Sudden Death Caused by Fulminant Bacterial Infection: Background and Pathogenesis of Japanese Adult Cases

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Abstract

Objective To analyze a risk factor for the onset of fulminant bacterial infection.

Patients and Methods Nine unexpected acute death cases were clinicopathologically analysed. All cases represented the sudden onset of shock symptom, led to acute death within a few days, and later bacteremia was identified. Pathogens were *Streptococcus pneumoniae* (*S. pneumoniae*) (5 cases), group A beta Hemolytic *Streptococcus pyogenes* (*S. pyogenes*) (3 cases), and *Vibrio vulnificus* (*V. vulnificus*) (1 case).

Results Seven of the nine patients had underlying chronic illness. *S. pneumoniae* infection was associated with splenic dysfunction, and group A beta Hemolytic *S. pyogenes* and *V. vulnificus* infections were associated with alcoholic liver injury. Group A beta hemolytic *S. pyogenes* and *V. vulnificus* infections involved necrotizing fasciitis, and alcoholic liver cirrhosis was confirmed in two of the four patients.

Conclusion Despite the different type of bacteria, the onset of fulminant bacterial infection depended upon depressed bacterial phagocytosis in the liver or spleen. Underlying chronic illnesses should be identified as a predisposing common risk factor. It is important to understand the relations between underlying chronic illness and the onset of fulminant infection.

Key words: autopsy, fulminant bacterial infection, alcoholic liver injury, necrotizing fasciitis, splenectomy

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Introduction

Fulminant bacterial infection can cause sudden onset of sepsis and multiple organ failure, leading to death within a few days (1-3). Since the identification of group A beta hemolytic *Streptococcus pyogenes* (*S. pyogenes*) in the 1980s, cases of flesh-eating bacteria have been reported (1-7). Fulminant infections by *Vibrio vulnificus* (*V. vulnificus*) (8-10) and *Streptococcus pneumoniae* (*S. pneumoniae*) (11-16) have been also introduced. Once infected, the patient's condition deteriorates within hours, and emergent therapy is necessary. Mortality rates for flesh-eating bacterial infections are as follows: 15%-34% for group A beta hemolytic *S. pyogenes* (1, 2, 4, 5, 7), 50%-75% for *V. vulnificus* (by primary septicemia) (8, 9), and 40%-60% for *S. pneumoniae* (11-13,

16).

A suspicion of malpractice can arise in cases of unexpected death. Recently, developed streptococcus grouping latex kits may be useful for early diagnosis (17, 18). However, the false negative results as well as the possibility of another bacteria such as *S. pneumoniae* are possible. There have been numerous reports on the molecular mechanisms of fulminant bacterial infection (1, 5, 6, 8, 11-16). However, there are few reports on the general pathologic features of fulminant bacterial infection in Japan (10, 19). Here, the findings from nine cases of fulminant bacterial infection were examined.

Patients and Methods

Nine patients had visited Showa University Fujigaoka

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Table 1. Clinical Information for Cases of Fulminant Infection

No	Age, sex	Chief complaint	History	Septic shock	Bacteria	Culture	Onset to death
1	74, M	shock syndrome	unknown	(+)	<i>S.pneumoniae</i> (23F)	blood	1 day
2	43, M	dyspnea, vomiting	splenectomy due to HSC	(+)	<i>S.pneumoniae</i>	blood	3 days
3	32, F	throat pain	splenectomy due to ITP	(+)	<i>S.pneumoniae</i> (12F)	blood, tonsil cerebrospinal	2 days
4	43, M	dyspnea	unknown	(+)	<i>S.pneumoniae</i>	blood, sputum	3 days
5	57, F	vomiting, diarrhea	alcohol hepatic injury appendicitis	(+)	<i>group A beta</i> HSP	blood, pharynx	3 days
6	73, M	vertigo, limb pain	subtotal (stomach)	(+)	<i>group A beta</i> HSP	blood, pleural effusion	1 day
7	57, M	limb pain, diarrhea	alcohol hepatic injury gallstone	(+)	<i>Vibrio vulnificus</i>	blood, stool,	3 days
8	61, M	dyspnea	alcohol hepatic injury emphysema	(+)	<i>S.pneumoniae</i>	blood, sputum	5 days
9	84, F	limb pain	mamma ca colon ca	(+)	<i>group A beta</i> (T11, speB+C)	blood	4 days
ITP, idiopathic thrombocytopenic purpura					No, case number		
HSC, hereditary spherocytosis					ca, carcinoma		
HSP, hemolytic <i>Streptococcus pyogenes</i>					<i>S. Streptococcus</i>		
M, male							
F, female							

