Acta Med Kindai Univ Vol. 41, No. 1 31-36, 2016

Successful treatment of a necrotizing soft tissue infection with sepsis caused by *Aeromonas hydrophila* following gastric cancer surgery

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Abstract

A 70-year-old man underwent total gastrectomy and splenectomy for gastric cancer. On the second post-operative day, swelling with redness was noted at the site of drain insertion. The site of redness expanded rapidly and the patient developed purpura with blood blisters complicated by concomitant shock, respiratory failure, and disseminated intravascular coagulation (DIC), leading to a sudden worsening of his general condition. He was diagnosed with a necrotizing soft tissue infection. A drain was inserted through the superficial fascia to initiate irrigation drainage. *Aeromonas hydrophila* was detected in the subcutaneous effusion and blood cultures. The drainage region was enlarged as needed based on the amount of necrosis. Debridement was performed after his general condition had stabilized. Ninety-two days post-operation, he was transferred to another hospital for skin grafting. Necrotizing soft tissue infections due to *A. hydrophila* usually have a life-threatening course. However, irrigation drainage through the superficial fascia might be effective when extensive debridement cannot be provided immediately because of a bleeding tendency due to shock or DIC.

Key words: *Aeromonas hydrophila*, necrotizing soft tissue infection, post-operative complications

Introduction

A. hydrophila is an indigenous gram-negative facultative anaerobic bacillus found in the soil and water.[1] Although *A. hydrophila* has been reported to cause traumatosepsis and enteritis in humans, its pathogenicity is generally weak. However, in patients with impaired immunity, it can cause serious infections such as necrotizing soft tissue infections (NSIs), leading to death.[2]

In this study, we report the case of a patient who was successfully treated for sepsis and an NSI caused by *A. hydrophila* after surgery for gastric cancer. We also provide a brief review of the literature.

Case report

A 70-year-old man was diagnosed with progressive gastric cancer in the upper and middle thirds of the stomach. The clinical cancer stage was follows: cT3, cN1, cM0 and cStageIIIA. The patient underwent total gastrectomy (Roux-en-Y reconstruction), splenectomy, and group 2 lymph node dissection. The operative time was 226 min and the amount of bleeding was 352 mL. The final cancer stage was as follows: pT3, pN1, sP0, sH0, sCY0, sM0, fStageIIIA, D2 and curability B[3]. Figure 1 shows the post-operative course.

During the early morning on the second post-operative day (POD), the patient experienced dark-red bloody diarrhea and, hypotension and

Received February 25, 2016; Accepted April 14, 2016

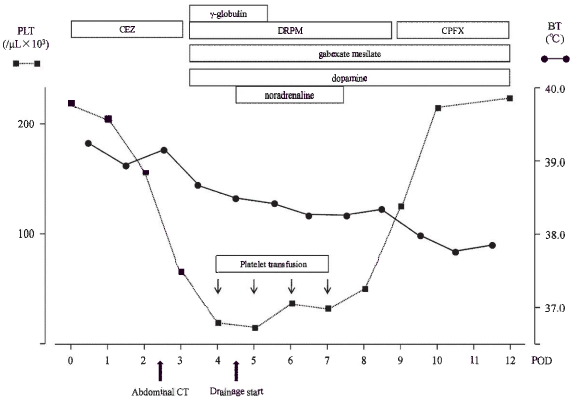

Fig. 1 Post-operative course
PLT : platelets ; CEZ : cefazolin, DRPM : doripenem hydrate ; CPFX : ciprofloxacin hydrochloride ; BT : body temperature ; POD : post-operative day

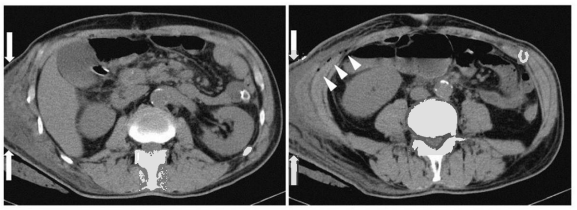

Fig. 2 Abdominal CT
There were no space-occupying lesions (e.g., abscesses) in the abdominal cavity. However, marked edema (arrow) and gas retention (arrowhead) were found throughout the right superficial fascia.

