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An Autopsy Case of Rupture of Infectious Thoracic Aortitis Induced by Methicillin-Resistant *Staphylococcus Aureus*

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Data Interpretation D
Manuscript Preparation E
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Patient: Female, 83
Final Diagnosis: Rupture of infectious thoracic aortitis
Symptoms: Cardiac pulmonary arrest
Medication: —
Clinical Procedure: Medication
Specialty: Pathology

Objective: Rare disease

Background: Infectious aortitis has a poor prognosis and high mortality rate if untreated. Here, we report a case of rupture of infectious aortitis induced by methicillin-resistant staphylococcus aureus (MRSA).

Case Report: An 83-year-old female patient was hospitalized due to continuous fever and diarrhea, which was diagnosed as colitis. The colitis was determined to have been induced by small vessel vasculitis upon histological examination. Fasting and central venous hyperalimentation using a peripherally inserted central catheter (PICC) were carried out for rest of the intestine. Swelling and pus were observed at the insertion site of the PICC. Since methicillin resistant staphylococcus aureus (MRSA) was detected in the culture of the pus and the blood, the patient was treated with vancomycin. After confirming that the blood culture became negative, prednisolone (PDL) was started as therapy for the colitis. Her diarrhea and fever improved. After vancomycin was stopped, MRSA-arthritis appeared. She suddenly died due to acute massive hemorrhage into the mediastinum and left thoracic cavity from the atherosclerotic ulcer of the thoracic aorta. It took 98 days from the first detection of MRSA in her blood to her death. We found gram-positive coccus in the ruptured aortic ulcer and we also detected MRSA gene by polymerase chain reaction in the ulcer. These results suggest that MRSA could colonize in the aortic ulcer during the MRSA-bacteremia and the MRSA could contribute to the vulnerability of the aortic wall.

Conclusions: After septicemia occurrs in an elderly person, the patient should be followed up by considering infectious aortitis, especially when the patient has several risk factors.

MeSH Keywords: Aorta, Thoracic • Aortic Rupture • Aortitis • Autopsy • Bacterial Infections • Methicillin-Resistant *Staphylococcus aureus*

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Background

Infectious aortitis has a poor prognosis and high mortality rate if untreated [1]. Making a diagnosis of infectious aortitis could be difficult due to its non-specific symptoms [2]. Here, we present a case of rupture of an infectious aortic ulcer in an elderly female patient.

Case Report

An 83-year-old female patient presented to a hospital due to fever persisting for 1 week and diarrhea containing blood. She had hypertension, atrial fibrillation, and left ureteral stones (after extracorporeal shock wave lithotripsy). The computed tomography (CT) scan revealed wall-thickness from the ascending colon to descending colon. On Day 12 of her hospitalization, an endoscopic examination of lower alimentary tract was performed and furred ulcers were found from the descending colon to the rectum. Upon microscopical examination of the biopsy specimens, there was no neoplastic change and inflammatory cells infiltrate not only in the epithelial layer and interstitial tissue but also blood vessel walls (Figure 1). Inflammatory cells including neutrophils infiltrated into the blood vessel walls. Therefore, colitis due to vasculitis of small blood vessels was suspected. Upon her blood examination, both proteinase 3-antineutrophil cytoplasmic antibodies (PR3-ANCA) and myeloperoxidase-ANCA (MPO-ANCA) were negative, and anti-nuclear antibody (ANA) was slightly positive (1: 40; under 1: 40 on the reference level). For the rest of the colon and rectum, a peripherally inserted central catheter (PICC) was indwelled. Central venous hyperalimentation and fasting were carried out on hospital Day 13 to Day 21. After fasting, her diarrhea was gradually improved. On hospital Day 20, redness, swelling and pus were observed at the insertion site of the PICC. Culture of the pus and blood were carried out, and administration of piperacillin and tazobactam were started. On hospital Day 22, methicillin-resistant staphylococcus aureus (MRSA) was detected on the culture of the pus and blood obtained on hospital Day 21. The MRSA in the blood culture and the MRSA in the pus culture showed similar patterns

