Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8976-17
Intern Med 57: 1375-1380, 2018
http://internmed.jp

【 ORIGINAL ARTICLE 】

A Clinicopathological Analysis of Six Autopsy Cases of Sudden Unexpected Death due to Infectious Aortitis in Patients with Aortic Tears

Marin Ishikawa[1], Mishie Ann Tanino[1], Masaya Miyazaki[2], Taichi Kimura[1], Yusuke Ishida[1], Lei Wang[1], Masumi Tsuda[1], Hiroshi Nishihara[3], Kazuo Nagashima[4] and Shinya Tanaka[1,3]

Abstract:

Objective Cardiovascular disease is a leading cause of sudden unexpected death even in hospitalized patients. Infectious aortitis is a rare disease that has the potential to cause aortic tears and hemorrhage followed by sudden death. The aim of this study was to reveal the clinicopathological features of infectious aortitis that are related to sudden unexpected death.

Methods We retrospectively reviewed 1,310 autopsy cases over 15 years and selected the cases involving patients who died suddenly due to aortic tears. We analyzed the clinical information and pathological findings.

Results One hundred thirty-three of 1,310 cases (10.2%) were autopsied under the clinical diagnosis of unexpected sudden death. Aortic tears were identified in 33 cases (2.5%) and infectious aortitis was diagnosed in 6 (18.2%) of these cases. All cases involved male patients (middle-aged to elderly) with risk factors for atherosclerosis (*i.e.,* hypertension). The laboratory data showed continuous leukocytosis and C-reactive protein elevation, even during the improvement phase, in patients with pre-existing infectious disease. The autopsy findings revealed three types of aortic tears (aneurysms, dissections and penetrating atherosclerotic ulcers with moderate to severe atherosclerosis), and the infiltration of numerous neutrophils at the site of rupture. Gram-positive bacteria were detected in four cases and Gram-negative bacteria were detected in two cases.

Discussion We demonstrated that sudden unexpected death caused by infectious aortitis rarely occurred in hospitalized patients, even in the recovery phase of the preceding infectious disease. We therefore recommend that clinicians pay attention to infectious aortitis in patients with infectious disease, particularly elderly patients with atherosclerotic disease, even those who are in the improvement phase.

Conclusion Unexpected sudden death by infectious aortitis in the recovery phase of antecedent infection.

Key words: aortic aneurysm, aortic dissection, atherosclerosis, infectious aortitis, penetrating atherosclerotic ulcer, sudden death

(Intern Med 57: 1375-1380, 2018)
(DOI: 10.2169/internalmedicine.8976-17)

[1]Department of Cancer Pathology, Hokkaido University Graduate School of Medicine, Japan, [2]Department of Renal and Genitourinary surgery, Hokkaido University Graduate School of Medicine, Japan, [3]Department of Translational Pathology, Hokkaido University Graduate School of Medicine, Japan and [4]Department of Diagnostic Pathology, Sapporo Higashi Tokushukai Hospital, Japan
Received: February 1, 2017; Accepted: September 2, 2017; Advance Publication by J-STAGE: January 11, 2018
Correspondence to Dr. Mishie Tanino, tanino@med.hokudai.ac.jp

Table. Clinicopathological Data of Six Autopsy Cases with Infectious Aortitis.

	Clinical Information					Pathological Information		
Case no.	Age, Sex	Pre-existing Disease	Past Medical History	Microorganism (Blood culture)	Treatment	Type	Location	Microorganism
1	70, M	Right purulent knee arthritis	Chronic subdural hematoma	NA	Arthroscopic synovectomy Continuous washing	Aortic aneurysm	Descending thoracic aorta	GPC
2	62, M	Pneumonia	Traumatic acute subdural hematoma Posttreatment of ruptured thoracic aorta	NA	Antibiotics (iv)	Aortic aneurysm	Infrarenal abdominal aorta	No bacteria+
3	70, M	Purulent discitis	Diabetes mellitus Atrial fibrillation Heart failure Chronic pulmonary embolism	NA	Antibiotics (iv)	Aortic dissection	Descending thoracic aorta	GPC
4	77, M	Pneumonia	Cerebral infarction Vascular dementia Hypertension Recurrent aspiration pneumonia	NA	Antibiotics (iv)	Aortic dissection	Ascending thoracic aorta	GPC
5	83, M	Pyelonephritis and Sepsis	Diabetes mellitus Hypertension Hyperlipidemia Bladder cancer Gastric cancer Cerebral infarction	*Escherichia coli* (continuous)	Antibiotics (iv)	Aortic dissection	Descending thoracic aorta	GNB
6	87, M	Infectious enteritis	Diabetes mellitus Hypertension Chronic kidney disease Gastric ulcer Hemorrhagic enteritis Frostbite	*Escherichia coli* (disappeared after antibiotics)	Antibiotics (iv) (po)	Penetrating atherosclerotic ulcer	Descending thoracic aorta	GPC

+: Both phagocytized Klebsiella pneumoniae and *Escherichia coli* were obtained from a smear culture from the ruptured part on autopsy.

