

Observations on *Aeromonas* Infection in 7 Patients with Acute Leukemia

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Abstract

Background: *Aeromonas* infections in humans are becoming increasingly frequent. They have the potential to infect humans and are associated with a variety of illnesses, such as enterocolitis, septicemia, skin and soft tissue infectious and peritonitis. However, *Aeromonas* is not well known, and few studies showed a comprehensive research on *Aeromonas* infection of different clinical features in patients with acute leukemia.

Objectives: Our study was conducted to summarize the clinical characteristics of *Aeromonas* infection in 7 patients with acute leukemia.

Methods: We retrospectively reviewed 7 *Aeromonas* infection cases occurred in our hematology ward from 2012 to 2014, analyzing the epidemiology, clinical manifestations, the pathogenic microbiology and treatment outcomes of them.

Results: In the past three years, 7 patients with acute leukemia in our department were infected by *Aeromonas*. There were 5 acute myelogenous leukemia patients, 2 acute lymphocytic leukemia patients. Among them, 3 patients presented *Aeromonas* septicemia, 1 patient presented respiratory tract infection, 1 patient presented genitourinary tract infection, and 2 patients presented necrotizing fasciitis. In our report, 3 patients (42.9%) were dead, 2 of them died from necrotizing fasciitis, the other patient died from primary disease progression and perennial neutropenia.

Conclusion: *Aeromonas* infection has diversified manifestations. In addition, it can be associated with high fatality, especially cellulitis. But abundant and effective antibiotics, especially carbapenems, can significantly improve its prognosis.

Keywords: *Aeromonas* species; Acute Leukemia; Infection

Introduction

Reports from around the world of *Aeromonas* infections in humans are becoming increasingly frequent. It appears of greater clinical importance than we used to suspected [1-3]. *Aeromonas* species, Gram-negative, rod-shaped bacteria, are ubiquitous in the aquatic environment, located in tropical or subtropical climates. As a known etiology of diseases, *Aeromonas* species can cause various human illnesses, including intestinal and extra-intestinal diseases or syndromes, infectious to both immunocompetent and immunocompromised hosts systemically or locally [4,5]. The immunocompromised patients with hepatobiliary diseases or hematologic malignancy are most vulnerable to *Aeromonas* infections [6]. Among the gram-negative bacilli isolated from blood cultures of patients with acute leukemia, *Aeromonas* was ranked as the second frequent incidence behind *Pseudomonas aeruginosa* [7]. However, unlike *Paeruginosa*, *Aeromonas* is not well known. In addition, due to the lack of a systemic report on *Aeromonas* infection, we could not fully master the knowledge of clinical manifestations and treatments of it. Here we retrospectively reviewed 7 *Aeromonas* infection cases that occurred in our hematology ward from 2012 to 2014. By analyzing the epidemiology, clinical manifestations, the pathogenic microbiology and treatment outcomes of them, we enhanced our current understanding of the rare gram-negative bacilli infections in patients with acute leukemia.

Methods and features of cases

This study was conducted at the Affiliated Cancer Hospital of Zhengzhou University, a 1000-bed hospital located in He-Nan province, China. We reviewed the case records of all patients with acute leukemia who had *Aeromonas*, alone or in combination with other organisms, isolated from one or more body fluids or blood culture specimens in our hematology ward during the period from 2012-2014. The diagnosis of *Aeromonas* infection was based on the positive results of cultures result for at least one time or the positive evidence of clinical infection. The onset of infection was regarded as being the time when the first positive result was obtained (Table 1).

Case No.	Age(yr)&Sex	Primary disease	Initial ANC(μ l)	Initial BT($^{\circ}$ C)	Presentation	Source of <i>A. hydrophila</i>	Other bacteria isolated from lesion	Antimicrobial therapy	Treatment outcome
1	21 M	ALL	390	37.3	Pyrexia	Blood	None	IPM+TEC	Cured
2	40 M	AML	630	39.2	Gingivitis	Throat swab	Burkholderia cepacia	IPM+VA	Cured
3	48 M	AML	510	39.4	Cellulitis	Secretion	None	IPM+VA+SCF	Died
4	43 M	ALL	710	39	Pneumonia	Blood	Escherichia coli	TAP+AK	Died
5	35 F	AML	2170	37.1	Cystitis	Urine	Citrobacter Freundii	IPM+LEV	Cured
6	21 F	AML	680	38.8	Cellulitis	Secretion	None	IPM +TEC+SCF	Died
7	28 M	AML	62	40.1	Pneumonia	Blood	Pseudomonas aeruginosa	IPM+ VA	Cured

ALL: acute lymphocytic leukemia, **AML:** acute myelogenous leukemia, **IPM:** imipenem, **TEC:** Teicoplanin, **VA:** Vancomycin, **SCF:** Cefoperazone and Sulbactam, **TZP:** Piperacillin and Tazobactam, **AK:** Amikacin, **LEV:** Levofloxacin

