*Case Report*

# Unexpected fungal aortitis leading to aortopulmonary fistula: an autopsy case

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**ABSTRACT**

We present a possibly unique autopsy case of fatal aortopulmonary fistula associated with subclinical infectious aortitis in an elderly man. After 6-week antifungal therapy for candidiasis in his eyes accompanying leakage from anastomoses following gastrectomy, β-D-glucan levels remained elevated despite negative blood cultures. Six weeks after completion of the antifungal therapy, he was re-hospitalized for hematochezia possibly due to bleeding associated with the anastomosis sites, and arterial embolization was successfully performed. However, about three weeks after the embolization, he died of hemorrhagic shock due to sudden bloody "vomiting". Autopsy revealed no anastomosis-related bleeding but an unexpected non-aneurysmal *Candidal* aortitis-related aortopulmonary fistula. This had caused massive fatal hemorrhage into the lung parenchyma and resultant bloody "vomiting". We believe that the long-standing elevated β-D-glucan level, even with negative blood culture results, may indicate subclinical fungal aortitis. This may have directly contributed to our patient's death, although such a fatal event may be rare.

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**Key Words**
Aortopulmonary fistula, β-D-glucan; candidiasis, infectious aortitis

## I. Introduction

Infectious aortitis (IA) is an uncommon disease causing mycotic or infectious aneurysms, but it is also known to provoke life-threatening aortic rupture or perforation due to infection-related aortic wall fragility even without aneurysm formation.[1)-7)] Common causes of primary aortic infection include bacterial pathogens such as *Staphylococcus*, *Streptococcus*, and *Salmonella* species.[1)-5)] Fungal pathogens -- such as *Candida, Aspergillus*, *Cryptococcus,* or *Histoplasma* -- may cause aortic infection, too, albeit infrequently.[2)-5),8)-13)] From the therapeutic point of view, early detection and diagnosis of IA are clinically required. However, the antemortem diagnosis of IA is challenging in cases without aneurysmal changes because patients with non-aneurysmal IA are often asymptomatic and lack specific manifestations.[1)-3),6),7)] Here, we describe the unique clinicopathological features of a case (an elderly

man) with non-aneurysmal IA. Autopsy revealed a fungal aortitis-associated aortopulmonary fistula contributing to massive pulmonary hemorrhage. We also reviewed the laboratory data obtained in the present case for findings that might aid the detection of subclinical fungal aortitis.

## II. Case presentation

Patient: A 79-year-old man

Past history: Diabetes mellitus, gastric cancer, rectal cancer

The patient developed leakages at two intestinal sites with localized abscess-formation during the post-operative course of laparoscopic total gastrectomy for gastric cancer. Culture from the drainage fluid collected on post-operative Day-3 and blood cultures on post-operative Day-12 revealed positive results for *Candida albicans*. *Candida* infection-related endophthalmitis was also diagnosed. A six-week antifungal therapy regimen was instituted. This led to shrinkage of the abscess cavity near the leakage site, and thereafter blood cultures were negative for *Candida*. The serum (1 → 3)-β-D-glucan (BDG) level, which was 757 pg/mL (normal range: ≤ 20 pg/mL) at the time of the first positive blood culture (post-operative Day-13), decreased to 133 pg/mL after completion of the antifungal therapy (post-operative Day-86). The patient was considered to be recovered and was discharged 3 months after the gastrectomy, but he was re-hospitalized for hematochezia 10 days after discharge. Laboratory data obtained at re-hospitalization showed anemia (Hb 4.5 g/dL), a normal white blood-cell count (4,900/μL), and an elevated serum C-reactive protein (CRP) level (4.4 mg/dL). On the fourth day of re-hospitalization, the serum CRP level had increased to 14.9 mg/dL, and the serum BDG remained positive (108 pg/mL). Empiric antibiotic therapy for possible bacterial infection was initiated, and endoscopy confirmed fresh bleeding near the previous anastomosis leakage site. The responsible jejunal branch artery was successfully embolized. Cultures from the central venous catheter tip and urine were negative. No blood culture was obtained during the second hospitalization. About three weeks after the embolization (4 months after the gastrectomy), the patient died of massive hemorrhagic "vomiting", which was clinically suggested to be attributable to recurrent anastomosis-related bleeding. Clinical course and laboratory data are summarized in **Table 1**.

