Aeromonas Bacteremia in Patients with Hematologic Diseases

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Over a 23-year period, 17 patients with hematologic diseases developed Aeromonas bacteremia while in our hematology ward. Male predominance (14 patients, 82%) was seen, with a predilection for the elderly. Hematologic malignancies, especially acute leukemia, accounted for 15 (88%) of all patients. Cancer chemotherapy and neutropenia (15 patients each) were the most common preceding host conditions. Aeromonas bacteremia generally occurred in the second half of the year (July–December), with no exposure to water or fish. Seven recent isolates comprised Aeromonas sobria (five isolates) and Aeromonas hydrophila (two isolates). Twelve patients (71%) showed a clinical picture ranging from mild gastroenteritis to severe enterocolitis. Anorectal and hepatobiliary infections were also noted in a few patients. The overall mortality rate was 35%. Ten (77%) of the 13 patients who were treated with aminoglycoside plus cephalosporin or carbapenem survived in association with marrow recovery.

Key words: acute leukemia, neutropenia, intestinal infections

Introduction

Aeromonas bacteremia, although uncommon, is most likely to occur in patients with hematologic malignancy, particularly acute leukemia (1). Among the gram-negative bacilli other than Enterobacteriaceae isolated from blood cultures of patients with acute leukemia, Aeromonas ranks second in incidence behind Pseudomonas aeruginosa (2). In contrast to P. aeruginosa bacteremia, however, Aeromonas bacteremia is little known. Most of such cases have been reported only anecdotally. We describe here 17 patients with hematologic diseases who developed Aeromonas bacteremia in our hematology ward during a 23-year period. This is, to our knowledge, the second largest series from a single institution next to that of 24 patients reported by Harris et al (3).

Patients and Methods

Patients studied

We reviewed the case records of all patients with hematologic diseases who had Aeromonas, alone or in combination with other organisms, isolated from one or more blood culture specimens in our hematology ward during the period from 1972–1994.

Bacteremia

The diagnosis of bacteremia was based on one or more positive blood cultures from a patient with a consistent clinical setting. The onset of bacteremia was regarded as being the time when the first positive blood culture was obtained.

Blood cultures

Blood cultures were carried out as previously described (2). Isolates of the motile, mesophilic Aeromonas species, often referred to collectively as the Aeromonas hydrophila complex, were identified according to the description of Cowan and Steel (4). In our bacteriology laboratory, from 1987 Oxy-Ferm Tube II (Japan Roche, Tokyo) has been used according to the manufacturer’s directions to identify the isolates as belonging to this complex of organisms. Species identification was performed on the latest seven isolates by the criteria of Popoff (5). Susceptibility testing was performed by the conventional disk diffusion method using Tridisks or KB Disks (Eiken, Tokyo).

Results

Patients with bacteremia

During the 23-year period, 17 patients with hematologic diseases in our department developed Aeromonas bacteremia (Table 1). The patient population showed a large numerical preponderance (14:3) of males over females, with a median age...
Table 1. Clinical Summary of Patients with Aeromonas Bacteremia