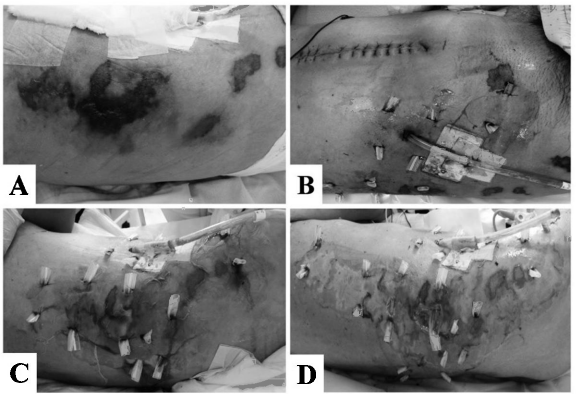

Fig. 3 Physical examination
A : Redness and swelling expanded from the right anterior abdominal area to the back. Blisters, purpura, and blood blisters developed.
B : A necrotizing soft tissue infection was suspected, and the primary site of necrotic changes was incised. Penrose drains were then inserted through the superficial fascia.
C and D : We extended the drainage site based on the amount of necrosis, resulting in extension to the right chest and right femoral region.

was treated with an infusion. In the afternoon of the same day, swelling with redness was noted around the drain in the foramen of Winslow and high fever persisted. Computed tomography (CT) was performed, and merked edema was observed around the right abdominal wall. Although we initially suspected cellulitis, retention of gas was also detected on the images (Fig. 2). No abnormal findings, such as abscesses in the abdominal cavity, were seen and the possibility of suture failure was ruled out based on effective drainage. The patient's blood pressure gradually decreased during the night and he started complaining of respiratory discomfort. On POD 3, the patient was diagnosed with infectious shock and disseminated intravascular coagulation (DIC) based on his vital signs and blood test results. The antimicrobial was changed (cefazolin [CEZ] to doripenem hydrate), and immunoglobulin preparations and gabexate mesylate were administered. As the patient began experiencing loss of consciousness and respiratory failure at the same time, mechanical ventilation was initiated.

On POD 4, the site of redness had expanded and formed a blister. Furthermore, purpura and a blood blister were observed, indicating an NSI (Fig. 3A). Once the necrotic site had been incised, serous fluid began to drain, forceps were inserted, and the superficial fascia layer was easily removed. To effectively use the extra space that was created after the layer had been removed, multiple Penrose drains were placed and irrigation was initiated using saline (Fig. 3B). The number of drains was increased based on the extent of necrotic changes in the skin, and irrigation drainage was continued (Fig. 3C and D).

On POD 7, the patient's blood pressure began to increase slightly. *A. hydrophila* was evident in the blood cultures that had been submitted on POD 3, as well as in the sputum and subcutaneous effusion cultures that had been performed on POD 4. The results of the antibiotic sensitivity test on POD 9 showed high sensitivity to levofloxacin and ciprofloxacin hydrochloride (CPFX) and low sensitivity to ampicillin, CEZ, and cefoxitin (Table 1). As a result, the antimicrobials were switched to CPFX and the thrombocytopenia improved. On POD 11, the progress of the necrotic changes was under control. As his bleeding tendency had improved and respiration and circulation were stable on POD 21,

Table 1 Antibiotic susceptibility of *Aeromonas hydrophila* isolated in blood cultures

Drug	MIC (μg/mL)	Effect
ABPC	≧32	R
CEZ	≧64	R
CFX	≧64	R
CFPM	≦1	S
AZT	≦1	S
IPM/CS	≦1	S
GM	≦1	S
AMK	≦2	S
MINO	≦1	S
LVFX	≦0.25	S
CPFX	≦0.25	S
ST	≦20	S