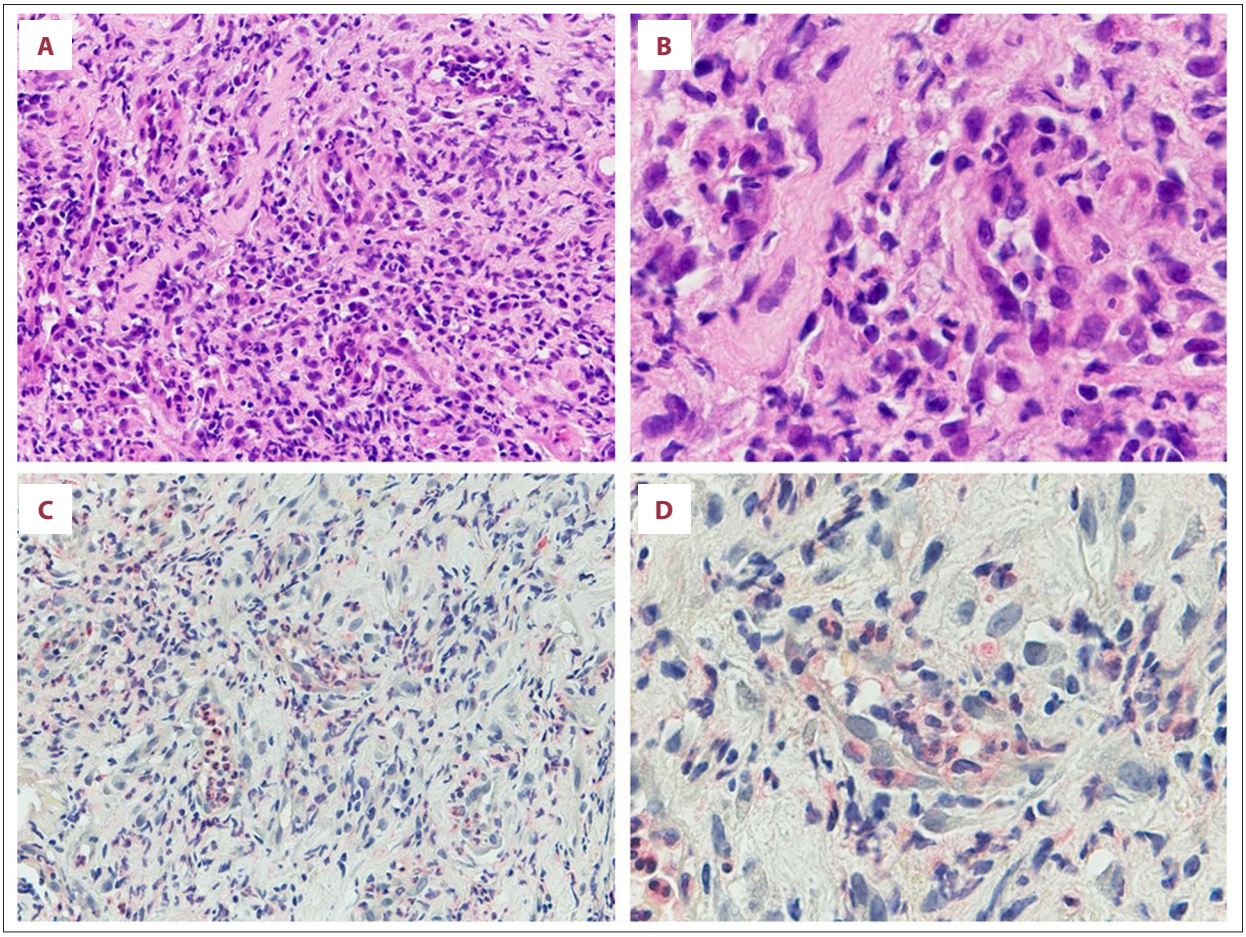

Figure 1. Suspicion of small vessel vasculitis upon biopsy specimen of the colon. (**A, B**) Hematoxylin and eosin stain of the specimens. (**C, D**) Esterase stain of the specimens. In A and C the original magnification of the objective lens was 40×, while the original magnification of the objective lens was 100× in **B** and **D**.

