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Necrotizing fasciitis and sepsis caused by *Aeromonas hydrophila*

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SUMMARY

Aeromonas hydrophila (*A. hydrophila*) occasionally causes necrotizing fasciitis (NF) and sepsis in immunocompromised hosts. NF is associated with high mortality. In cases of septic shock due to *A. hydrophila,* mortality is nearly 100%. Our 47-year-old male patient was diagnosed with NF and septic shock due to *A. hydrophila.* He had not been exposed to fresh or slightly salty water, which is where the bacterium is typically found, so its origin in this case is unclear. This is the first known case in which the patient was able to be completely cured without amputation. NF was suspected from his sepsis, medical history including alcoholic cirrhosis, and a severely poor general condition, but his skin lesions were mild. We promptly made an exploratory incision and debrided his legs. NF could then be diagnosed. At an early stage, *A. hydrophila* was recognized as a possible pathogen of NF because of the patient's medical background and the Gram stain findings of intraoperative exudate. Minocycline in addition to carbapenem and vancomycin plus clindamycin were administered as empiric therapy. When *A. hydrophila* was detected in the blood culture, ciprofloxacin was administered as definitive therapy. Successful treatment of NF requires early diagnosis, prompt debridement from onset and adequate empirical antibiotic therapy.

Keywords: sepsis, soft-tissue infection, infectious disease, fasciitis, necrotizing, *Aeromonas.*

INTRODUCTION

Aeromonas species occasionally cause soft tissue infections and sepsis in immunocompromised hosts [1]. Mortality rates associated with the bacteria are high, reportedly between 60% and 75% [1, 2]. In cases of septic shock due to *Aeromonas hydrophila* (*A. hydrophila*), the mortality rate approaches 100% [3].

Necrotizing fasciitis (NF) is an aggressive subcutaneous infection that spreads along the superficial fascia, which comprises all tissues between the skin and underlying muscles [4, 5]. It can reportedly occur among healthy individuals with no medical history or clear portal of entry in any age group [6]. There are conditions with possible association, however, including use of injected drugs, and chronic debilitating comorbidities (*e.g.*, diabetes mellitus, immune suppression, and obesity) [7-10].

Prompt surgical consultation is recommended for patients with aggressive infections with signs of systemic toxicity or suspicion of NF [11]. Diagnosis and treatment of NF is commonly delayed, which may result in development of shock and multiple organ failure [11, 12].

CASE REPORT

A 47-year-old man was admitted to our hospital because he was confused and febrile and he had urinary incontinence beginning on that day. The patient had been in his usual state of health until several days before this admission, when diarrhea and abdominal distension developed. On the day before admission, he worked at his office, then ate a meal and drank alcohol in the evening. He got

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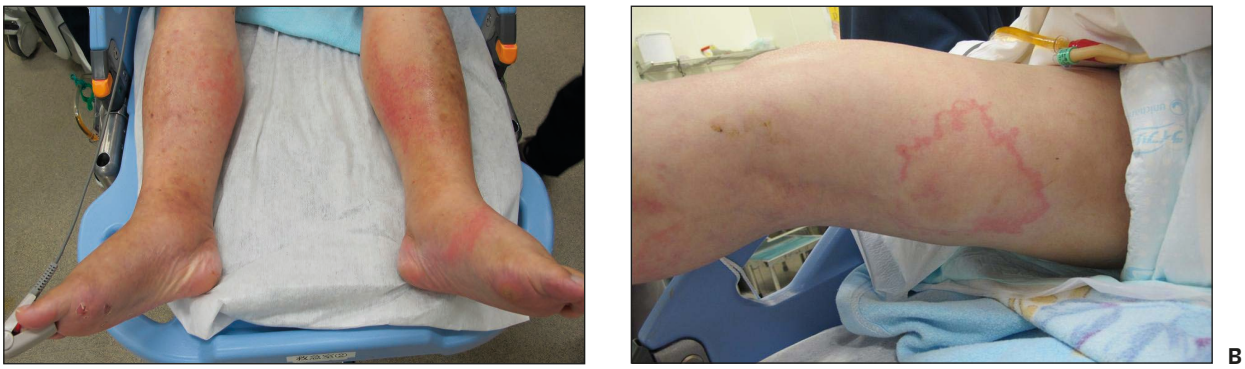