M: male, F: female, NA: not available, iv: intravenous, po: per os, GPC: Gram positive coccus, GNB: Gram negative bacillus

Introduction

Despite tremendous technological advances in health care, the sudden unexpected death of a hospitalized patient sometimes occurs and is an important concern. The World Health Organization (WHO) definition of sudden death is death that is non-violent, and not otherwise explained, within 24 hours from the onset of symptoms (1). Due to the nature of sudden death, several studies have shown that autopsies reveal that physicians often incorrectly diagnose the causes of death, particularly in cases involving the sudden unexpected death of hospitalized patients (2, 3).

The most common causes of such a death are reported to be cardiovascular disease including arrhythmia with or without myocardial infarction, followed by hemorrhage and pulmonary thromboembolism (4). Infectious aortitis (IA) is a rare cardiovascular disease, especially in the age of antibiotics; however, it has the potential to cause aortic tears and hemorrhage followed by sudden death. In this study, we focused on autopsied cases of IA and analyzed the clinicopathological features with the aim of preventing the sudden unexpected death of hospitalized patients.

Materials and Methods

A retrospective clinicopathological study of cases of sudden death was conducted using medical records. We investigated 1,310 autopsy cases that were performed in our department between 1 January 2001 and 31 December 2015. Death was classified as sudden death when the patient died unexpectedly within 24 hours from the onset of their clinical symptoms. Individuals who were dead on arrival at the hospital were excluded from the study. In all cases of sudden death with aortic tears, clinical information including personal information, pre-existing disease history, treatment and the medical investigations that were performed were obtained from the patients' medical records. Autopsies were performed by several approved pathologists and diagnoses were made macroscopically and microscopically using H&E and special staining methods (*i.e.,* Elastica-Masson and Gram staining). The study was approved by the ethics committee of Hokkaido University School of Medicine.