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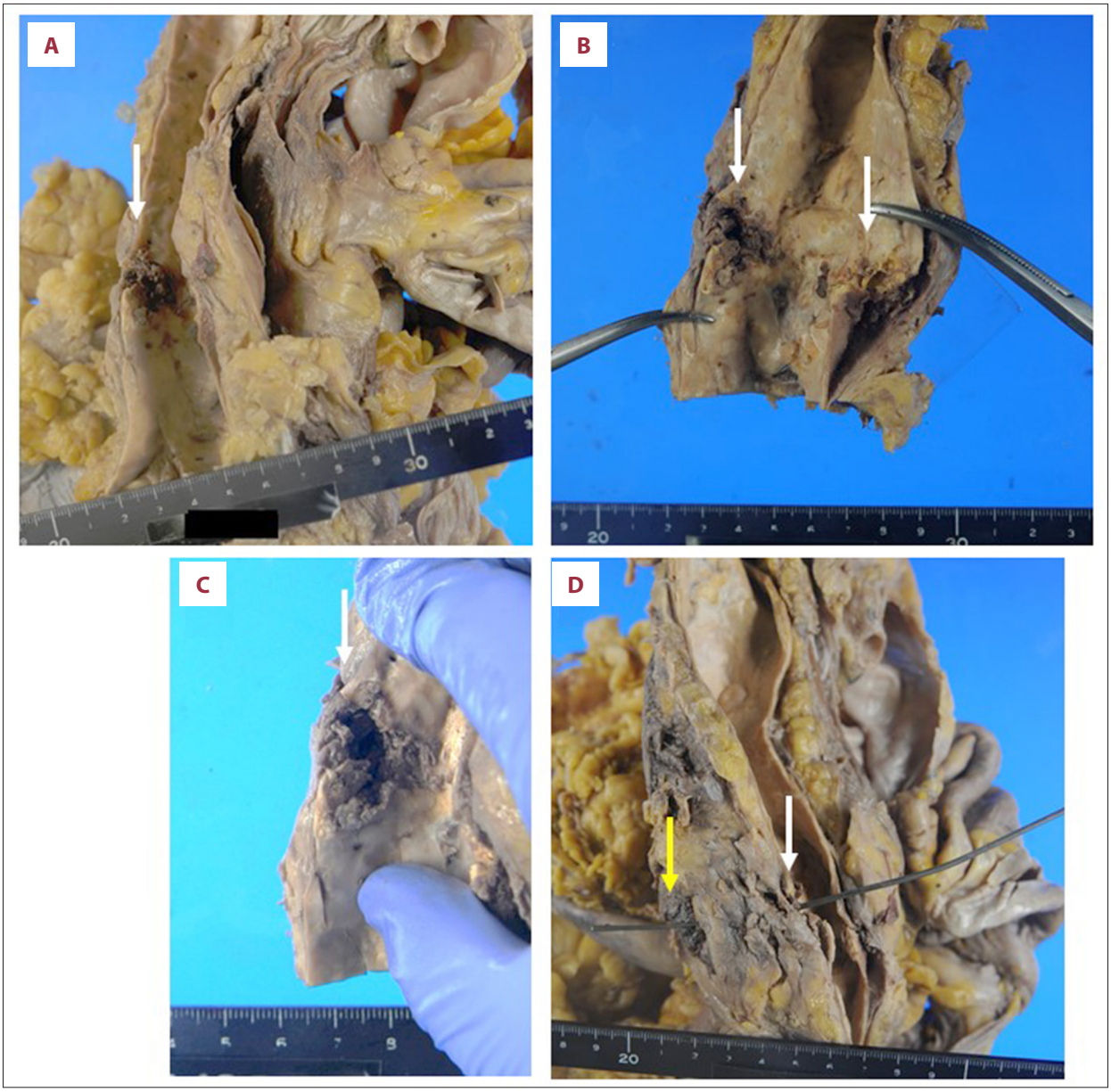