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Figure 1 - (a) Mild erythema lesions without sharp margins were bilaterally present on the legs without bullae, necrosis, ecchymosis, or crepitus on admission. (b) Erythema with bulging margin was present on the right inner thigh.

home and went to bed without any symptoms at night. About six hours before admission, he woke up in the morning with weakness and delirious. About one hour before hospital admission, he got confused and his wife called an ambulance. He did not present headache, neck pain, back pain, urinary retention, fever, chills, dark stools, melena, or hematemesis.

He had a history of untreated alcoholic cirrhosis and vertebral compression fracture owing to heavy drinking and having fallen several times. He was taking loxoprofen sodium hydrate for existing conditions. The patient had high alcohol intake on a daily base. His status was otherwise unremarkable; he had no history of traveling abroad, trauma, or exposure to fresh or slightly salty water, or exposure to animals, and he had not eaten raw seafood.

On hospital evaluation, body temperature was 40.8°C, blood pressure was 137/95 mm Hg, pulse rate was 157 beats per minute, respiratory rate was 26 breaths per minute, and the oxygen saturation 99% while the patient was breathing with an oxygen mask 10L/min. He was awake, but not alert or cooperative. Glasgow Coma Scale was E4V2M4. Erythema lesions were present on the legs (Figures 1a and 1b). Edema of the legs extended beyond the visible erythema. First and second heart sounds were normal. Respiratory sounds were bilaterally normal, without wheezes or rhonchi. Bowel sound was normal, and the abdomen was soft, mildly distended, and not tender on palpation. There was no stiffness of the neck. The remainder of the physical examination was unremarkable.

Laboratory test results are shown in Table 1. Electrocardiogram showed sinus tachycardia and chest X-ray showed nothing abnormal. Contrast-enhanced computed tomography (CT) showed edema of soft tissue on the legs without production of gas.

Bolus injection of lactated Ringer's solution and a thiamine infusion were administered. The patient was diagnosed with sepsis caused by soft tissue infections and toxic shock syndrome. Infusions of meropenem at 1 g every 12 hours, vancomycin at 1500 mg with a target serum trough concentration of 15 to 20 mcg/mL and clindamycin at 600 mg every 6 hours were administered. Two hours after admission, he was hypotensive and had tachycardia, so volume resuscitation and norepinephrine infusion were administered. The patient was referred to the intensive care unit (ICU) for further management. Endotracheal intubation and mechanical ventilation were performed to treat septic shock. An orthopedist was consulted for further diagnostic tests because NF was suspected as a possibility in this patient from his erythema, medical history of alcoholic cirrhosis and severely poor general condition. Skin lesions, however, were mild and LRINEC (the Laboratory Risk Indicator for Necrotizing Fasciitis) score was two out of 13 points.

Approximately two and a half hours after hospital admission, exploratory incision of the legs was performed in ICU by orthopedists. Incisions were made from the ankle to the knee of both legs. Direct examination revealed the fascia was swollen with necrosis and dishwater-gray exudate and it was easily separated by blunt dissection.

Table 1 - Laboratory data on admission.