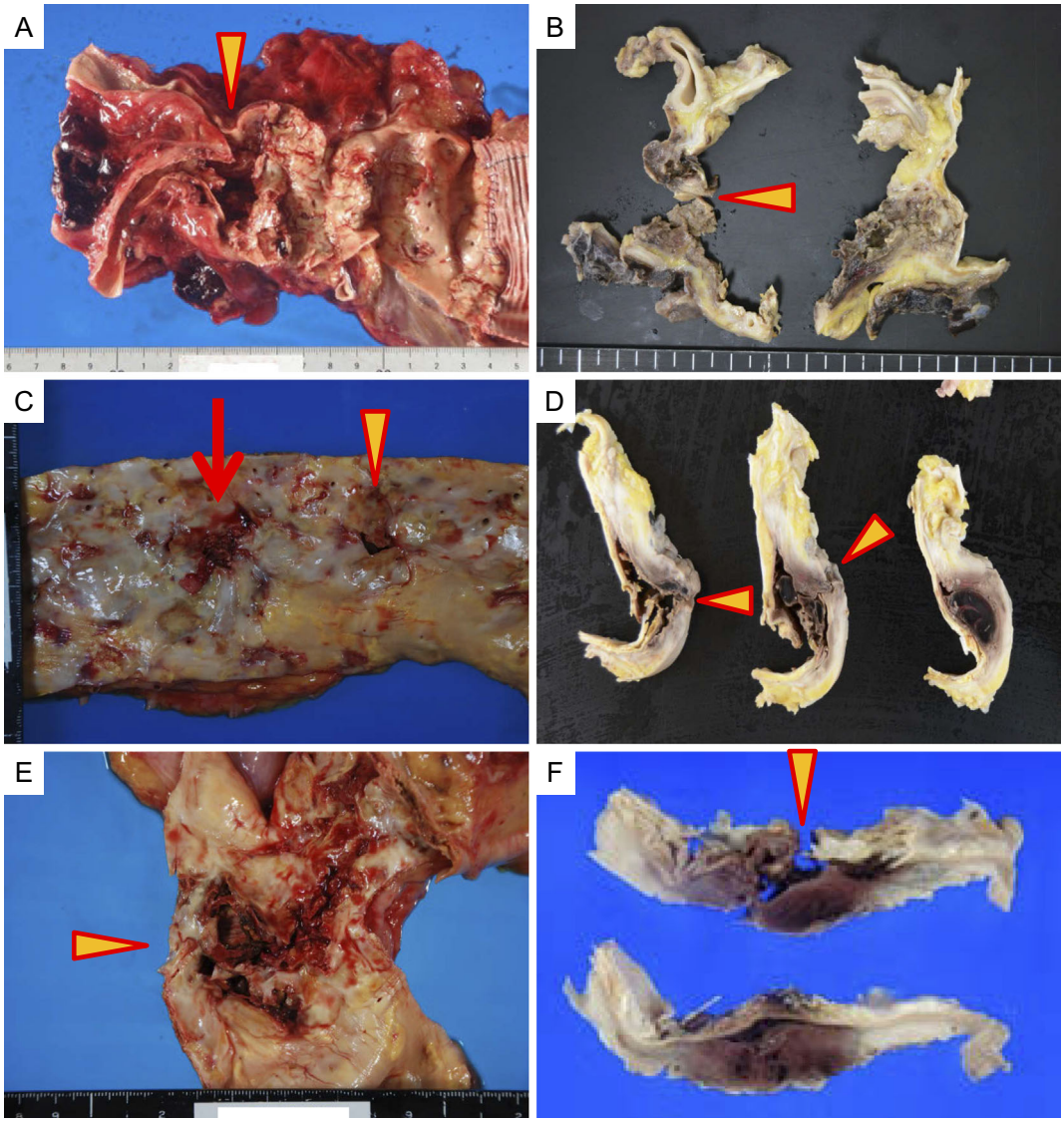

Figure 1. **The macroscopic findings of three representative patients with aortic aneurysm, dissection and PAU. (A) and (B): Case 2, Aortic aneurysm. (A): The abdominal aorta shows severe atherosclerosis. The arrowhead shows a ruptured aneurysm. (B): A transverse section of the rupture site (arrowhead). (C) and (D): Case 5, Aortic dissection. (C): The descending thoracic aorta shows moderate to severe atherosclerosis and laceration. The arrowhead shows entry and the arrow shows re-entry. (D): A transverse section of the perforation perforated site (arrowhead). Hematoma formed in the false lumen. (E) and (F): Case 6, Penetrating atherosclerotic ulcer (PAU). (E): The descending thoracic aorta shows moderate to severe atherosclerosis and ulceration. The arrowhead shows the aortic tear. (F): A transverse section of the rupture site (arrowhead)**

Results

In 1,310 autopsy cases during 15 years, 133 cases (10.2%) were autopsied under a clinical diagnosis of unexpected sudden death. In 33 cases (2.5%) death occurred due to an aortic tear; 6 of these cases (18.2 %) were diagnosed as IA (Table). All 6 cases involved elderly men [average age, 74.8 years (range, 62-87 years)] who had been receiving treatment for ongoing infectious disease. These cases included patients with orthopedic disease (n=2), pneumonia (n=2), urinary tract infection (n=1) and infectious enteritis (n=1). With regard to risk factors for atherosclerosis, half of the patients had diabetes mellitus and hypertension, while patients (33%) had cerebral infarction. Blood culturing was performed and positive results were obtained in two cases (33%). Both cases were diagnosed with *Escherichia coli* bacteremia. Five of the six cases (83%) were treated with parenteral antibiotics. Case 1 was not given antibiotics but had been treated with arthroscopic synovectomy and continuous washing. The patients' general pre-existing disease conditions showed improvement during treatment; however, leukocytosis and C-reactive protein positivity continued. The causes of the aortic tears among these 6 patients included