Figure 2. Penetration of the ulcer of the thoracic aorta to the mediastinum, followed by perforation into the left thoracic cavity. The aorta was opened from behind. (**A–C**) A ulcer in the thoracic aorta (arrows). (**D**) Penetration from the thoracic aorta to the left thoracic cavity. The white allow shows the perforation site of the aorta, while the yellow arrow shows the penetration site of the left thoracic cavity.

of drug-sensitivities, suggesting that the MRSA-infection at the insertion site of the PICC induced MRSA-bacteremia. Therefore, the PICC was decannulated and administration of vancomycin was started. On hospital Day 38, the patient's stool became almost solid but rectovaginal fistula due to the proctitis was found. Blood culture carried out on hospital Day 47 became negative. On hospital Day 49, administration of prednisolone (PDL) (30 mg/day) was started. On hospital Day 51, her fever and C-reactive protein (CRP) declined. After that time, dosages of PDL was gradually decreased. On hospital Day 90, vancomycin was stopped. From around hospital Day 101, her right knee pain appeared. Administration of NSAIDs was started, resulting in no effects and redness and swelling of the right knee appeared. On hospital Day 115, she became febrile and the titer of CRP increased. Upon arthrocentesis of the right knee, purulent synovial fluid was obtained and MRSA was detected in the culture of the synovial fluid. On hospital Day 116, administration of vancomycin was restarted. On hospital Day 119, her cardiorespiratory arrest suddenly occurred, and resuscitation had no effects, resulting in her death. At the time of her death, PSL had

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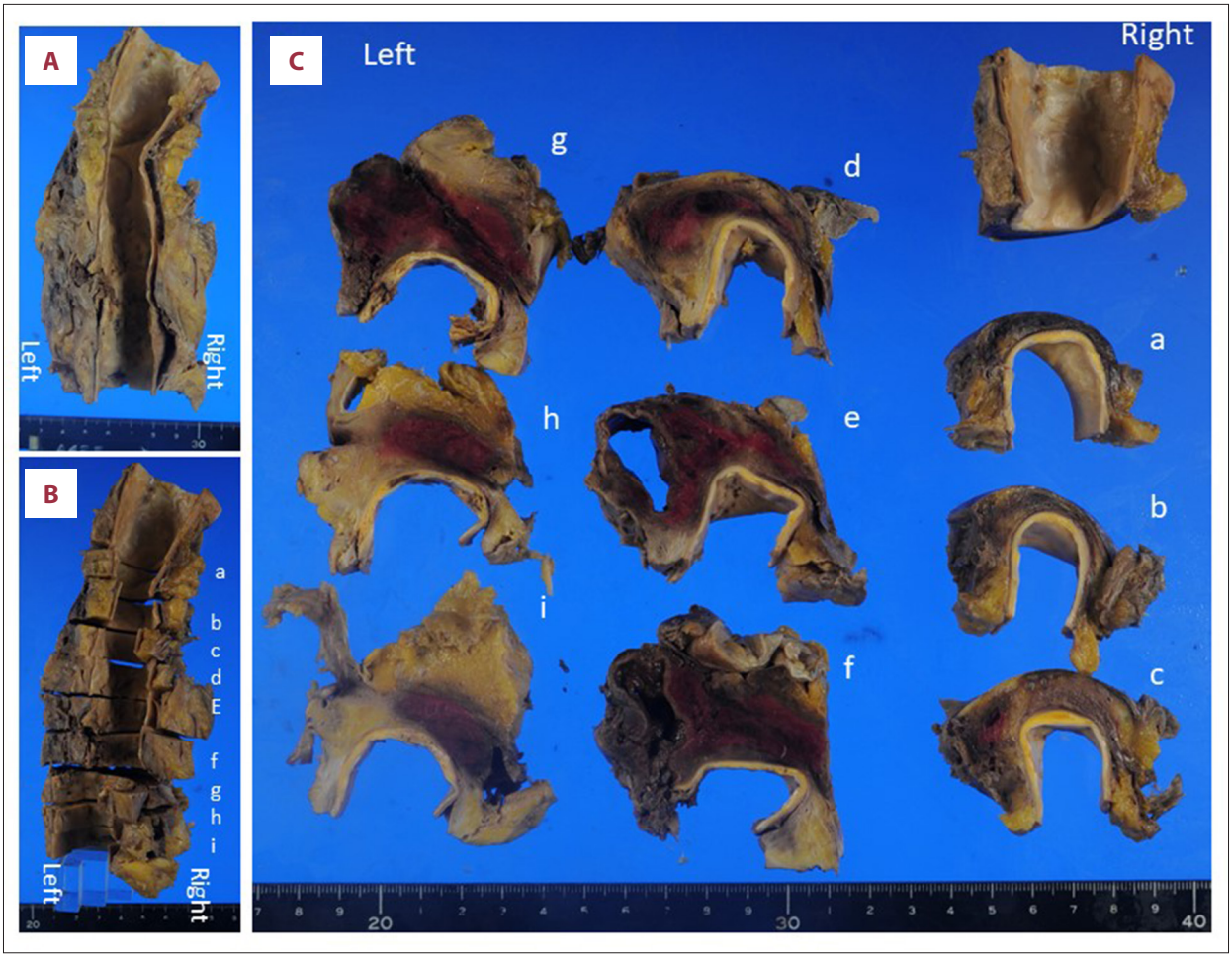