ABPC : ampicillin ; CEZ : cefazolin ; CFX : cefoxitin ; CFPM : cefepime ; AZT : azidothymidine ; IPM/CS : imipenem/cilastatin ; GM : gentamicin ; AMK : amikacin ; MINO : minocycline ; LVFX : levofloxacin ; CPFX : ciprofloxacin hydrochloride ; ST : sulfamethoxazole trimethoprim
MIC : minimum inhibitory concentration ; S : susceptible ; R : resistant

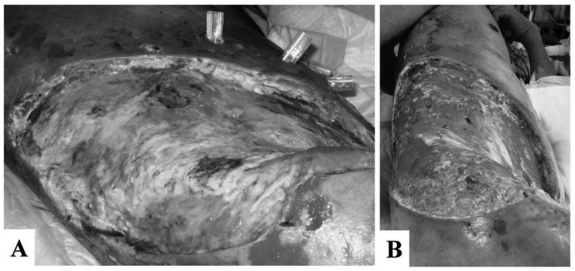

Fig. 4 Physical examination (after debridement)
A : On post-operative day (POD) 21, the first debridement was performed around the initial lesion in the area with the greatest necrosis. The superficial fascia was light gray, edematous, and vulnerable.
B : On POD 29, the second debridement was performed in all areas with Penrose drains.

debridement was performed in the area around the primary site of necrotic changes. The superficial fascia was light gray, edematous, and vulnerable (Fig. 4A). On POD 29, extensive debridement was performed in all of the areas where the drains had been inserted (Fig. 4B). Although the patient's slight fever persisted even after sepsis was cured, defervescence was achieved after the completion of debridement and the mechanical ventilator was removed on POD 56.

The area of the wound was stabilized using infection control materials and wound dressing.

Fig. 5 Physical examination (after skin grafting)
On POD 94, split-thickness skin graft surgery was performed in the femoral region using six-fold extended mesh.
A : Day 12 after skin grafting.
B : Month 9 after skin grafting.

On POD 92, he was transferred to another hospital for skin grafting. The patient showed no decrease in activities of daily living and was able to resume his normal life (Fig. 5A and B).

Discussion

A. hydrophila is a gram-negative facultative anaerobic bacillus classified in the *Vibrionaceae Aeromonas* family. It is found in the soil or water and can proliferate even in relatively cold environments (5° C).[1] There are three kinds of this bacillus that can cause infections in humans : *A. hydrophila*, *Aeromonas veronii* biovar sobria, and *Aeromonas caviae*. However, most cases of infection are caused by *A. hydrophila*. The routes of infection include percutaneous infection and oral infection, and reported cases of oral infection are relatively common in Japan. *A. hydrophila* has been detected in 20.5% of sea fish, and 39.6% of shellfish ; many foods, including frozen foods, can be sources of infection.[4] In addition, *A. hydrophila* is clinically classified as either an enteric or a parenteral infection. The former is caused by oral infection and leads to enteritis symptoms such as stomachache, fever, and watery/bloody diarrhea. The latter is caused externally and leads to (1) cellulitis, (2) gallstones that can result in cholecystitis, (3) sepsis, or (4) sepsis in addition to an NSI.[2] Our patient had both sepsis and an NSI, which is considered the most severe form. However, because he had no symptoms of enteritis and no clear trauma, we were not able to identify the route of infection. Nonetheless, a later interview revealed that he enjoyed a raw

Table 2 Reported cases of *Aeromonas hydrophila* infection after digestive surgery in Japan