Hospital and other hospitals during the period 1999 through 2008 and had unfortunately died; - seven of these nine cases were subjected to autopsy. Autopsy was performed because of sudden unknown death, and infectious bacterial pathogens were later identified in blood cultures. Criteria for the diagnosis of fulminant infection include bacteremia and unexpected death within a few days after the acute onset of shock symptoms. Five patients had *S. pneumoniae* infection, three had group A beta hemolytic *S. pyogenes* infection, and one had *V. vulnificus* infection. Cases 5, 6 and 9 were diagnosed according to the criteria established by the working group on severe *S. pyogenes* infections (3). Also, Case 7 was of *V. vulnificus* induced septicemia (sudden onset of systemic symptoms) within 24 hours of eating seafood (shellfish) in the summer (9). Thoracotomy and ventrotomy were performed in five cases, and thoracotomy, ventrotomy, and craniotomy were performed in two cases. Informed consent was obtained from the families of all patients, and the study was performed in accordance with the Declaration of Helsinki (1975).

Histologic examinations

Resected tissue specimens were fixed at autopsy in 10% neutral-buffered formalin and embedded in paraffin. Three-micron-thick sections were generated and stained with Hematoxylin and Eosin and examined microscopically. Each tissue sample was analyzed histopathologically. When the existence of bacteria was suspected histologically, the tissue was subjected to Gram and Giemsa staining.

Detection of bacteria

Microbiologic blood cultures were performed in SN and

SA bottles (Japan, bioMerieux, Tokyo) and analyzed with BacT/ALERTt (bioMerieux). When a positive signal was obtained, the sample was incubated on sheep blood agar (M 58), chocolate agar, and subjected Brucella HK agar and subjected to Gram staining to isolate and identify the organism. *S. pneumoniae* was identified as an α -hemolytic, Gram-positive coccus sensitive to des deoxycholic acid (10%) and optochin (ethylhydrocupreine-HCl). *S. pyogenes* was identified as a β -hemolytic, Gram-positive coccus sensitive to bacitracin and negative to catalase. *V. vulnificus* was identified as a glucose-fermentable Gram-negative bacillus sensitive to oxidase and tolerant to 3% sodium chloride (peptone water) (ID test; EB20 kit; Nissui Pharmaceutical, Tokyo, Japan).

Results

Clinical findings

Nine patients were analyzed in the study. The mean age was 57.8 years (range, 32-84 years) (Table 1). Six were males, and three were females. The patients experienced rapidly progressive bacterial infection characterized by septic shock, leading to multiple organ involvement. The capsular type of *S. pneumoniae* was 23F in Case 1 and 12F in Case 3. Group A beta hemolytic *S. pyogenes* in case 9 was identified in the strain of T-agglutination (serotype 11), and possessed *S. pyogenes* exotoxin B and C genes. Five patients with *S. pneumoniae* infection experienced sudden onset of shock symptoms, and two of the four patients with group A beta *S. pyogenes* or *V. vulnificus* infection experienced gastrointestinal involvement and melalgia with shock

Table 2. Autopsy Findings in Cases of Fulminant Vacterial Infection

No	Necrotizing fasciitis	Lung	Spleen weight	Adrenal bleeding	Bacteria location	Cause of death	Background
1	(-)	congestion and bleeding pneumonia (-)	120 g	(-)	Gram (+) diplococci, various organs	circulatory collapse	Plasma cell myeloma
2	(-)	congestion and bleeding pneumonia (-)	S	(+)	Gram (+) diplococci, heart, lung, kidney	circulatory collapse, subarachnoid bleeding	not confirmed
3	(-)	congestion and bleeding pneumonia (-)	S	(+)	Gram (+) diplococci, tonsil, heart, lung, kidney	circulatory collapse	not confirmed
4	(-)	congestion and bleeding pneumonia (-)	60 g	(+)	not confirmed	circulatory collapse, subarachnoid bleeding	not confirmed
5	(+) left arm	congestion and bleeding pneumonia (-)	90 g	(+)	Gram (+) coccus left arm	circulatory collapse	liver cirrhosis
6	(+) left limb	congestion pneumonia (-)	75 g	(-)	Gram (+) coccus left limb, lung	circulatory collapse	not confirmed
7	(+) shoulder, legs	congestion and bleeding pneumonia (-)	190 g	(-)	not confirmed	circulatory collapse	liver cirrhosis