Autopsy revealed no bleeding at anastomosis sites or other enteric regions, although fresh blood clots were present in the oral cavity, esophagus, and trachea. The thoracic aortic wall was severely atherosclerotic but without obvious aneurysmal dilatation (**Figure 1a**), and it was firmly adherent to the left lung surface (**Figure 1b-c**). No left hemothorax was found. Histologically, the aortic wall structure, where it was tightly adherent to the left lung, was not only fibrously disrupted with scattered loss of elastic fibers, but also showed a transmural neutrophilia with *Candida*-like fungal growth and fistula formation (**Figure 2a-d; 3a-b**). A massive blood accumulation was found within the left lung parenchyma, resulting from aortic hemorrhage caused by this aortopulmonary fistula. (**Figure 3c**). Blood influx to the contralateral lung was also found, and it had probably occurred via the airway from the left lung. We concluded fungal aortitis-related aortopulmonary fistula causing pulmonary hemorrhage. Autopsy disclosed fungal growth in both kidneys, but it failed to reveal a similar fungal infection in the aortic wall other than in the adherent thoracic aorta.

Retrospective evaluation of computed tomography (CT)

**Table 1** Summary of clinical course and data.

| Post-operative day | 0* | 3 † | 12 | 13 | 14 | 16 | 18 | 23 | 86 | 101 ‡ | 102 § | 104 | 113 | 120 ¶ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| WBC (× 1,000/μL) | 5.0 | 13.7 | 7.0 | 7.8 | 9.6 | 8.6 | 9.9 | 7.2 | 4.7 | 4.9 | 8.2 | 5.2 | 5.8 | 6.7 |
| CRP (mg/dL) | 0.4 | 26.5 | 13.6 | 16.3 | 25.2 | 17.4 | 10.8 | 11.5 | 4.8 | 4.4 | 3.8 | 14.9 | 14.8 | 12.1 |
| Hb (g/dL) | 11.9 | 10.0 | 10.7 | 9.0 | 9.7 | 8.2 | 9.1 | 7.6 | 9.0 | 4.5 | 7.2 | 8.9 | 9.1 | 7.9 |
| BDG (pg/mL) | | | | 757 | | | | 945 | 133 | | | 108 | | |
| Culture results for *Candida* | | + (d) | + (b) | | | + (d)<br>- (b) | | - (d)<br>- (b) | | | | - (c) | - (u) | |
| Antifungal medication | | | | | MCFG (~Day15) | CPFG (~Day17) | L-AMB (~Day59) | | | | | | | |

Important events occurring on certain days are indicated as follows: Day 0*: gastrectomy. Day 3 †: anastomosis leakage.
Day 101 ‡: The patient was re-admitted and IVR (interventional radiology) was administered. Day 102 §: 2nd IVR.
Day 120 ¶: Patient death.
Abbreviations: WBC, white blood cell count; CRP, C-reactive protein; Hb, hemoglobin; BDG, β-D-glucan;
+ (d), positive in drainage fluid; + (b), positive in blood; - (b), negative in blood; - (d) negative in drainage fluid;
- (c) negative at central venous catheter tip; - (u) negative in urine; MCFG, Micafungin; CPFG, Caspofungin;
L-AMB, Liposomal Amphotericin B.