No.	Author	Year	Age	Sex	Past history	Primary disease	Operation	Initial symptoms/ Signs	Onset	*Aeromonas hydrophila* detection culture	Sepsis	DIC	NSI	NSI-involved area	Onset of NSI	Surgical treatment for NSI	Antimicrobics after onset (based on susceptibility)	Outcome (date of death)
1	Takashima[6]	1999	64	M	Diabetes	Duodenum papilla cancer (Stage II)	Pancreatoduodenectomy	Fever/Tachycardia	POD 1	Blood	(+)	(+)	(−)				IPM/CS (+)	Alive
2	Hasegawa[7]	2001	74	F	Diabetes	Malignant lymphoma of the stomach	Total gastrectomy	Hypotension/ Fever/Respiratory failure	POD 1	Wounded area/ Blood	(+)	(+)	(+)	Around midline wound-whole abdomen	POD 1	Incision irrigation drainage	IPM/CS (+)	Dead (POD 2)
3	Tokunaga[8]	2003	63	M	Diabetes	Gallstones/ Common bile duct stone	Laparoscopic cholecystectomy/ Choledocholithotomy	Hypotension/ Fever/Respiratory failure	POD 1	Blood	(+)	(+)	(+)	Right flank (around the drain)-midline wound	POD 2	Subcutaneous drainage (at exploratory laparotomy)	IPM/CS (+)	Dead (POD 3)
4	Sakata[9]	2003	72	F	No comments in particular	Gastric cancer (Stage IA)	Total gastrectomy	Hypotension/ Fever/Respiratory failure	POD 1	Ascites	(−)	(+)	(+)	Right flank (around drain)-side chest	POD 2	Not done	IPM/CS (−)	Dead (POD 3)
5	Terashita[10]	2006	55	M	After gastrectomy	Adhesive intestinal obstruction	Partial resection of the small bowel	Decreased urine volume	POD 2	Wounded area/ (Blood blister)/ Stool	(−)	(−)	(+)	Right flank	POD 2	Not done	No record	Dead (POD 3)
6	Takeuchi[11]	2006	65	M	After gastrectomy	Strangulation ileus	Partial resection of the small bowel	Hypotension	POD 2	Blood/Ascites	(+)	(+)	(+)	Right abdomen	POD 2	Not done	MEPM (+)	Dead (POD 3)
7	Kawasaki[12]	2009	79	M	After gastrectomy	Gallbladder cancer	Cholecystectomy/ Choledochectomy	Tachycardia/ Hypotension	POD 1	Wounded area/ Blood/Drain drainage/Sputum/ Gastric juice	(+)	(+)	(−)				MEPM (−)	Dead (POD 2)
8	Kawasaki[12]	2009	73	M	Diabetes	Esophageal cancer	Subtotal excision of the esophagus	Wound infection	POD 5	Wounded area	(+)	(−)	(−)				ST (+)	Death from other illness (POD 144)
9	Kawasaki[12]	2009	72	M	Bladder cancer	Sigmoid neoplasm	Sigmoidectomy	Wound infection	POD 5	Wounded area	(−)	(−)	(−)				PZFX (Unknown)	Alive
10	Morita[13]	2009	56	M	After gastrectomy Crohn's Disease	Gallbladder cancer (Stage IIIa) /Pancreatic cancer (Stage III)	Extended right hepatectomy/ Complication : ablation of pancreatic body and tail, as well as spleen	Fever/Tachycardia	POD 4	Blood/Drain drainage	(+)	(+)	(−)				MEPM (+)	Alive
11	Ariake[14]	2009	77	M	Diabetes	Duodenum papilla cancer (Stage I)	Pancreatoduodenectomy	Fever/Respiratory failure	POD 2	Blood/Ascites	(+)	(+)	(+)	Abdomen	POD 2	Not done	IPM/CS (−)	Dead (POD 4)
12	Takata[15]	2011	73	M	Diabetes	Thoracic esophageal cancer (Stage II, after chemotherapy)	Subtotal excision of the esophagus	Hypotension/Respiratory failure	POD 1	Wounded area/ Blood	(+)	(−)	(+)	Abdomen (around midline wound) *Gastric tube bilateral side chest thoracoabdominal area-abdomen	POD 1	Debridement *Resection of necrotized gastric tube	TAZ/PIPC・CPFX (+)	Alive
13	Tomihara[16]	2011	61	M	No comments in particular	Thoracic esophageal cancer (Stage IVA, after chemotherapy)	Subtotal excision of the esophagus	Hypotension/Respiratory failure	POD 1	Ascites/Blood	(+)	(+)	(+)	*Gastric tube bilateral side chest thoracoabdominal area-abdomen	POD 3	Not done *Resection of necrotized gastric tube	MEPM (+)	Dead (POD 16)
14	Our case	2015	70	M	No comments in particular	Gastric cancer (Stage IIIB)	Total gastrectomy/ Splenectomy	Hypotension/ Fever/Melena	POD 2	Subcutaneous/ Blood	(+)	(+)	(+)	*Gastric tube right flank (around midline wound) →Right side chest-Femoral region	POD 2	Resection of necrotized gastric tube/Extended debridement	DRPM (+)	Alive