Table 1: Demographic data, underlying conditions, clinical presentations, infection details, and treatment outcomes of 7 patients with *Aeromonas hydrophila* from 2012 to 2014

Results

In the past three years, 7 patients with acute leukemia in our department were infected by *Aeromonas* (Table 1). Most of them are middle-aged persons. Their median age was 35 (range, 21-48), 5 patients with acute myelogenous leukemia and 1 patient with acute lymphocytic leukemia. 3 patients developed simple *Aeromonas* infection, 4 patients developed polymicrobial infection. Among them, 2 patients (Case 1 and 5) had chronic hepatitis. 3 patients presented *Aeromonas* septicemia, 1 patient had respiratory tract infection, 1 patient had genitourinary tract infection, and 2 patients had necrotizing fasciitis. None of them contacted with fish or outdoor natural waters. 5 patients were infected by *Aeromonas* in the summer, while the other 2 were infected in the spring.

During 10 days before the onset of infections, chemotherapy (for 7 patients) and neutropenia ($< 1,000/\mu$ l) (for 6 patients) were the most common conditions, followed by central venous catheterization (except for patient 2 and 6). Temperatures were elevated to 38.5° C or higher in 4 patients (57.1%). Patient 1, 3, 4 and 7 had septic shock, although it was only considered to be the direct cause of death for one patient (patient 4). As for antimicrobial therapy, 6 patients received carbapenem antibiotics as their first-line therapy. In our report, among the 3 dead patients, patient 3 and 6 died from necrotizing fasciitis. Carbapenem used to be the initial treatment of myonecrosis, however, the treatment with carbapenem alone was insufficient for them. Treatments combined with vancomycin, teicoplanin, cefoperazone and sulbactam were then implemented. The minimum inhibitory concentration (MIC) of carbapenem in each case was ≤ 4 , the MIC of cefoperazone and sulbactam was $\leq 16/8$, and the MICs of the other two medicines were not tested. However, those patients did not respond to the treatment and died on the fifth day since onsets of infection. Patient 4 suffered from a persistent neutropenia, which led to various kinds of bacterial infections. The infections progressively developed to central nervous system, and finally result in the death of this patient.

Discussion

Aeromonas are essentially ubiquitous in the microbial biosphere. They can be isolated from virtually every environmental niche where bacterial ecosystems exist. These include aquatic habitats, fish, foods, domestic pets, invertebrate species, birds, ticks and insects, and natural soils [6]. Most studies have found the recovery of *Aeromonas* from fecal specimens to increase coincidentally with the warmer months of the year [8,9]. Similarly, in our case, bacterial infections were mostly observed in summer. *Aeromonas* have also been isolated from stool, urine and sputum samples without ascertainable pathogenicity, suggesting that they can be a constituent of normal human flora. Most available data suggests that the majority of mesophilic isolates are acquired via contact with contaminated drinking water or through the ingestion of foods (produce, dairy, or meats) [10]. However, patients in our research did not contact with outdoor fresh water or fish. In this study, *A. hydrophila* was the most common *Aeromonas* species (in all patients except for patient 6) followed by *A. caviae*, which is different from previous reports: *A. caviae* and *A. veronii* were the most common *Aeromonas* species causing bacteremia and gastroenteritis in France; *A. caviae* is the most frequent pathogen causing *Aeromonas* bacteremia in Japan; the *A. hydrophila* was the most common *Aeromonas* species causing bacteremia, followed by *A. veronii* biovar sobria in Taiwan [11-13]. The percentage of monomicrobial infections (42.8%) in our study was lower than the one in previous reports (64% to 75.6%). When polymicrobial infections occur, *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* can be identified along with *Aeromonas* species [6,14,15]. As Altwegg [16] found, *Aeromonas* species were most likely to infect patients with acute leukemia among the patients with all kinds of hematologic malignancy. *Aeromonas* can cause mild illnesses such as intestinal and extraintestinal diseases and syndromes. Based on the frequency, *Aeromonas* clinical infections can be divided into four categories: (i) gastrointestinal tract syndromes, (ii) wound and soft tissue infections, (iii) bloodborne dyscrasias, and (iv) a miscellaneous "catch-all" category which includes a myriad of less frequently encountered ailments and infectious processes [7].

Aeromonas septicemia occurs throughout the whole year, with a higher frequency of the incidence during the summer or warmer months [14,15,17]. Tsai found, among hematologic malignancies, acute myelocytic leukemia (AML) ranks first in the *Aeromonas* infections, followed by myelodysplastic syndromes (MDS), non-Hodgkin's lymphoma (NHL), acute lymphocytic leukemia (ALL), and various other hematologic conditions, including Aplastic Anaemia (AA), thalassemia, multiple myeloma (MM), and Waldenstrom's macroglobulinemia (WM) [15,16,18,19]. The most common symptoms associated with *Aeromonas* bacteremia include fever (74% to 89%), jaundice (57%), abdominal pain (16% to 45%), septic shock (40% to 45%), and dyspnea (12% to 24%) [6,14]. Patients 1, 4 and 7 suffered from the *Aeromonas* septicemia, all of them presented septic shock, 2 of them had hyperpyrexia, and patient 4 got dyspnea.