No, case number
S, splenectomy

Figure 1. Gram staining of sputum in Patient 8. Numerous gram-positive cocci are linked side by side, with no observation of polymorphonuclear leukocytes.

symptoms. Seven of nine patients had an underlying chronic disease. In addition, two of the five patients with *S. pneumoniae* infection had a history of splenectomy for treatment of a hematologic disorder, and three patients were alcohol abusers, one of them also had *S. pneumoniae* infection. Three of the five patients with *S. pneumoniae* infection had a hematologic disorder (13), and three patients had alcoholic hepatic injury. No clinical information was available for two patients. An antibiotic therapy was not available in several cases because of acute death. Also, an emergent incision and debridement to treat necrotizing fasciitis could not be undertaken except for case 7 because general condition was deteriorated. No improvements were observed in any of the cases despite intensive care treatment. In Case 1, chemotherapy for treatment of hematologic malignancy was not per-

formed. Also, emergent gram staining of sputum in case 8 showed numerous diplococci (Fig. 1A), and urinary antigen of *S. pneumoniae* was also confirmed. Also, *V. vulnificus* was also confirmed in the smear of an emergent archenteron of incision in the left shoulder.

Autopsy findings

On postmortem examinations performed seven of the nine dead cases (except cases 8, 9), showed petechiae on the body surface and subcutaneous hemorrhages, consistent with Disseminated intravascular coagulation (DIC) (Table 2). Group A beta *S. pyogenes* and *V. vulnificus* infections involved necrotizing fasciitis (Fig. 2) (1, 5, 6). Some patients showed blisters from the epidermis to the dermis (19, 20). Pulmonary congestion complicated by bacterial colonization was observed (Fig. 3) (20-23). Four of the seven patients showed adrenocortical hemorrhage (24). Histopathologically, Gram-positive diplococci were confirmed in three of the four patients with *S. pneumoniae* infection. In Case 1, numerous bacteria in various organs were also observed (Fig. 4). Gram-positive cocci of group A beta *S. pyogenes* in two patients were present around the necrotizing fasciitis (Fig. 5); however, colonization by *V. vulnificus* was not identified. Death was attributed to rapid progressive sepsis due to bacteremia, leading to circulatory collapse. Subarachnoid bleeding caused by circulatory collapse was present in two cases. In the cases of pneumococcal infection, plasma cell myeloma was identified after death (13, 25, 26). Two of the three patients with group A beta *S. pyogenes* and *V. vulnificus* infection showed alcoholic liver cirrhosis (1, 5, 8-10).

Figure 2. Gross findings of patient 6. (A) Desquamation and erosion with bluish-purple discoloration of the left inner femur. (B) Incision of the left inner femur shows subcutaneous hemorrhage and necrosis. (C) Hemorrhagic and necrotic muscle and fascia.

Figure 3. Gross and histologic findings of the lung in patient 1. (A) Severe right hemorrhagic pulmonary congestion (lung weight, 980 g). (B) Pulmonary congestion complicated by bacterial colonies (arrows) (Hematoxylin and Eosin staining).