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age &amp; Sex</th>
<th>Disease to onset</th>
<th>Initial ANC (µl)</th>
<th>Initial BT (°C)</th>
<th>Presentation</th>
<th>Blood isolates</th>
<th>Shock</th>
<th>Prior treatment</th>
<th>Antibiotic treatment</th>
<th>Survival (days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64 M</td>
<td>AML</td>
<td>26</td>
<td>390</td>
<td>Abdominal</td>
<td>Aeromonas sp.</td>
<td>+</td>
<td>–</td>
<td>KM + GM</td>
<td>&gt;30</td>
<td>Mild left upper quadrant pain</td>
</tr>
<tr>
<td>2</td>
<td>51 M</td>
<td>AML</td>
<td>19</td>
<td>680</td>
<td>Abdominal</td>
<td>Aeromonas sp.</td>
<td>+</td>
<td>–</td>
<td>CET + KM</td>
<td>&gt;30</td>
<td>Abdominal pain, psoas abscess, subcutaneous nodules of both legs</td>
</tr>
<tr>
<td>3</td>
<td>63 M</td>
<td>AML</td>
<td>42</td>
<td>620</td>
<td>Anorectal</td>
<td>Aeromonas sp.</td>
<td>+</td>
<td>CBPC + GM</td>
<td>CEZ + GM</td>
<td>&gt;30</td>
<td>Anorectal abscess</td>
</tr>
<tr>
<td>4</td>
<td>50 M</td>
<td>AML</td>
<td>24</td>
<td>340</td>
<td>Abdominal</td>
<td>Aeromonas sp.</td>
<td>+</td>
<td>SBPC + GM</td>
<td>CEZ + AMK</td>
<td>17</td>
<td>Mild abdominal pain</td>
</tr>
<tr>
<td>5</td>
<td>60 M</td>
<td>AML</td>
<td>11</td>
<td>510</td>
<td>Anorectal</td>
<td>Aeromonas sp.</td>
<td>+</td>
<td>–</td>
<td>CEZ + GM</td>
<td>&gt;30</td>
<td>Anorectal abscess</td>
</tr>
<tr>
<td>6</td>
<td>74 M</td>
<td>AML</td>
<td>6</td>
<td>1,190</td>
<td>Hepatobiliary</td>
<td>Aeromonas sp.</td>
<td>+</td>
<td>–</td>
<td>PIPC + GM</td>
<td>11</td>
<td>Cholecystitis due to gallstones</td>
</tr>
<tr>
<td>7</td>
<td>50 M</td>
<td>AML</td>
<td>33</td>
<td>40</td>
<td>Pneumonia, anorectal, abdominal</td>
<td>Aeromonas sp.</td>
<td>–</td>
<td>–</td>
<td>SBPC + AMK</td>
<td>7</td>
<td>Anorectal abscess, abdominal pain, bloody diarrhea, disseminated aspergillosis at autopsy</td>
</tr>
<tr>
<td>8</td>
<td>58 M</td>
<td>AML</td>
<td>59</td>
<td>1,340</td>
<td>Hepatobiliary</td>
<td>Aeromonas sp.</td>
<td>–</td>
<td>–</td>
<td>Clostridium perfringens</td>
<td>&lt;30</td>
<td>Positive stool culture, obstructive cholangitis due to cholangiocarcinoma</td>
</tr>
<tr>
<td>9</td>
<td>57 M</td>
<td>AML</td>
<td>10</td>
<td>520</td>
<td>Abdominal</td>
<td>Aeromonas sp.</td>
<td>–</td>
<td>–</td>
<td>CMZ + GM</td>
<td>&gt;30</td>
<td>Positive stool culture, diarrhea</td>
</tr>
<tr>
<td>10</td>
<td>46 M</td>
<td>ALL</td>
<td>4</td>
<td>0</td>
<td>Abdominal</td>
<td>Aeromonas sp.</td>
<td>–</td>
<td>–</td>
<td>CMZ + GM</td>
<td>7</td>
<td>Abdominal pain, bloody diarrhea, positive stool culture</td>
</tr>
<tr>
<td>11</td>
<td>50 F</td>
<td>AML</td>
<td>9</td>
<td>0</td>
<td>Pneumonia, anorectal</td>
<td>A. sobria</td>
<td>–</td>
<td>–</td>
<td>CMZ + GM</td>
<td>16</td>
<td>Bloody diarrhea, disseminated aspergillosis at autopsy</td>
</tr>
<tr>
<td>12</td>
<td>77 M</td>
<td>NHL</td>
<td>18</td>
<td>220</td>
<td>Abdominal</td>
<td>A. sobria</td>
<td>–</td>
<td>–</td>
<td>CMZ + GM</td>
<td>&gt;30</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>13</td>
<td>58 F</td>
<td>SAA</td>
<td>110</td>
<td>10</td>
<td>Hepatobiliary</td>
<td>A. hydrophila</td>
<td>–</td>
<td>–</td>
<td>IPM + GM</td>
<td>&gt;30</td>
<td>Liver abscess</td>
</tr>
<tr>
<td>14</td>
<td>56 F</td>
<td>AML</td>
<td>160</td>
<td>0</td>
<td>Abdominal</td>
<td>A. sobria</td>
<td>–</td>
<td>–</td>
<td>CMZ + GM</td>
<td>&gt;30</td>
<td>Abdominal pain, bloody diarrhea</td>
</tr>
<tr>
<td>15</td>
<td>28 M</td>
<td>AML</td>
<td>59</td>
<td>0</td>
<td>Abdominal</td>
<td>A. sobria</td>
<td>+</td>
<td>–</td>
<td>IPM + GM</td>
<td>&gt;30</td>
<td>Abdominal pain, diarrhea</td>
</tr>
<tr>
<td>16</td>
<td>49 M</td>
<td>AML</td>
<td>72</td>
<td>39.4</td>
<td>Anorectal, abdominal, pneumonia</td>
<td>A. sobria</td>
<td>+</td>
<td>–</td>
<td>IPM + VCM</td>
<td>Not changed</td>
<td>Abdominal pain, bloody diarrhea, anorectal cellulitis, systemic CMV infection at autopsy</td>
</tr>
<tr>
<td>17</td>
<td>68 M</td>
<td>SAA</td>
<td>26</td>
<td>240</td>
<td>Abdominal</td>
<td>A. hydrophila</td>
<td>–</td>
<td>–</td>
<td>IPM + GM</td>
<td>&gt;30</td>
<td>Mild diarrhea</td>
</tr>
</tbody>
</table>