Figure 3. Mediastinal hematoma induced by the perforation of the ulcer of the thoracic artery. (**A**) The ulcer of the thoracic artery and the left side-mediastinal hematoma was shown. (**B**) The cutting sites of the specimen are shown. (**C**) The horizontal sections of the thoracic artery and the mediastinum are shown.

been reduced to 7.5 mg/day. It took 98 days from the first detection of MRSA in her blood to her death.

Autopsy findings

Autopsy was started 4 hours after her death. In the thoracic aorta, 20×20 mm arteriosclerotic ulcer and a rupture of the ulcer was found (Figure 2). In the left thoracic cavity, 1200 mL of blood and 602 g of blood clot were found. Large mediastinal hematoma was also found (Figure 3). These suggest acute bleeding into the mediastinum followed by bleeding into the left thoracic cavity. The total blood of thoracic cavity and mediastinum was more than 2000 mL. These results suggest that the fragile aortic wall in the arteriosclerotic ulcer ruptured to the mediastinum, followed by the perforation into the left thoracic cavity, and that the perforation into the mediastinum and thoracic cavity induced acute massive hemorrhage, resulting in the acute cardio-respiratory arrest. There were no significant changes in the heart and lungs histologically.

Microscopical examination

In the aortic ulcer, arteriosclerosis containing cholesterin crystals was found in the aortic wall. Bleeding, necrotic tissue and severe infiltration of neutrophils were observed in the adventitia and the surrounding interstitial tissue of the aorta (Figure 4). The necrotic tissue contained bacterial colonies, which were gram-positive coccus, suggesting that bacterial infection to the arteriosclerotic ulcer accelerated fragility of the ulcer, followed by induction of the rupture.

Polymerase chain reaction (PCR) for detection of MRSA

As we have described, MRSA was detected in the patient's blood culture and the pus from the injection site of PICC, as well as in the synovial fluid of the right knee. These MRSA cultures showed similar drug-sensitivity. These data suggest that MRSA in the PICC-injected site induced bacteremia, followed by the MRSA-arthritis of the knee joint. Moreover, we detected