Hematology		
White blood cell	23500	/μL
Neutrophils	46	%
Band	20	%
Segment	46	%
Lymphocytes	17	%
Monocytes	10	%
Hematocrit	39.2	%
Hemoglobin	13.1	g/dL
Red-cell count	326×10^4	/μL
Mean corpuscular volume	120.1	fL
Platelet count	28,000	/μL
Activated partial thromboplastin time	42	sec
Prothrombin time	34	%
Blood chemistry		
Total bilirubin	5.2	mg/dL
Direct bilirubin	3.1	mg/dL
Alanine transaminase	29	U/L
Aspartate transaminase	112	U/L
Total protein	5.6	g/dL
Serum albumin	2.3	g/dL
Sodium	137	mEq/L
Potassium	3.2	mEq/L
Chloride	102	mEq/L
Urea nitrogen	14.2	mg/dL
Creatinine	1.23	mg/dL
Glucose	107	mg/dL
CPK	1859	U/L
D-Dimer	5.9	μg/mL
C-reactive protein	4.3	mg/dL
Hepatitis C antibody	(-)	
Hepatitis B surface antigen	(-)	
Venous blood gas		
pH	7.55	
$PvCO_2$	25.9	mmHg
HCO_3-	22.7	mmol/L
Lactate	5	mmol/L

NF diagnosis was established by the findings of surgery. Debridement of the necrotic tissues could be performed without amputation. The depth of the debridement reached the fascia from ankle to knee of both legs. The debridement was extended beyond the necrotized area into the normal tissue until bleeding was seen. The thighs were not considered to be necrotized because normal bleeding was observed from the fascia near the thigh. Gram-negative bacillus was detected in the deep tissue exudate, which should be considered *Vibrio vulnificus (V. vulnificus)* or *A. hydrophila*. The patient was therefore administered minocycline at 100 mg every 12 hours instead of clindamycin. His shock vitals could not be improved, so infusion of vasopressin and hydrocortisone were initiated for septic shock.

On the second hospital day, reinspection was performed about 16 hours after the first incision but there was no additional debridement because necrotic tissue was absent. Direct hemoperfusion with a polymyxin B immobilized fiber column and continuous hemodiafiltration using a polymethylmethacrylate member hemofilter were initiated for septic shock and acute kidney injury. Vasopressors were gradually reduced. Blood culture showed growth of Gram-negative bacilli. On the fifth hospital day, *A. hydrophila* was identified from blood culture. On the fifth hospital day, *A. hydrophila* was identified from blood culture, with oxidase-positive, fermentation of glucose positive by triple sugar iron agar (Nissui), indolepyruvate negative, indole and motility positive by SIM agar (Nissui), Voges-Proskauer test positive by VP agar (Eiken), lysine and ornithine decarboxylase negative by Ornithine-Indol-Mobility-Lysine agar (Eiken). It was also identified by ID Test EB-20 (Nissui). The antimicrobial agents were de-escalated to ciprofloxacin at 200 mg every 12 hours, with reference to the susceptibility results (Table 2). The susceptibility testing results revealed carbapenem resistance, but carbapenemase production was negative by disk method and carbapenemase-producing genes were negative by the polymerase chain reaction method. On the eighth hospital day, vasopressors were withdrawn. He was extubated, and the antimicrobial agents were completed when vital signs were stabilized on the 14th hospital day. Hemodialysis was finished on the 15th hospital day. The patient was transferred to the rehabilitation center on the 46th hos-

Table 2 - Susceptibility of *Aeromonas hydrophila* isolated in our patient.

Antibiotics	*Minimum inhibition concentration (mg/mL)*	*Susceptibility*
Cefazolin	>16	Resistant
Ceftriaxone	<1	Susceptible
Ceftazidime	<1	Susceptible
Cefepime	<1	Susceptible
Imipenem	>8	Resistant
Meropenem	2	Intermediate
Amikacin	<1	Susceptible
Minocycline	<1	Susceptible
Trimethoprim-sulfamethoxazole	<10	Susceptible
Levofloxacin	<0.25	Susceptible
Ciprofloxacin	<0.5	Susceptible

pital day, when he was cured without sequelae, although he had difficulty walking from ICU-acquired weakness.

DISCUSSION

The present case of NF due to *A. hydrophila* was successfully treated without amputation. Early diagnosis and intervention are key to successful treatment of NF. Early consideration of *A. hydrophila* infection, even without history of exposure, is also clinically important.