Incidence of bacteremia in patients with acute leukemia

During the study period, Aeromonas bacteremia occurred in 14 (2.6%) of 541 patients with acute leukemia, accounting for 4.3% of 329 episodes of bacteremia in this patient population. The frequency decreased from 8.9% (eight of 90 episodes) during the first 10-year period (1972–1981), to 3.3% (three of 91 episodes) during the last 5-year period (1990–1994), but with no statistically significant difference.

Contact with fish or water

Aeromonas bacteremia occurred after a median of 26 (range, 4–160) days of stay in hospital. None of the patients had had any known contact with fish or outdoor activities involving natural waters, either fresh or salt.

Seasonal occurrence of bacteremia

Fourteen patients (82%) developed Aeromonas bacteremia in the second half of the year, and the other three patients in the first half of the year (Fig. 1). None of the cases were associated in time, and the cases were evenly distributed over the years studied.

Isolates from blood

Blood cultures yielded Aeromonas twice or more in nine patients and only once in the other eight patients. In one patient...
(Case 8), *Aeromonas* was isolated together with *Clostridium perfringens*. The seven isolates speciated comprised *Aeromonas sobria* (five isolates) and *A. hydrophila* (two isolates).

Blood was the only site from which *Aeromonas* was isolated in 14 of all 17 patients. In the other three patients, the organism was isolated from surveillance stool cultures in addition to blood cultures.

**Preceding host conditions**

During the 10 days before the onset of bacteremia, cancer chemotherapy and neutropenia (<1,000/µl) (15 patients each) were the most common conditions, followed by thrombocytopenia (<50,000/µl) and hypoproteinemia (<6.5 g/dl) (13 patients each), and central venous catheterization (12 patients).

Four patients were receiving a β-lactam antibiotic (carboxypenicillin or carbapenem) combined with aminoglycoside or vancomycin for another infection at the onset of bacteremia. In these patients, each *Aeromonas* isolate proved resistant to the β-lactam drugs which had been administered when isolated, but sensitive to the aminoglycosides administered. One *A. sobria* isolate from a patient (Case 16) proved resistant to imipenem but susceptible to ceftazidime.

Steroid-induced diabetes was seen in three patients, including two with severe aplastic anemia. Leukemic relapse was associated with disseminated intravascular coagulation (three patients), and liver dysfunction with icterus and urate nephropathy (one patient each). In addition, one patient with acute leukemia had concomitant cholangiocarcinoma.

**Clinical manifestations**

A temperature elevation to 38.5°C or higher occurred in all but one of the 17 patients. Septic shock was documented in nine patients (53%), although it was considered to be the direct cause in only one patient (Case 16). Hypotension responded to conventional therapy in the other eight patients, but three of them died of uncontrollable underlying disease (Cases 4 and 6) or another systemic infection (Case 7). The clinical course of one patient (Case 2) was complicated by both psoas abscess and subcutaneous nodules of both legs. Incidentally, none of the patients developed ecchymatous lesions.

Abdominal symptomatology ranging from mild gastroenteritis to severe enterocolitis was observed in 12 (71%) of the 17 patients. Nine patients produced diarrhea, which contained blood in five, all with platelet counts below 40,000/µl. The anorectal region was the next most common site of infection prior to the onset of bacteremia (four patients), followed by the hepatobiliary tract (three patients).

**Outcome**

All but one of the 17 patients survived for a week or longer after the onset of bacteremia. All six patients who died within a month of onset presented refractoriness to various antileukemic therapies. Four of the five patients with bloody diarrhea died within a month of onset. In three of them, autopsy revealed gastrointestinal involvement of disseminated aspergillosis (two patients) or systemic cytomegalovirus infection (one patient).

In contrast, a favorable rise in neutrophil count during therapy was observed in eight of the 11 patients surviving beyond one month. Ten (77%) of the 13 patients who were treated with aminoglycoside plus cephalosporin or carbapenem survived beyond one month.

**Discussion**

The present study showed that *Aeromonas* bacteremia was most likely to occur in elderly male patients with acute leukemia during the second half of the year. In contrast to the report of Wolff et al (6), however, outdoor contact with fresh water or fish was not observed in the present patients, all of whom developed bacteremia while in the hospital.