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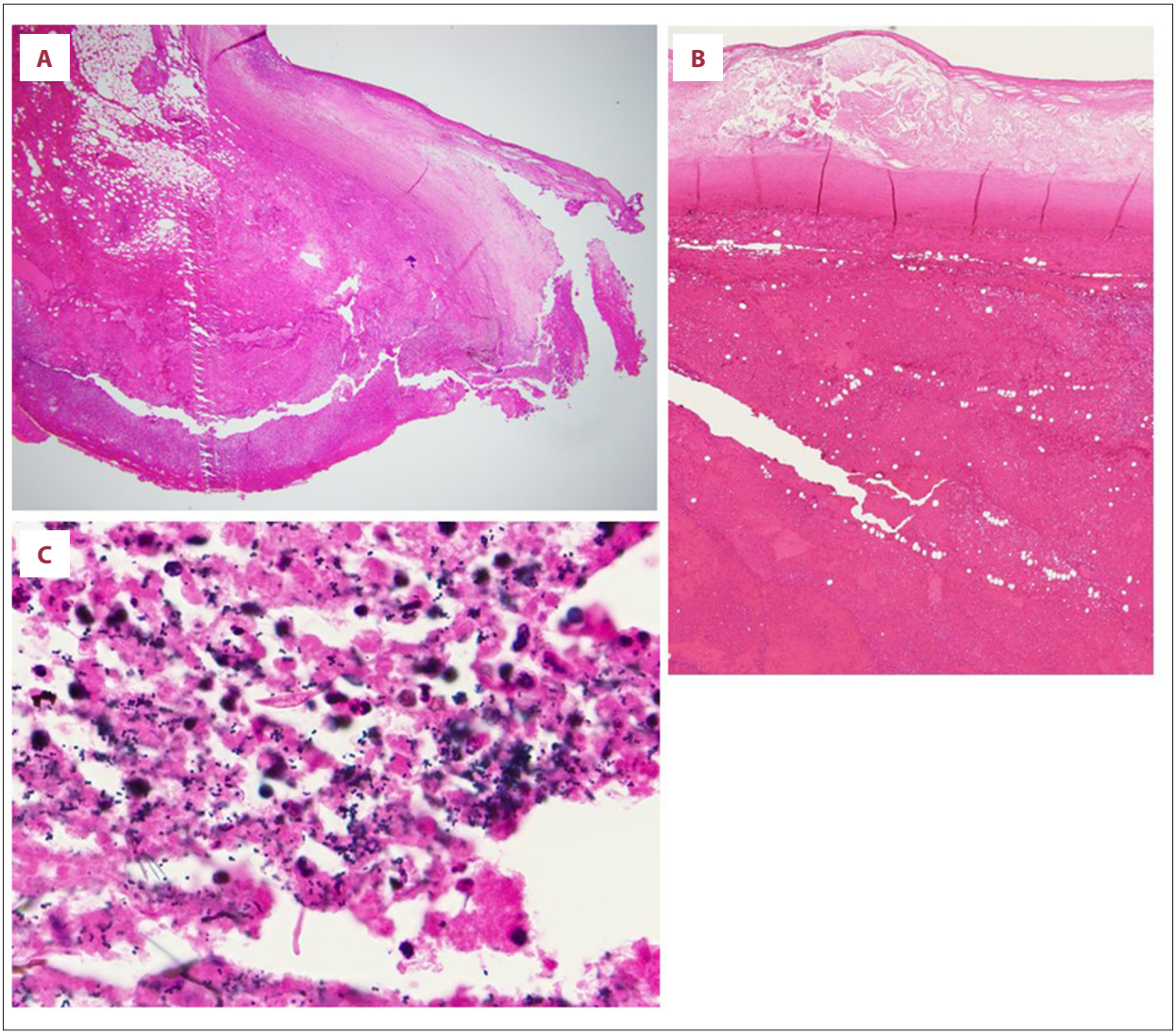

Figure 4. Histological examination of the aortic ulcer. (**A**) The artic ulcer and bleeding in the aortic wall and circumference of the aorta (original magnification of the objective lens 2×). (**B**) The aortic wall close to the aortic ulcer (original magnification of the objective lens 2×). (**C**) Gram stain of the necrotic tissue of the aortic ulcer (original magnification of the objective lens 100×).