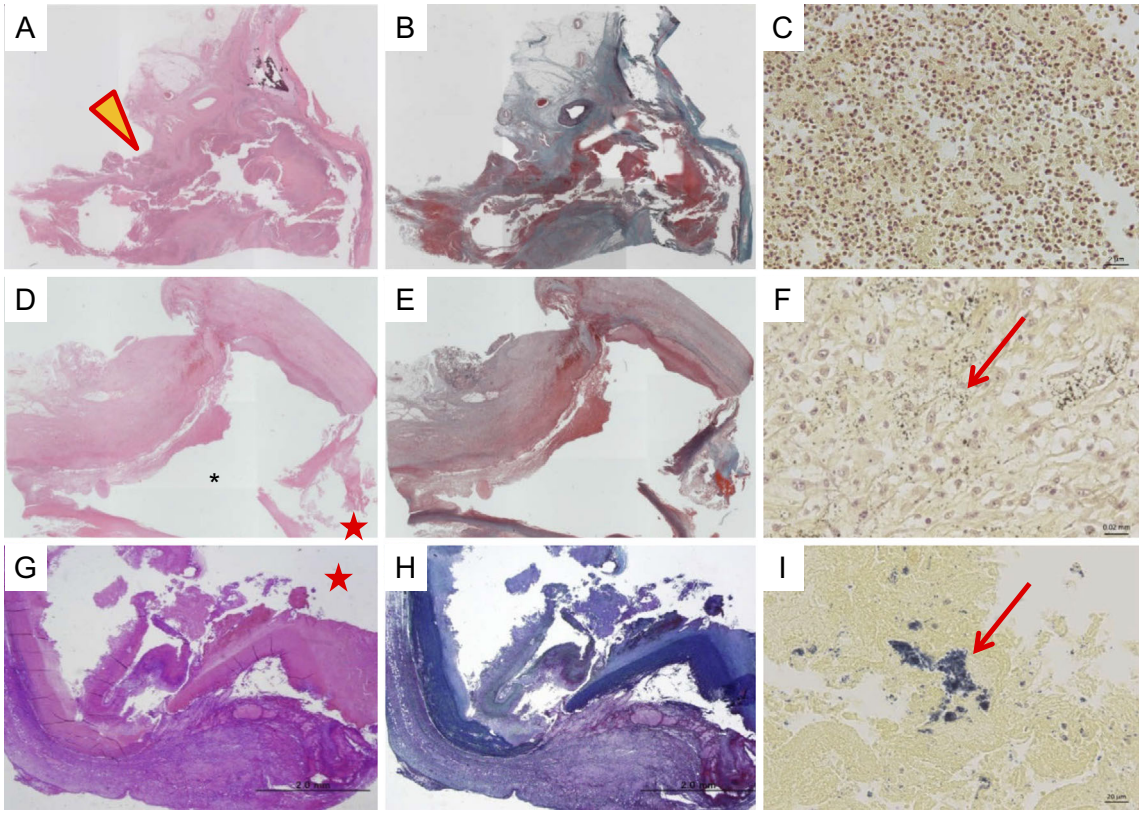

Figure 2. **Microscopic findings of three representative patients with aortic aneurysm, dissection and PAU. (A)-(C): Case 2, Aortic aneurysm. (A): The overall view of the aortic wall with calcification and abscess (arrowhead) (Hematoxylin and Eosin (H&E) staining; Loupe). (B): The same part as (A) (Elastica-Masson; Loupe). (C): Abscess without bacteria (Gram; ×400). (D)-(F): Case 5, Aortic dissection. (D): The overall view of the divided aortic wall (H&E staining; Loupe). Abscess and hematoma were observed to have formed in the false lumen (*) and from the media to the tunica externa. The star (★) indicates the lumen. (E): The same part as (D) (Elastica-Masson; Loupe). The aortic wall was dissected in the media. (F): Bacterial colonies of gram-negative bacillus (arrow) in the abscess of the false lumen (Gram; ×400). (G)-(I): Case 6, Penetrating arteriosclerotic ulcer (PAU). (G): The overall view of the divided aortic wall (H&E staining; ×1.25). Numerous neutrophils were observed to have infiltrated, and an abscess had formed in all layers. The star (★) indicates the lumen. (H): The same part as (G) (Elastica-Masson; ×1.25). (I): Bacterial colonies of gram-positive coccus (arrow) in the hematoma (Gram; ×400).**

dissection [n=3 (Cases 3, 4, and 5), 50%], aneurysm [n=2 (Cases 1 and 2), 33%] and a penetrating atherosclerotic ulcer [PAU; n=1 (Case 6), 17%] (Fig. 1). The descending thoracic aorta was the most commonly affected site (67%); other sites included the ascending thoracic aorta and the infrarenal abdominal aorta. The microscopic findings showed moderate to severe atherosclerosis of the aorta, infiltration of numerous neutrophils at the aortic wall and abscess of the site of rupture in all cases (Fig. 2). Microorganisms were detected by Gram staining in specimens obtained from the rupture site in five of the six cases (Cases 1, 3-6; 83%). In Case 2, both phagocytized *Klebsiella pneumoniae* and *Escherichia coli* were obtained on autopsy from a smear culture of the site of rupture. The causative microorganisms included gram-positive coccus (n=4, 67%) and gram-negative bacillus (n=2, 33%). Clinically, blood cultures were positive in two of six cases, which corresponded to the autopsy findings. In one case (Case 2), an aneurysm was detected by enhanced CT scans, which were performed before the death of the patient. CT, enhanced CT, MRI and magnetic resonance angiography (MRA) were not performed in the other 5 cases (83%) because the clinicians did not detect aortitis.