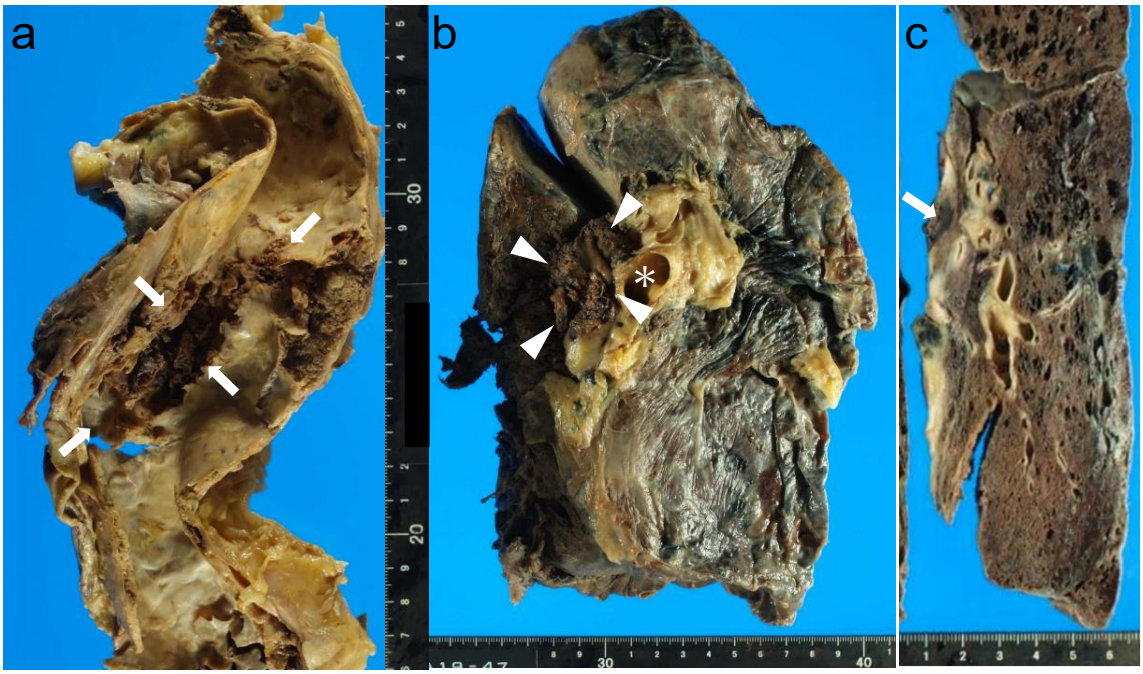


**Figure 1** Gross appearance of the descending aorta a) and the left lung b-c).

**a**) Severely atherosclerotic thoracic descending aorta without distinct aneurysmal features. Aortic wall was tightly adherent to the left lung, with its detachment from the lung causing a partial tissue defect (arrows).

**b**) Mediastinal side of the left lung showing partial aortic wall (arrowheads) tightly attached to the lung behind the left main bronchus (asterisk).

**c**) On the cut surface, emphysematous lung changes and dark brown discoloration are present, along with hematoma formation at the site of aortic adhesion (arrow).

revealed progressive enlargement of a shadow outside the calcified atherosclerotic thoracic aorta with no apparent aneurysmal changes (**Figure 4a-d**).

## III. Discussion

Cases with IA are usually at risk of aortic rupture/perforation via aneurysmal changes, but their aorta infrequently ruptures without such changes.[1)-7)] Non-aneurysmal IAs may develop a fistula to the esophagus, duodenum, or jejunum,[2)-4)] and Orend *et al*[7)] noted that non-aneurysmal IAs had perforated in 8% of 54 cases of aortic rupture. In the current case a non-aneurysmal IA directly penetrated the left lung, resulting in a massive hemorrhage. The adherent aortic wall and medial elastic fibers meshwork were vaguely disrupted by a fungal infection. These findings suggest that the fragility of the infected aortic wall may have played a critical role in the development of the fatal aortopulmonary fistula. In addition, at the fistula site there were severe atherosclerotic changes. These changes may have provoked weakening of the aortic wall and the formation of a close adhesion to the paraaortic structures, which can sometimes result in a fistula.[14)] Moreover, the adhesion of *Candida* species can be triggered by severe atherosclerosis-related intimal ulceration and/or coarseness.[3)]

An IA-related aortopulmonary fistula is rare, and our review of the literature disclosed only five cases for which detailed clinicopathological findings were published (**Table 2**).[15)-18)] Among these, four cases (all cases with description) were accompanied by aneurysmal or pseudo-aneurysmal aortic changes. The current case lacked any obvious IA-related aneurysmal changes. The fistula occurred between the aorta and the left lung in all 6 cases, possibly due not only to its anatomical proximity to the descending aorta, but also to this being the favored IA-related fragile site with or without aneurysmal changes. Regarding the pathogen of IA, in all four of the above cases with description, the IA was caused by bacteria, while the present case alone was infected by fungus. BDG was not measured in any of the previous cases. Three patients died of their disease, suggesting that it is often a fatal condition. The other 2 patients were alive after surgery, and in one of these the fistula was detected fortunately by bronchoscopy. The remaining case was diagnosed as a fistula by CT scanning for evaluation of massive bloody "vomiting". Accordingly, aggressive examination at the time of hemoptysis or massive bloody "vomiting" seems likely to lead to the early detection of an aortopulmonary fistula and contribute to a good prognosis. However, hemoptysis was noted in only half of the