POD : post-operative day ; NSI : necrotizing soft tissue infection ; DIC : disseminated intravascular coagulation

DRPM : doripenem ; IPM/CS : imipenem/cilastatin ; MEPM : meropenem ; PZFX : pazufloxacin ; ST : sulfamethoxazole trimethoprim ; TAZ/PIPC : tazobactam/piperacillin ; CPFX : ciprofloxacin

diet and had eaten sashimi on the pre-operative day. In addition, retrospectively, bloody diarrhea was noted on POD 2. Therefore, a germ carried in the intestinal tract from an oral infection was the most probable cause. Furthermore, the patient had underlying diseases that are known to decrease host defense (i.e., leukemia and cirrhosis). Studies have shown that malignant tumors easily aggravate the condition of such patients and lead to a high mortality rate.[5,6] In this study, the patient had advanced gastric cancer and was using an oral proton pump inhibitor to control gastric acid secretion just before surgery. In addition, operative stress caused by the total gastrectomy may have resulted in an immunocompromised state after the splenectomy had decreased host defense, leading to the onset of infection.

As mentioned above, this patient was thought to carry bacteria in the intestinal tract prior to surgery. It is possible that the bacteria had been disseminated in the abdominal cavity during the operation and then infected the sites at which the drains were placed. These infections may then have become NSIs, which may have spread and led to sepsis. Bacterial translocation may also have occurred, leading to sepsis. However, few reports have examined such bacterial infections during the peri-operative period, and only 13 reports have analyzed digestive surgery in Japan (Table 2).[7–17] As described in these reports, most of the patients showed systemic symptoms, such as sepsis or DIC, and eight patients had complications from NSIs. Seven of the eight patients who had NSIs died, and the median period to death was 3 PODs (range: 2-16). One study[16] showed that one surviving patient was sensitive to antibiotics and underwent debridement, similarly to our patient. This previously reported patient also showed high-level sensitivity to carbapenem, third-generation cephems, aminoglycoside derivatives, and tetracycline with low-level sensitivity to penicillins and first- and second-generation cephems,[18] as did our patient (Table 1).

Furthermore, with an NSI, a thrombus forms in the microvessels that run through the muscular fasciae region that has been invaded by a bacterial infection. This is thought to cause extensive necrosis in the skin and subcutaneous tissues.[19] Several findings are useful to diagnose an NSI, including: (1) the presence of liquefaction necrosis of the subcutaneous tissues after an experimental skin incision, (2) confirmation of separation from the muscular layer and the influence of rapid inflammation in the subcutaneous tissues, and (3) confirmation of gas retention on CT. In cases of NSI, early diagnosis is extremely important.[20,21] In addition, complete removal of the involved site by debridement is recommended because antimicrobials cannot be expected to be delivered to the NSI-involved site.[22] However, our patient developed shock due to sepsis and showed a bleeding tendency caused by DIC. Therefore, debridement was judged to be too difficult and the patient was treated by irrigation drainage until his condition stabilized. The patient's treatment after onset was similar to a treatment outlined in a report by Hasegawa et al.[8] However, in our case, in order to drain as wide an area as possible, several Penrose drains were inserted in the space under the necrosis after the superficial fascia had been removed, where the connective tissue had been exfoliated and removed. Having undergone the above-mentioned procedures, the patient was successfully treated after switching to broad-spectrum antibiotics to treat the bacterium, and the superficial fascia[23] (the main locus of the infection) was drained effectively. Given that post-operative patients are potentially immunocompromised, sepsis should be considered as a potential cause of serious post-operative infection, especially when complicated with an NSI.

Conflicts of interest

The authors declare that they have no potential conflicts of interest.

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