Discussion

The present study described the clinical course, laboratory results, and histopathological findings of six sudden unexpected deaths of hospitalized patients that were related to IA. Clinically, the patients were all middle-aged to elderly men who were receiving antibiotic treatment for their preceding disease. With regard to the patients' past history, three of the six patients had been suffering from hypertension and four had diabetes mellitus. Although the antibiotics worked well in the treatment of the preexisting disease, leu-

kocytosis continued and blood cultures were positive in two of six patients. With the exception of one case, all of the tears occurred in the thoracic aorta. The aortic tears were classified into three types: aneurysm, dissection and PAU with bacterial infection.

IA has recently become a rare because of the development of antibiotics. Normally, the aortic intima is resistant to infections; however, atherosclerosis, cystic necrosis of the tunica media, or trauma can reduce the resistance. Other risk factors for aortic infection include diabetes, alcoholism, cancer, pre-existing aneurysm, vascular malformation, medical devices and immunosuppressive therapies (5-7). When it occurs, the mortality rate of ruptured IA is reported to be approximately 90% (8).

Various microorganisms have been associated with IA, with the most common being *Staphylococcus*, *Enterococcus*, *Streptococcus* and *Salmonella* species (9). Clinically, blood microorganisms are reported to be detectable 50% to 85% of cultures from patients with IA; the rate in cultures of surgically-excised aortic tissue from IA patients is reported to be up to 76% (10, 11). In our study, clinicians detected microorganisms before death in two of six cases (33%). It might be difficult to detect microorganisms during antibiotic treatment. Most cases of IA are reported to be caused by gram-positive bacteria. However, while IA rarely occurs due to infection with gram-negative bacteria, gram-negative infection is associated with a higher incidence of rupture leading to death in comparison to gram-positive bacteria (72% vs. 25%, respectively) (10). The high rate of mortality in patients with gram-negative bacteria-related aortitis may be related to the differences in the proteolytic activity of gram-negative and gram-positive bacteria (12).

Aortic aneurysm is defined as the dilation of the circumference of the local aorta. In thoracic aortic aneurysms, the diameter is dilated to >4.5 cm, while in abdominal aortic aneurysms, the aorta is dilated to >3 cm. Aortic dissection is defined as the condition in which the aortic wall is separated in the media and forms a dual chamber. PAU is defined as an atherosclerotic lesion with ulceration that penetrates the internal elastic lamina and which allows for hematoma formation within the media of the aortic wall (13). Microscopically, the following features were commonly found: 1) atheroma from the intima to the tunica media; 2) high destruction of the elastic fiber in the tunica media; 3) failed smooth muscle cells in the tunica media; and 4) the infiltration of T cells and macrophages. In addition to these features, other common findings included: 1) infiltration by numerous neutrophils; 2) necrosis or abscess; and 3) bacteria around the area of rupture or perforation (14, 15).

In Japan, 226,567 autopsies were conducted from 2001 to 2013, and ruptured aortic aneurysms or aortic dissection were identified in 3,621 cases (2.5%). Although epidemiological investigations have revealed that environmental factors such as ambient temperatures also contribute to the onset of cardiovascular disease and mortality, no relationship between geographic location and the incidence of aortic rapture has been reported. Furthermore, IA has not been reported as a cause of rupture or dissection (16). Indeed, it is reported that infectious aortic aneurysms account for only 0.5% to 1.3% of all aortic aneurysms (9, 17, 18). The incidence of IA related to sudden unexpected death in our department was similar to that of previous reports; however, the patterns of aortic rapture were different. In this study, dissection and aneurysm were diagnosed in three of six cases (50%) and two of six cases (33.3%), respectively, while PAU was diagnosed in one case. In cases of infectious aortic aneurysm, the rapid enlargement of the aorta can be observed by CT or MRI; however, cases of sudden dissection and PAU may lack the typical findings. Although it may be more difficult to detect PAU by CT or MRI (in comparison to aneurysm or dissection), in cases in which IA is suspected from an earlier period, the patient can be expected to survive after successful operations with intense antibiotic treatment.

