioner water, as well as central line flush fluids and total parenteral nutrition solutions, were negative for *A. xylosoxidans*. Furthermore, the organism was not isolated from sputum, stool, urine, or gastrointestinal biopsies. A culture of a surgically excised right axillary lymph node grew *Candida parapsilosis* and *A. xylosoxidans*. Histology of the lymph node demonstrated a polymorphous infiltrate composed of small and large lymphoid cells, plasma cells, and scattered histiocytes (figure 1). Multiple special stains were negative for microorganisms. Flow cytometry studies on cells obtained from the lymph node showed a predominance of T cells with no phenotypic abnormalities, compatible with a reactive lymphoid infiltrate (data not shown).

The central venous catheter was removed at the time of the right axillary lymph node excision at a time when the patient was not receiving antimicrobial therapy. The catheter tip did
not grow any organisms. A new central venous catheter was placed 1 week later, yet the patient continued to have recurrent *A. xylosoxidans* bacteremias.

Antimicrobial susceptibilities were similar for the lymph node isolate and blood isolates (table 1). The susceptibility pattern of 1 blood isolate with a single band shift on PFGE resembled the other isolates. All *Achromobacter* isolates were highly resistant to trimethoprim-sulfamethoxazole, ampicillin, ampicillin-sulbactam, amoxicillin-clavulanic acid, ticarcillin-clavulanic acid, cephalothin, cefepime, cefotaxime, ceftazidime, ciprofloxacin, and mezlocillin. All isolates except 1 were susceptible to amikacin, tobramycin, and imipenem. One blood isolate appeared to be resistant to imipenem and tobramycin and intermittently resistant to amikacin. During the latter episode, the patient’s symptoms resolved during therapy with imipenem and tobramycin, and blood culture tested negative for *A. xylosoxidans*.

Restriction patterns from 12 of 13 *A. xylosoxidans* isolates were found to be indistinguishable by PFGE; 1 blood isolate differed from the others by only a single fragment shift (figure 2, lane 10). This isolate was considered clonally related to the other isolates. The lymph node isolate demonstrated the same restriction pattern as the blood isolates (figure 2, lane 7).

### Discussion

*A. xylosoxidans* is a weakly virulent bacterium, and in most cases it infects immunocompromised hosts with indwelling catheters, endotracheal tubes, or other medical devices [2]. The bacterium may disseminate, causing sepsis, meningitis, and death. Cases of local and systemic infections with *A. xylosoxidans* have been reported in patients with HIV infection [5, 7, 9], cancer [11, 14], neutropenia [10], cystic fibrosis [33], bone marrow or liver transplant [15, 16], and IgM deficiency [8], as well as in neonates [12, 17, 18].

*Achromobacter* infection has not been previously reported in patients with either classical or CD40L-positive HIM. In one series, bacterial sepsis occurred in 8 (14%) of 56 patients with X-linked HIM, and infections were the cause of death for 6 (11%) [34]. *Escherichia coli* has been described as the predominant pathogen in bloodstream infections in X-linked HIM [34]. Infections caused by organisms more characteristic of T lymphocyte deficiency, such as *Pneumocystis carinii*, *Cryptococcus neoformans*, *Mycobacterium tuberculosis*, *Cryptosporidium*, *Cytomegalovirus*, and other viruses, have also been reported in cases of HIM [34, 35].

Although the gastrointestinal tract has been suggested as a source for *A. xylosoxidans* bacteremia in patients with cancer [11], repeated cultures from stool and gastrointestinal biopsies from this patient were negative for *Achromobacter* species. We considered whether persistent central venous catheter infection was the source of the bacteremias; however, removal of 7 different central venous catheters did not prevent recurrent *A. xylosoxidans* bacteremias. The catheter tip of the central venous catheter removed at the time of the infected right axillary lymph node excision was the only tip of the 7 removed catheters that was cultured. This tip did not grow bacteria. The sensitivity of catheter tip cultures for identifying *Achromobacter* species is unknown.

Epidemiological data suggest that water and moist soil are the natural sources of *A. xylosoxidans*. In nosocomial infections, *Achromobacter* species have been recov-