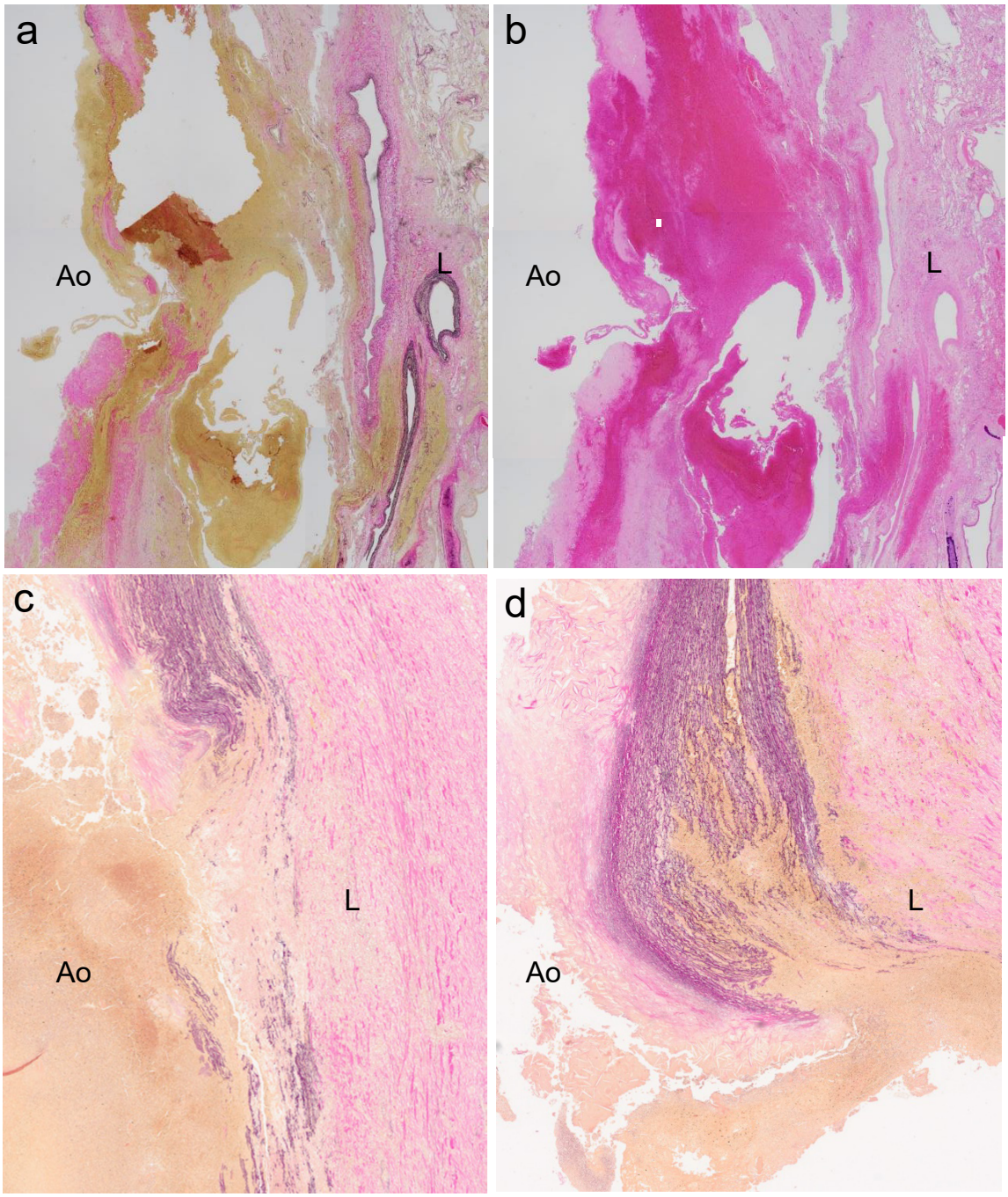


**Figure 2**

**a, b**) In the panoramic image of the aortopulmonary adhesion (a: EVG, b: HE), aortic wall rupture with hemorrhage can be observed.