Diagnosis of NF is commonly delayed, and NF has poor prognosis because it can be difficult to distinguish from other soft-tissue infections. The LRINEC score, objective scoring system for distinguishing NF from other soft tissue infections, was reported to have high specificity and negative predictive value for diagnosing of NF [9]. The cut-off value for the score was six out of 13 points with a positive predictive value of 92.0% and negative predictive value of 96.0%. However, it should not be used to rule out particularly in the setting of early infection [13]. In our case, although LRINEC score was only two points, with attention to the patient's critically ill appearance and his medical history, we made early consultation with the surgeon. NF was therefore diagnosed at an early stage and treatment was ultimately successful without the need for amputation.

A. hydrophila causes NF and septic shock in an immunocompromised host, such as due to liver disease or malignancy. Our patient's untreated alcoholic cirrhosis was a risk factor of NF. At an early stage, *A. hydrophila* could be recognized as a pathogen of NF because of the patient's medical background and the Gram stain findings of intraoperative exudate.

Administration of antimicrobial therapy without debridement has been historically associated with a mortality rate approaching 100% in NF [7]. Case series report in-hospital or 30-day mortality rates between 9% and 76%, with average rates between 20% and 40% [14]. Survival rate is significantly higher among patients taken to surgery within 24 hours after admission than that of patients whose surgery is delayed longer. Freischlag (1985) reported that operations performed more than 24 hours after recognition of infection resulted in 70% mortality, whereas operations performed before that had 36% mortality [15]. Furthermore, guidelines state that prognosis improves with earlier surgical intervention (*e.g.*, ≤6 hours) [7]. Hadeed (2016) reported significantly shorter lengths of hospital stay and ICU stay when there is early intervention (<6 h) than when there is later intervention (≥6 h) [16]. Overall, the mortality rate of patients with necrotizing soft tissue infections was 12.5%, whereas in patients who had earlier intervention it was 7.5% [16]. Early recognition of NF is critical because rapid progression to extensive destruction can occur, leading to sepsis, limb loss, and death. In addition to prompt surgical exploration, debridement of all necrotic tissue until healthy tissue is encountered is also the mainstay of NF treatment [17]. Prompt surgical consultation is

recommended for patients suspected to have NF [11]. In this case, surgical intervention was performed within about two hours after admission to our hospital and within about eight hours after the onset of symptoms.

Clinical presentation of NF changes rapidly based on each clinical stage [18]. Early clinical recognition of NF and distinguishing it from other soft-tissue infection, such as cellulitis and erysipelas, is key to successful treatment. In NF, margins of tissue involvement are often poorly defined with tenderness and intense pain extending beyond the apparent area of involvement. In the early stages, we may see tenderness and intense pain extending beyond the apparent area of skin involvement, erythema, swelling and warmth to touch. In intermediate stages, we may see blisters or bullae formation (serous fluid), skin fluctuation and skin induration. In the later stages, we may see hemorrhagic bullae, skin, crepitus and skin necrosis with dusky discoloration progressing to frank gangrene. In NF, fever, tachycardia, and systemic toxicity may also be observed.

Diagnosis of NF is established by surgical exploration of the soft tissues with physical examination of the skin, subcutaneous tissue, fascial planes, and muscle. Surgical exploration is the only way to establish diagnosis of necrotizing infection. When there is clinical suspicion for necrotizing infection there should be no delay while awaiting results of radiographic imaging, culture results, or other diagnostic information [11, 19]. Even if enough suspicion exists to do a biopsy, the diagnosis is usually evident on gross inspection without histologic confirmation [11]. In addition, sampling errors of biopsy alone may produce a false-negative result [11]. In our case, although histology of the tissue was not available, NF could be diagnosed at an early stage by using surgical findings and prompt surgical consultation was possible because we gave attention to the patient's severe general condition. The patient's skin lesion, another commonly reported symptom of NF, was mild and except for edema, imaging revealed nothing remarkable.