gram-positive coccus in necrotic tissue of the ruptured aortic ulcer upon histological analyses, suggesting that MRSA also infected to the aortic ulcer. Therefore, we carried out polymerase chain reaction (PCR) to detect MRSA genes in the aortic wall and the necrotic tissue of the aortic ulcer [3]. DNA was prepared from the spleen, hematoma in the left thoracic cavity, the necrotic tissue of the aortic ulcer and aortic ulcer using Kaneka Easy DNA Extraction Kit, Kaneka, Tokyo, Japan. Genes of 16SrRNA, mec A, nuc, and human G3PDH were amplified using KAPA 2G Fast HotStart (Kapa biosystems, Boston, MS, USA). Primers for 16SrRNA (16 S rRNA gene of *Staphylococcus aureus*) mec A (methicillin resistant gene) and nuc (thermostable nuclease) were prepared, while primers for human G3PDH (glyceraldehyde 3-phosphatedehydrogenase) were obtained from Takara (Kusatsu, Japan). We examined 16S rRNA, mec A, nuc, and human G3PDH in the necrotic tissue of the aortic ulcer, the aortic ulcer, and cultured MRSA colonies obtained from the knee joint (positive control for MRSA) (Figure 5). We detected only human G3PDH and did not detect MRSA gene in the spleen, which contained a lot of peripheral blood, suggesting that MRSA did not exist in the blood at the time of the patient's death. On the other hand, we clearly detected MRSA gene in samples from the ruptured aortic ulcer and from the colony from the synovial fluid. We prepared 2 samples from the hematoma in the left thoracic cavity. Since we detected very low levels of PCR products of MRSA in the one of hematoma samples, these PCR-products could be contamination of necrotic tissue of the aortic ulcer into the hematoma. These results suggest that MRSA infected the aortic wall and induced the rupture to the mediastinum, and that the status of MRSA bacteremia was not known at the time of her death.

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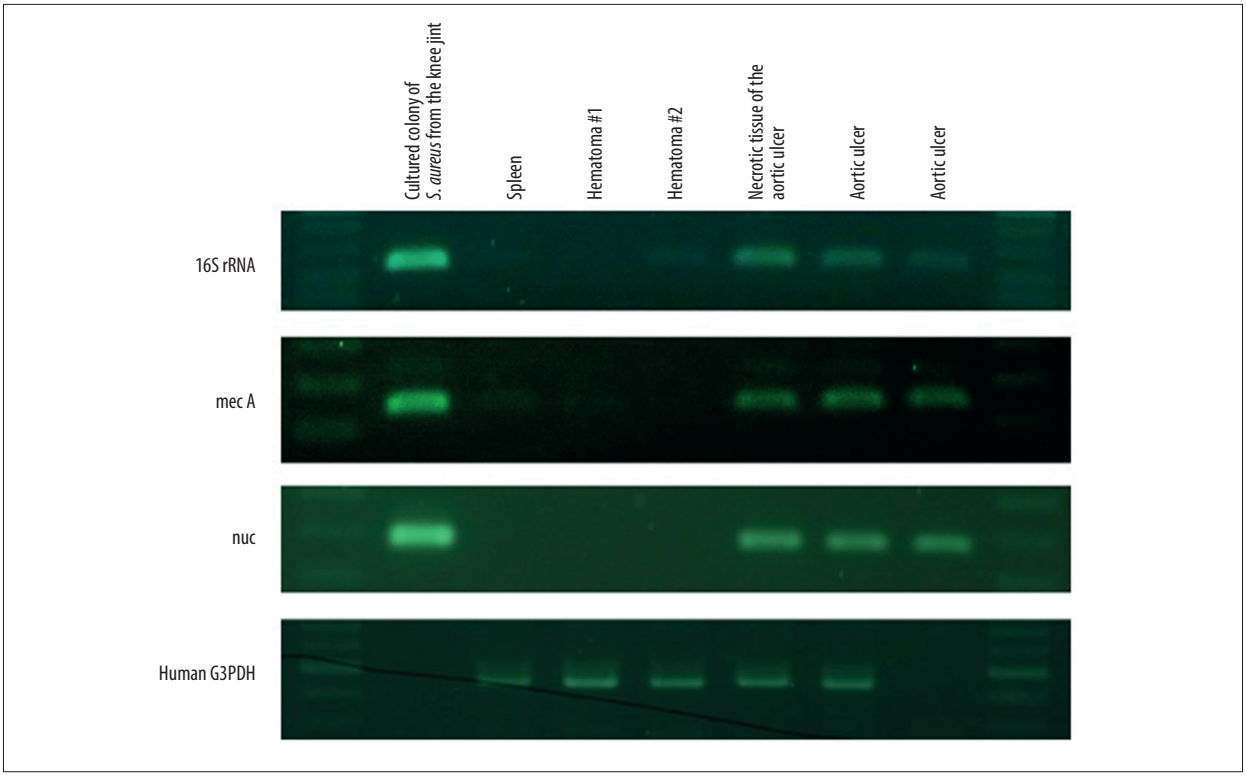