**c, d**) Aortopulmonary fistula (EVG). c) The aortic wall shows degeneration, loss of elastic fibers, and d) eventual rupture due to complete tear.

**Ao**: aortic lumen, L: lung, EVG: elastica van Gieson stain, HE: hematoxylin eosin stain

aortopulmonary fistula cases, although this complaint may have been clinically misdiagnosed as enteric bleeding. Thus, the antemortem diagnosis of aortopulmonary fistula remains challenging, and is based chiefly on the patients' complaints. The absence of a hemothorax may play a role in an aortopulmonary fistula being difficult to recognize.

*Candida* infection can occur after esophageal surgery and is significantly associated with esophageal anastomosis leakage.[19] For establishing a diagnosis of invasive *Candida* infection, BDG testing is useful. BDG is a major fungal cell-wall polysaccharide and its measurement is based on the G-test, which has the same origin as the Limulus Amebocyte Lysate cascade reaction.[20)21)] In this

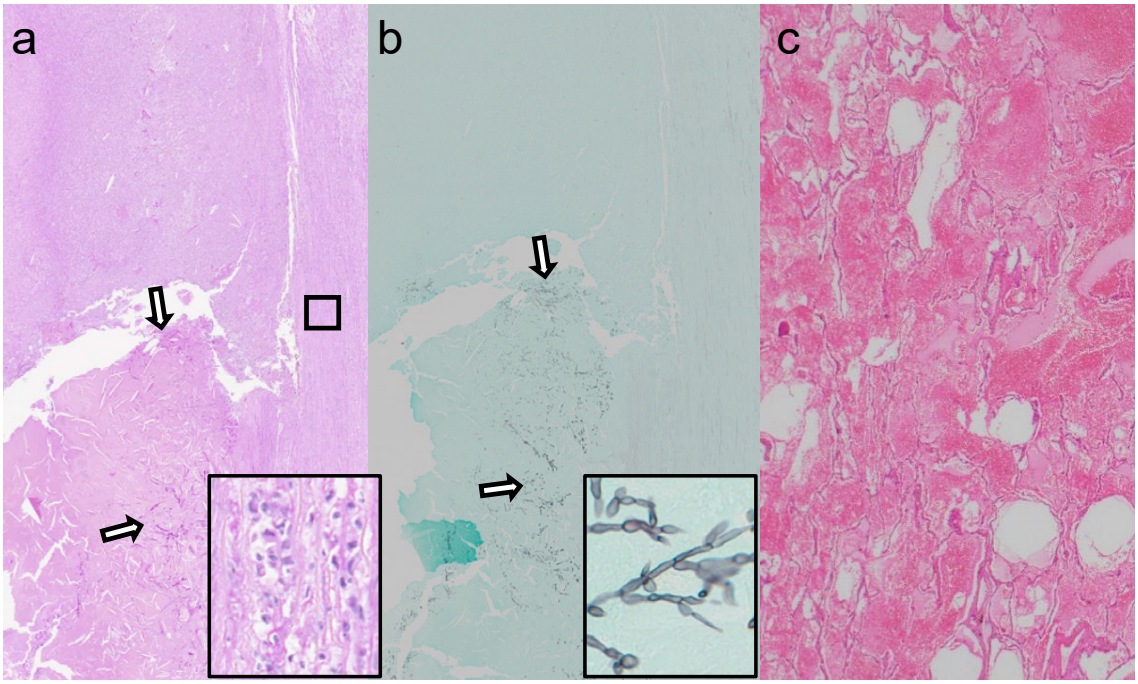


**Figure 3**

**a**) The panoramic image of the infected aorta shows diffuse inflammation and proliferations of *Candida*-like fungi in the atherosclerotic plaque (arrows). In the magnified view of the aortic wall shown in the inset, a marked infiltration of neutrophils can be observed (Periodic Acid-Schiff stain).

**b**) *Candida*-like fungi are highlighted particularly in the atherosclerotic plaque (arrows) (Grocott stain). In the inset, characteristic branching *Candida*-like hyphae can be observed.

**c**) In low magnification image of the peripheral left lung, diffuse accumulation of blood is observed in the alveolar space.