In conclusion, sudden unexpected death associated with IA rarely occurs in hospitalized patients and-in the clinical setting-it may be difficult to detect in patients with dissection or PAU. Thus, clinicians consider the possibility of IA in patients with infectious diseases, particularly elderly patients with atherosclerotic diseases-even in the recovery phase-and examine the patients using enhanced CT or MRI. If clinicians are aware that aortic tears due to IA are a cause of unexpected sudden death, then the incidence of such deaths in hospitals may be reduced by careful patient management.

The authors state that they have no Conflict of Interest (COI).

Financial Support

This work is supported in-part by grant from MEXT in Japan [grant number 15K08359].

Acknowledgement

Dr. Yasunori Fujioka enthusiastically guided the members of the Department of Cancer Pathology.

References

1. International classification of diseases (icd-10). World Health Organization, Geneva, 2005.
2. Tavora F, Crowder CD, Sun CC, Burke AP. Discrepancies between clinical and autopsy diagnoses: A comparison of university, community, and private autopsy practices. Am J Clin Pathol **129**: 102-109, 2008.
3. Heriot GS, Pitman AG, Gonzales M, McKelvie P. The four horsemen: clinicopathological correlation in 407 hospital autopsies. Intern Med J **40**: 626-632, 2010.
4. Nichols L, Chew B. Causes of sudden unexpected death of adult hospital patients. J Hosp Med **7**: 706-708, 2012.
5. Restrepo CS, Ocazionez D, Suri R, Vargas D. Aortitis: imaging spectrum of the infectious and inflammatory conditions of the aorta. Radiographics **31**: 435-451, 2011.
6. Johnson JR, Ledgerwood AM, Lucas CE. Mycotic aneurysm. New concepts in therapy. Arch Surg **118**: 577-582, 1983.

7. Revest M, Decaux O, Cazalets C, Verohye JP, Jego P, Grosbois B. [Thoracic infectious aortitis: microbiology, pathophysiology and treatment]. Rev Med Interne **28**: 108-115, 2007 (in French, Abstract in English).
8. Bronze MS, Shirwany A, Corbett C, Schaberg DR. Infectious aortitis: an uncommon manifestation of infection with *Streptococcus pneumoniae*. Am J Med **107**: 627-630, 1999.
9. Muller BT, Wegener OR, Grabitz K, Pillny M, Thomas L, Sandmann W. Mycotic aneurysms of the thoracic and abdominal aorta and iliac arteries: Experience with anatomic and extra-anatomic repair in 33 cases. J Vasc Surg **33**: 106-113, 2001.
10. Gomes MN, Choyke PL, Wallace RB. Infected aortic aneurysms. A changing entity. Ann Surg **215**: 435-442, 1992.
11. Lopes RJ, Almeida J, Dias PJ, Pinho P, Maciel MJ. Infectious thoracic aortitis: a literature review. Clin Cardiol **32**: 488-490, 2009.
12. Abfalter CM, Schmidt TP, Wessler S. Proteolytic activities expressed by gastrointestinal pathogens bacillus cereus, listeria monocytogenes and enterococcus faecium in different growth phases. Br Microbiol Res J **7**: 62-70, 2015.
13. Nathan DP, Boonn W, Lai E, et al. Presentation, complications, and natural history of penetrating atherosclerotic ulcer disease. J Vasc Surg **55**: 10-15, 2012.
14. Hao H. Pathology of aortic aneurysm and aortic dissection. Jpn J Vasc Surg **23**: 957-963, 2014.
15. Stone JR, Bruneval P, Angelini A, et al. Consensus statement on surgical pathology of the aorta from the society for cardiovascular pathology and the association for european cardiovascular pathology: I. Inflammatory diseases. Cardiovasc Pathol **24**: 267-278, 2015.
16. Gornik HL, Creager MA. Aortitis. Circulation **117**: 3039-3051, 2008.
17. Chan FY, Crawford ES, Coselli JS, Safi HJ, Williams TW Jr. *In situ* prosthetic graft replacement for mycotic aneurysm of the aorta. Ann Thorac Surg **47**: 193-203, 1989.
18. Klontz KC. Frequency of infected aneurysms among patients in department of veterans affairs hospitals, 1986-1990: the role of salmonella. Mil Med **162**: 766-768, 1997.