### Table 1. Susceptibilities of *Achromobacter xylosoxidans* isolated from a lymph node and from blood.

<table>
<thead>
<tr>
<th>Date of isolate</th>
<th>Source</th>
<th>Imipenem</th>
<th>Tobramycin</th>
<th>Gentamicin</th>
<th>Amikacin</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>31 October 1995</td>
<td>Blood (CVC)</td>
<td>&lt;2</td>
<td>2</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>21 November 1999&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Blood (NR)</td>
<td>&lt;2</td>
<td>4</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>24 November 1999&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Blood (CVC)</td>
<td>2</td>
<td>2</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>3 July 1996</td>
<td>Blood (CVC)</td>
<td>&lt;2</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>14 January 1997</td>
<td>Blood (NR)</td>
<td>&lt;2</td>
<td>4</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>iv Imi</td>
</tr>
<tr>
<td>16 September 1997</td>
<td>Blood (NR)</td>
<td>&lt;2</td>
<td>2</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>iv Imi</td>
</tr>
<tr>
<td>7 January 1998</td>
<td>Lymph node</td>
<td>2</td>
<td>4</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>...&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>29 April 1998</td>
<td>Blood (NR)</td>
<td>&lt;2</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>iv Imi</td>
</tr>
<tr>
<td>29 July 1998</td>
<td>Blood (NR)</td>
<td>&lt;2</td>
<td>2</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16</td>
<td>iv Imi</td>
</tr>
<tr>
<td>13 November 1998&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Blood (NR)</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>4</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>16 November 1998&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Blood (NR)</td>
<td>&gt;8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32&lt;sup&gt;d&lt;/sup&gt;</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>5 January 1999</td>
<td>Blood (NR)</td>
<td>&lt;2</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>iv Imi/iv Tm</td>
</tr>
<tr>
<td>16 February 1999</td>
<td>Blood (NR)</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
<td>iv Imi/iv Tm</td>
</tr>
</tbody>
</table>

**NOTE.** CVC, blood drawn through a percutaneously accessed subcutaneous central venous catheter; iv Imi, iv imipenem; NR, not reported; iv Tm, iv tobramycin. Results were interpreted according to National Committee for Clinical Laboratory Standards guidelines.

<sup>a</sup> Intermediate resistance.

<sup>b</sup> Separate isolates for a single symptomatic episode.

<sup>c</sup> The lymph node and the central venous catheter were removed. A culture of the central venous catheter tip was negative.

<sup>d</sup> Separate isolates for a single symptomatic episode.

<sup>e</sup> Resistance.
To our knowledge, A. xylosoxidans has not been isolated from any of multiple cultures from the patient’s environment or from an excised left cervical lymph node obtained when the patient was 14 years old. However, A. xylosoxidans was isolated from an excised right axillary lymph node when the patient was 16 years old. Although we obtained only these 2 lymph node cultures for culture, we believe that the latter lymph node may be representative of all of the hyperplastic lymphoid tissues as a possible reservoir of infection. It is unlikely that the second excised lymph node was the only persistently infected lymphoid source of the organism, because 6 episodes of bacteremia occurred after this lymph node removal. It is not clear whether the lymph node was infected as a result of hematogenous seeding during a previous bacteremia or a more localized process.

PFGE was used to analyze the clonality of the lymph node isolate. A. xylosoxidans was isolated from an excised right axillary lymph node when the patient was 16 years old. Although we obtained only these 2 lymph node cultures for culture, we believe that the latter lymph node may be representative of all of the hyperplastic lymphoid tissues as a possible reservoir of infection. It is unlikely that the second excised lymph node was the only persistently infected lymphoid source of the organism, because 6 episodes of bacteremia occurred after this lymph node removal. It is not clear whether the lymph node was infected as a result of hematogenous seeding during a previous bacteremia or a more localized process.

Figure 2. Pulsed-field gel electrophoresis patterns of XbaI-digested genomic DNA from lymph node and blood isolates of Achromobacter xylosoxidans in a patient with hyper-IgM syndrome show clonal relatedness. Lane M, molecular weight markers in kilobase (kb) pairs. Lanes 1–6 and lanes 8–13, blood isolates in chronological order. Lane 7, lymph node isolate.

Table 2.

<table>
<thead>
<tr>
<th>MW (kb)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>534</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>340</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>245</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>149</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>49</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Penetration of gentamicin, the MICs showed alternating values corresponding to either “sensitive” or “intermediate sensitive” ranges. However, these values were within the acceptable reproducibility of the test, which is within one 2-fold dilution of the end point [28]. The lymph node isolate demonstrated the same resistance pattern as the blood isolates, again suggesting that lymph nodes serve as a source for the recurrent A. xylosoxidans bacteremias in this patient. The resistance pattern of the 1 blood isolate with a single band shift in PFGE did not differ from that of the other isolates.

A. xylosoxidans is a rare but important cause of bacteremia in immunocompromised patients, and strains are usually multiply resistant to antimicrobial therapy. We have shown by sensitivity testing and molecular techniques that recurrent A. xylosoxidans bacteremias in a patient with HIM likely originated from persistently infected lymph nodes. Lymphoid hyperplasia, as in this patient, is a prominent characteristic of HIM. Such lymphoid tissues may harbor other low-pathogenicity organisms and serve as a source for bacteremia.

References