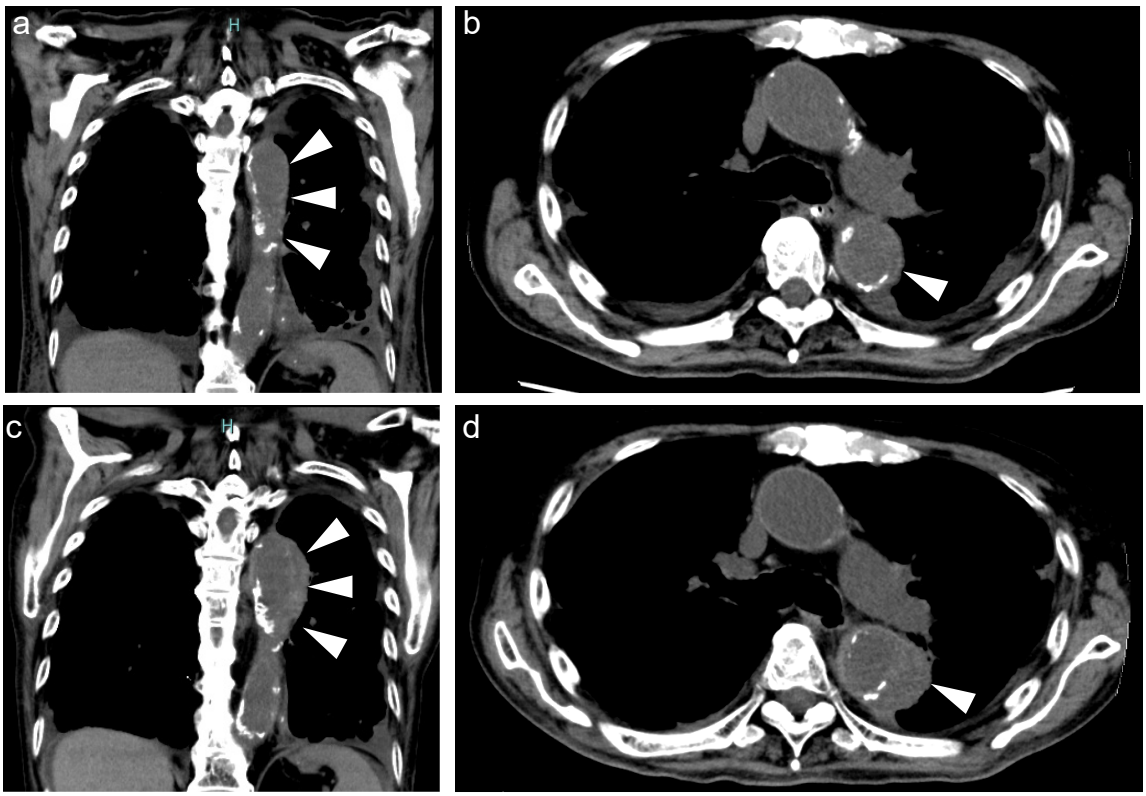


**Figure 4**

CT images obtained at the onset of candidiasis (**a**, **b**), and at 19 days before death (**c**, **d**). An obvious periaortic shadow (arrowheads) is observed in **c**) and **d**) versus **a**) and **b**).

**Table 2** Clinicopathological features of infectious aortitis-related aortopulmonary fistula with or without aneurysmal changes.