Discussion

Fulminant bacterial infections are mainly categorized as *S. pneumoniae* or group A beta hemolytic *S. pyogenes* and *V. vulnificus* infections. The former is associated with splenectomy, whereas the latter are associated with liver dysfunction and necrotizing fasciitis. The spleen comprises 25% of the body's lymph tissue, and is involved in bacterial phagocytosis, antigen presentation, and opsonin production. Splenic macrophages are more efficient than neutrophils with respect to trapping in the blood, especially in bacterial phagocytosis (11, 12, 14, 16, 27). Also, the polysaccharide capsule of *S. pneumoniae* makes it resistant to phagocytosis. Opsonin and specific antibodies to the polysaccharide capsule are significantly reduced with splenectomized patients;

Figure 4. Histologic findings of patient 1. (A) Bone marrow shows numerous Gram-positive diplococci (arrows) (Gram stain). (B) Hepatic sinusoid shows numerous Gram-positive diplococci (arrows) (Gram stain).

once the patient is infected, can occur readily bacteremia. Patients who have undergone splenectomy as treatment for reticuloendothelial disorders such as hematologic disease are susceptible to *S. pneumoniae* infection (11, 13, 14). No splenic dysfunction of three patients without histories of splenectomy was confirmed, however, it seems that immunocompromised state based on the depressed phagocytosis such as plasma cell myeloma (case 1) and an alcoholic liver injury (case 8) may have played a role in the onset of *S. pneumoniae* infection. Therefore, the possibility of *S. pneumoniae* infection is not always denied despite the lack of history of splenectomy. The Waterhouse-Friderichsen (W-F) syndrome is a clinicopathological entity consisting of sudden onset of a rapidly progressive illness, shock, cyanosis, a petechial rash, haemorrhages in both adrenal glands, and death usually within 24 hours. In the present study, it seems that the collapse of adrenocortical sinusoids caused

Figure 5. Histologic and bacterial findings of patient 6. (A) Subcutis shows inflammation surrounded by fibrin adjacent to torn muscle fibers (Hematoxylin and Eosin staining). (B) Numerous Gram-positive cocci are linked side by side (arrows) (Gram stain).

by the sepsis played a role in the development of adrenal hemorrhages (19, 24).

Alcoholic liver cirrhosis was confirmed at autopsy in two patients with group A beta *S. pyogenes* or *V. vulnificus*. The presence of alcoholic liver cirrhosis makes regulation of the host immune response difficult. Kupper cell depletion is associated with decreased activity of the reticuloendothelial system, and the presence of sinusoidal compression due to pericellular fibrosis facilitates the formation of arteriovenous shunts. Impairment of the host defense system can lead to bacteremia (28, 29). It appears that bacteria resistant to phagocytosis invade the blood from the intestinal tract and migrate to the liver via the portal vein, at which point marked bacterial proliferation and bacteremia occur (29). The pathogenesis of alcoholic liver injury caused by depressed bacterial phagocytosis depends on the onset of fulminant infection (29). *V. vulnificus* infection associated with

eating seafood such as raw oyster and shellfish in the summer must be distinguished from group A beta hemolytic *S. pyogenes* (10, 30).

The cause of death in each case is circulatory collapse caused by fulminant infection (10, 19). Bacterial infection may not be identified at first histologic assessment. Also, the initial focus of bacteria except for case 3 was unknown probably due to the very early entry of bacteria into circulation. Once infection occurs, it produces endotoxin derived from lipopolysaccharide caused by *S. pneumoniae* and *V. vulnificus*, or produces large amounts of cytokines caused by the host-immune response to the toxic superantigen by group A beta hemolytic *S. pyogenes*, leading to acute volume loss (3, 4, 20-23, 31-37). The onset of fulminant infection depends on the bacteria and the sensitivity of the host (38). In the present study, depressed bacterial phagocytosis such as splenic dysfunction or liver dysfunction was a predisposing common risk factor for the onset of fulminant bacterial infection (28, 29, 37).

A search of the literature found splenectomy in 91.9% of patients with fulminant *S. pneumoniae* infection (14), liver dysfunction in 10%-20% of patients with group A beta hemolytic *S. pyogenes* infection (1, 5, 7, 21, 39), and liver dysfunction in 66%-90.3% of patients with *V. vulnificus* infection (8, 36, 40), which supports our data. Clinically, empiric antibiotic therapy should be performed at first after examining cultures (21, 27), and underlying chronic illnesses should be identified. There are no published data comparing fulminant infection classified according to the type of bacteria, and each patient with depressed phagocytosis in liver or splenic dysfunction is a common risk factor. Analysis of additional cases of fulminant infection is needed to elucidate the pathogenic mechanisms involved. A general physician should always keep the possibility of fulminant bacterial infection in mind when examining patients with shock symptoms because the mortality rate of the disease depends on the first primary intensive care.

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