Wong (2003) reported that NF is caused by various kinds of organism, including *Streptococcus* species and *Staphylococcus aureus* [6]. Cheng (2012) reported *V. vulnificus* (7%) and *A. hydrophila* (4%) as common pathogens in addition to more common organisms, including *Streptococcus pyogenes* (12%), *Klebsiella pneumoniae* (11%), and *Staphylococcus aureus* (14%) [18]. *Aeromonas* species are ubiquitous inhabitants of both slightly salted and fresh water, including in hospital water supplies [20]. *A. hydrophila* is frequently present in the lake and sea water [21, 22]. These infections are often thought to be community-acquired and related to exposure to wild water or marine creatures [23]. However, only two reported (2.6%) patients with *Aeromonas* bacteremia were associated with a history of exposure [24]. The pathogenicity of *A. hydrophila* has been attributed to the ability of the bacterium to produce cytotoxic enterotoxin Act and cytotonic enterotoxins AST and ALT, as well as a variety of proteases and type III secretion systems (T3SSs) and surface structures, including pili and S-layer and lateral and polar flagella, which allow the organism to attach to cells and to enter tissue [20]. Carriage of multiple toxins appears to be a property of *A. hydrophila,* but not other *Aeromonas* species [20].

NF due to *Aeromonas* species is most often seen in people with liver disease or malignancy and it can be associated with high mortality rates approaching 60% to 75% [1, 2]. The mortality rate of septic shock caused by *A. hydrophila* approaches 100% [3]. *A. hydrophila* can cause NF and sepsis, which may have severe prognosis. In a case of NF, however, there is no apparent exposure. Our patient also had no history of trauma or exposure to wild water, but his medical history included alcoholic cirrhosis, a known risk factor. If a patient has a critically ill condition and skin lesions with suspicion of NF or sepsis and also has a risk factor of NF, such as liver cirrhosis or malignancy, we should consider the possibility of NF from *A. hydrophila*.

In general, empiric treatment of necrotizing infection consists of broad-spectrum antimicrobial therapy, including activity against Gram-positive, Gram-negative, and anaerobic organisms [7]. Acceptable empiric antibiotic regimens include a carbapenem or beta-lactam-beta-lactamase inhibitor plus an agent with activity against methicillin-resistant *S. aureus* (MRSA), such as vancomycin or linezolid plus clindamycin [11]. For patients who have particular exposure or background that may suggest infection by specific organisms, it is appropriate to ensure empiric therapy that includes antimicrobial agents with activity against such organisms. Organisms may include *Aeromonas* spe-

cies or *V. vulnificus* and background may be liver cirrhosis. Agents include doxycycline plus ciprofloxacin or ceftriaxone [11]. In this case, the patient was diagnosed as having NF, potentially due to *Aeromonas* species or *V. vulnificus*, because the Gram stain of the intraoperative tissue showed Gram-negative bacillus and because of high risk background. Minocycline in addition to carbapenem and vancomycin plus clindamycin were administered as empiric therapy. When *A. hydrophila* was detected in the blood culture, ciprofloxacin was administered as definitive therapy.

Amputation would be the standard indication for NF. In our case, however, important clinical factors led us to decide against it. First, very prompt surgical intervention and complete debridement of necrotic tissue were performed upon admission, soon after onset. Second, on careful re-inspection there was no appearance of additional necrotic tissue. The patient also did not have medical history of peripheral artery disease or diabetes mellitus and these would have been considered to be risks of amputation [25].

Necrotizing fasciitis, especially due to *A. hydrophila*, has very poor prognosis. This is the first report of a case of NF with septic shock caused by *A. hydrophila* to survive without amputation, to the best of our knowledge. The possibility of NF should be considered in cases presenting sepsis. At an early stage, *A. hydrophila* was recognized as pathogen of NF because of the patient's medical background and the Gram stain findings of intraoperative exudate. Early diagnosis and prompt debridement were keys to successful treatment.

Conflict of interest: The authors have no conflict of interests to declare.

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