| | Case 1[15] | Case 2[15] | Case 3[16] | Case 4[17] | Case 5[18] | Present case |
|---|---|---|---|---|---|---|
| Age (yrs)/gender | 80/F | 85/F | 25/M | 59/F | 40/F | 79/M |
| Chief complaint | Unknown | Unknown | Toothache | Massive bloody vomiting | Bloody vomiting* | Bloody vomiting † |
| Immunocompromised state or antecedent condition | Unknown | Unknown | Ludwig angina and mediastinitis | Advanced hepatic alcoholic liver cirrhosis, DM | Unknown | DM, Anastomosis insufficiency after gastrectomy |
| Diagnosis of IA | Autopsy | Autopsy | Surgery | CT scan | Thoracic exploration | Autopsy |
| Diagnosis of fistula | Autopsy | Autopsy | Bronchoscopy ‡ and subsequent surgery | CT scan | Bronchoscopy ‡ and subsequent surgery | Autopsy |
| Hemoptysis | Unknown | Unknown | Present | Present | Present* | Present † |
| Pathogen of IA | Cocci (details unknown) | Unknown | *K pneumoniae, P. aeruginosa, H. aphrophilus, S. epidermis* | *Streptococcus agalactiae* | Acid fast bacilli | *Candida albicans* |
| Aortic dilatation and/or aneurysm associated with fistula | Present (pseudoaneurysm) | Present (pseudoaneurysm) | Unknown | Present (saccular aneurysm) | Present (saccular aneurysm) | Absent |
| Hemothorax | Absent | Absent | Unknown § | Unknown | Absent | Absent |
| Location of fistula | DA to LL | DA to LL | DA to LL (lower lobe) | DA to LL | DA to LL (lower lobe) | DA to LL (lower lobe) |
| Outcome | DOD | DOD | Alive after surgery | Alive after surgery | DOD | DOD |

Abbreviations: CT, computed tomography; DA, descending aorta; DM, diabetes mellitus; DOD, dead of disease (aortopulmonary fistula); F, female; *H*, *Hemophilus*; IA, infectious aortitis; *K*, *Klebsiella*; LL; left lung; M, man; *P*, *Pseudomonas*; *S*, *Staphylococcus;* yrs, years.

* This hemorrhage was clinically misdiagnosed as duodenal ulcer-related bloody vomiting.

† This hemorrhage was clinically misdiagnosed as anastomosis leakage-related bloody vomiting.

‡ Bronchoscopic examination for evaluation of hemoptysis.

§ Purulent pleural effusion in the left thoracic cavity.

procedure, BDG activates Factor G, a serine protease zymogen found in the amebocytes of horseshoe crabs (Limulus). Activated Factor G then initiates a cascade of enzymatic reactions, and this results in the formation of an insoluble chromogenic substrate, which is measured to quantify BDG levels by either turbidimetric time analysis or synthetic substrate methods.[22] In our review of the laboratory data obtained in the current case, a negative blood culture was confirmed during the initial antifungal therapy, but the serum BDG levels were persistently elevated. Retrospective viewing of CT images revealed a progressive periaortic attenuated shadow outside the calcified aortic wall, which is considered one of the diagnostic imaging clues for infectious aortitis.[3,23] These findings suggest that a persistent deep-seated *Candida* infection provoked the aortitis in the present case. Indeed, fungal IA may be present even if the cultures are negative.[24,25] For detecting invasive candidiasis, the sensitivity of antemortem blood cultures has been found to be as low as 38% (in an analysis of 13 studies),[25] whereas that of serum BDG is higher at 75% (in 11 studies),[26] and Nguyen *et al*[24] highlighted the superiority of BDG versus blood culture. Therefore, a persistent BDG elevation may be the most reliable evidence of a subclinical prolonged fungal infection. However, it is important to note that false-positive results can occur due to the presence of hemodialysis, human blood products (albumin, immunoglobulin, coagulation factors, plasma protein fractions), surgical gauze, antibiotics (such as piperacillin-tazobactam and ampicillin-clavulanate), or systemic bacterial infections,[25] while false-negative results may be observed in infections caused by Cryptococcus, zygomycetes, and *Blastomyces dermatitidis*.[20-22] If results do not match the clinical course, further examination using

nucleic acid amplification is recommended.[25]

In conclusion, we describe a rare autopsy case of a non-aneurysmal *Candida* aortitis-related fatal aortopulmonary fistula. A prolonged increase in the serum BDG level would seem to indicate the possibility of a deep fungal-infection event despite blood cultures being negative. Our case might also indicate an increased risk associated with fungal aortitis in severely atherosclerotic patients, although such cases may be rare.

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**Author contribution statement**

OT drafted the original manuscript. OT, SO and MS conducted the pathological examination. SY, MT, and AM prepared the histological images and collected the references with interpretation of the autopsy results. NY and HT provided detailed information regarding the clinical course and insights about the CT images, OT, MO, SO, SM, NY and HT discussed the clinicopathological relationship. SO and SM reviewed the manuscript draft and revised it critically for intellectual content. All authors have read and approved the final version of the manuscript.

**Conflict of interest**

None of the authors have any conflict of interest relevant to the content of this article.

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