Although our hematology ward also treated patients with lung cancer undergoing intensive chemotherapy, *Aeromonas* bacteremia occurred only in patients with hematologic malignancies or marrow aplasia (2). Most of our patients with acute leukemia underwent chemotherapy including the administration of cytarabine or its derivative, enocitabine, both of which are likely to cause diarrhea. Indeed, neutropenic enterocolitis has recently been reported to occur most commonly in patients with hematologic malignancies who were treated with cytarabine-containing regimens (7). Thus, the disruption of mucosal barriers due to antileukemic chemotherapy is considered to predispose to *Aeromonas* infection.

*Aeromonas*, although ubiquitous in fresh and brackish water, has been described to cause intestinal infections in patients with hematologic malignancy (8). In the present series, 12 (71%) of all patients with bacteremia showed a clinical spectrum ranging from mild gastroenteritis to severe enterocolitis mostly characterized by bloody diarrhea just prior to or at the onset of bacteremia. *Aeromonas* bacteremia should therefore be considered in febrile cancer patients with neutropenia presenting with diarrhea. However, only three patients (18%) had positive stool cultures for the organism. Dryden and Munro (9) also reported that only one of the eight patients with abdominal symptomatology, mostly diarrhea, associated with bacteremia had positive stool cultures. This is in marked contrast to the fact that *P. aeruginosa* frequently colonizes many body sites including the throat and stool prior to the onset of bacteremia in patients with cancer (10, 11). Thus, the use of selective media for *Aeromonas* may be recommended in order to increase the isolation rate from diarrheal stools (12).

As indicated by the present study, *Aeromonas* has another propensity for developing hepatobiliary infections such as cholecystitis, cholangitis and liver abscesses (3, 13). One patient (Case 8) had positive stool cultures prior to the onset of obstructive cholangitis progressing to bacteremia, suggesting ascending infection. Moreover, anorectal infections preceded the onset of bacteremia in four patients.

Several recent studies have emphasized the speciation of clinical *Aeromonas* isolates, usually identified as the *A. hydrophila* complex (14). Within the genus, *A. hydrophila* and *A. sobria* are the major enteric pathogens, and the latter species has been suggested to be more pathogenic. In the present study,
A. sobria was more common than A. hydrophila among the isolates/speciated.

The striking seasonality of Aeromonas bacteremia, which occurs mostly in the second half of the year, may partly reflect the fact that the optimal temperature for the organism is between 25 and 30°C, although it usually grows at 1°C (4). Pickard and Goullet (15) noted the correlation of a seasonal variation in nosocomial Aeromonas infection with the number of the organisms in the hospital water supply, which increased during the months from summer to autumn. Aeromonas is well known to be recovered from sink drains as well as from water supplies in hospitals (15, 16). Indeed, Aeromonas was isolated from two of the 50 sink waste-traps we examined in the hospital, although tap water cultures were consistently negative for the organism. Döring et al (17) recently emphasized the risk of acquiring aerosolized organisms such as P. aeruginosa from sink drains during handwashing. It is suggested, therefore, that monitoring the water supplies including sink drains, particularly in the second half of the year is necessary at least on the hematology ward.

Similar to the report of Harris et al (3), the majority of cases of Aeromonas bacteremia in the present study were successfully treated with a β-lactam drug (excluding carboxypenicillins) plus an aminoglycoside. They received such combination therapy on an empirical basis before blood culture results were available. The empiric regimens currently recommended for febrile neutropenic patients with cancer consist of an antipseudomonal drug and an aminoglycoside, for example, ceftazidime plus amikacin (18), both of which cover the majority of clinical Aeromonas isolates at present (1).

At least 104 cases of Aeromonas bacteremia in patients with hematologic diseases have been reported in the English language literature (1). The overall mortality rate in the present study was 35% (6/17), similar to the 29% (5/17) in the series of Harris et al (3) reported in 1985, although a cumulative mortality rate reached almost 60% before 1980 (19). The improved prognosis in recent years can thus be attributed largely to both the substantial improvement in results of treatment of hematologic malignancies, especially acute leukemia (20) and the advent of β-lactam antibiotics with potent anti-Aeromonas activity, such as new cephalosporins and carbapenems (1). Indeed, the poor prognosis in the present series was due mostly to uncontrollable underlying disease and/or concomitant severe fungal or viral infection. In contrast, the one-week mortality rate in the present series was only 6% (1/17), compared with 61% (35/57) in almost the same type of hematology patients with P. aeruginosa bacteremia on our ward (21). This may suggest that Aeromonas bacteremia responds better to the current empiric antibiotics than bacteremia due to P. aeruginosa.

References