The second most common anatomic matter from which *Aeromonas* are recovered is the integument with deeper soft tissues underlying the epidermis. Necrotizing fasciitis or myonecrosis is the most common clinical manifestation in patients with liver disease or malignancy. For patients with serious illnesses of high mortality rates (approaching 60% to 75%), their favorable outcomes are dependent upon the early recognition of infectious conditions, and appropriate therapeutic intervention (debridement, irrigation, antimicrobial therapy) [20,21]. Patient 3 and 6 presented necrotizing fasciitis, clinically manifesting infested limbs pains, tension blisters, swelling, blackening of the skin, subcutaneous ecchymosis, and epidermal necrolysis. Surgical intervention plus antibiotics (β -lactam antibiotics and Glycopeptide antibiotics) were ineffective. They died eventually.

Very occasionally *A. hydrophila* has been described as a causal agent of respiratory tract diseases, leading to adult respiratory distress syndrome and high mortality (40%) [22]. Those infections result in epiglottitis, empyema, lung abscesses, or pneumonia in patients with no comorbid conditions or in individuals with traditional immunocompromised states associated with the genus. By far the most frequent respiratory complication associated with the genus *Aeromonas* is pneumonia. Patients often present with high fever, a productive cough (hemoptysis), vomiting, chest pain, and respiratory failure [23,24]. The most common specimen found positive for *Aeromonas* are blood cultures, followed by the others like endotracheal samples, bronchoalveolar lavage or secretions, postmortem samples, such as lung and pleural effusions. Patients 4 and 7 presented pneumonia, with high fever and shiver. Patient 2 had fever, sore gums and buccal mucosal swelling. Their cultures indicated polymicrobial infections, including *Aeromonas* species and other gram-negative bacillus (*Escherichia coli*, *Pseudomonas aeruginosa*, *Burkholderia cepacia*). *Aeromonas* pneumonia accompanying septicemia enhanced the risk of dying. The rapid demise of patients in this setting can be as quick as 9 hours from the initial insult to the moment of death [25].

Aeromonas species are rarely implicated in infections of the urogenital tract. To our knowledge, there were four cases reported in the English-language articles, caused by *A. hydrophila* [26], *A. veronii* biotype *sobria* [27], *A. caviae* [28], and *A. popoffii* [29]. Patient 5 occurred hemorrhagic cystitis in the twenty-eighth day after allogeneic stem cell transplantation, characterized by frequent urination, urgency, dysuria, positive urine occult blood, and positive polyoma virus. Urine culture indicated *Aeromonas hydrophila* and *Citrobacter Freundii* infections. According to the antimicrobial susceptibility tests, the patient was cured after treatment with antibiotics (imipenem, levofloxacin) within two weeks, though *Aeromonas hydrophila* was reported resistant to levofloxacin.

Although the gastrointestinal tract is the most common anatomic site from which *Aeromonas* were recovered by far, gastrointestinal symptoms were absent from clinical manifestations in our patients. And we didn't perform stool culture. *Aeromonas* species can also cause ocular disease, ranging from endophthalmitis, keratitis to corneal ulceration. In addition, *Aeromonas* species can also cause intra-abdominal infections, such as pancreatitis, acute cholangitis, hepatic abscesses and peritonitis.

The in vitro antibiotic resistance of *Aeromonas* species suggests that ceftazidime, imipenem, and aztreonam should be the first-line choices for *Aeromonas* infection treatment [30]. Our isolated strains were sensitive to most other β -lactams except for penicillins (such as piperacillin), quinolones and aminoglycosides, but resistant to the third generation cephalosporin (cefotaxime), piperacillin tazobactam, tobramycin, cotrimoxazole. Six-sevenths of our patients treated with imipenem obtained satisfactory effects, even for the hemorrhagic cystitis patient (patient 5) who was treated in combination with the levofloxacin which were considered to be resistant in most reports. Therefore, the combination therapy is reckoned to be better than monotherapy. Before we analyzed the blood culture results, our empirical therapy for febrile cancer patients with neutropenia was anti-*Pseudomonas* β -lactam antibiotics with or without aminoglycosides, which could kill the vast majority of clinical gas *Aeromonas* species.

In conclusion, we reported the clinical characteristics of *Aeromonas* infection in 7 patients with acute leukemia in China. *Aeromonas* species are not rare in clinical, it can be associated with high fatality. The overall mortality rate was 43% (3/7) in the present study, higher than 35% (6/17) in the series of Hisashi reported in 1997 [31]. The mortality rate reached up to almost 60% before 1980 [32]. Improved prognosis in recent years is largely attributed to both the substantial improvement of hematologic malignancy treatments and the advance potent anti-*Aeromonas* activity of β -lactam antibiotics, such as carbapenems and new cephalosporins.

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