Figure 5. PCR for detection of MRSA in the aortic ulcer. DNA was prepared from the spleen, hematoma in the left thoracic cavity, the necrotic tissue of the aortic ulcer, and aortic ulcer. Genes analyzed included 16SrRNA, mec A, nuc, and human G3PDH.

Discussion

In this paper, we reported a case of an elderly female patient with a ruptured aortic ulcer with infectious induced by MRSA.

Infectious aortitis has a poor prognosis if untreated. One of causes of the poor prognosis of infectious aortitis could be a delay in making a definitive diagnosis. Diagnosis of aortitis is often delayed as manifested symptoms are largely non-specific, such as, fever, chest pain, back pain [2]. Our case also did not show clear symptoms, and sudden cardio-respiratory arrest occurred due to acute massive bleeding. The risk factors of poor prognosis are female, elderly, *Staphylococcus aureus* infection, aneurysm rupture, lack of surgical treatments, aneurysm located above renal arteries, and extensive infection around periaortic site [4,5]. Risk factors in our case included an elderly female, MRSA infection, lack of surgical treatment, rupture of the aorta, aneurysm located above renal arteries, and extensive infection around periaortic site. Therefore, our case had several risk factors, suggesting that rupture of the aorta could easily occur, resulting in poor prognosis of patient.

It has also been reported that affected sites of aorta can have different pathogens [6,7]. Treponema pallidum affects the ascending aorta or aortic arch. Gram-positive bacteria (staphylococcus and enterococcus species) tend to affect the thoracic aorta, while gram-negative bacteria, especially salmonella species, affect abdominal aorta. In our case, MRSA induced infected aortitis, and affected thoracic aorta. Therefore, our case could be a typical case of infectious aortitis of Gram-positive bacteria.

It has been reported that infectious aortitis can occur in a previously diseased aorta, such as, intimal injury commonly from an atherosclerotic plaque, aneurysm, and direct inoculation from trauma to the intima [8]. Diabetes mellitus, alcoholism, medical devices, and immunocompromised individual containing patients with immunocompromised therapy [9]. In our case, the patient had at least 2 kinds of risk factors of infectious aortitis, atherosclerosis and steroid therapy. It has been reported that steroid therapy can suppress production of cytokines and functions of macrophages, neutrophils, and lymphocytes, resulting in the induction of immunosuppression. In our case, 70 day-steroid therapy could induce the status of immunosuppression [10]. Rupture occurred at the site of the atherosclerotic ulcer of the thoracic aorta and we detected MRSA in the aortic ulcer by PCR method. While MRSA was not detected in the spleen containing a large amount of peripheral blood, suggesting that the patient status was not septicemia at the time of her death. MRSA-septicemia could occur in the patient, because MRSA was detected several times in the blood from the artery, on hospital Day 22, 30, 35, and 40. Therefore, MRSA moved to the right knee joint and aortic ulcer

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and colonized during that the period, since arterial blood was negative for bacteria including MRSA on hospital Day 47, 62, and 118. Infection of MRSA in the atherosclerotic ulcer in the aorta destroyed the aortic wall, resulting in inducing perforation of the aorta. Previously, a similar case was reported [11]. In that case, aortic rupture of an atherosclerotic plaque of the ascending aorta was induced by MRSA, resulting in a cardiac tamponade. The patient was rescued from death by an emergency operation.

Conclusions

In this paper, we have described an autopsy case of rupture of infected aortitis induced by MRSA. These results suggest that clinicians should carefully follow-up with patient, who have septicemia, upon physical examination, blood examination, and diagnostic imaging. Moreover, when steroid therapy is given to the patient, blood cultures should regularly be carried out.

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Conflict of interest

None.

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