

Invasive aspergillosis in the aortic arch with infectious *Aspergillus* lesions in pulmonary bullae



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ABSTRACT

A patient with pulmonary bullae died of massive hemoptysis. At autopsy a hole was observed in the aortic wall. A microscopic examination indicated small *Aspergillus* lesions in pulmonary bullae and extensive necrotic lesions with *Aspergillus* hyphae in the media of the thoracic aorta. These findings led to a diagnosis of invasive aspergillosis in the aortic arch. This is a rare case in which *Aspergillus* invaded the aorta in a patient without hematologic neoplasms or neutropenia.

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1. Introduction

Aortic infection caused by *Aspergillus*, including infection in immunocompromised hosts [1–8] and after cardiovascular surgery [8, 9, 12–16], is a rare event. *Aspergillus* infection in immunocompromised hosts can occur in patients with hematologic disorders [1–5], acquired immunodeficiency syndrome [6], or immunosuppression following kidney or heart transplant [7, 8]. Most patients with invasive aspergillosis have underlying hematologic neoplasms and neutropenia [10], and the duration and extent of neutropenia are significant risk factors for invasive aspergillosis [11]. Here, we present a particularly rare case of invasive aspergillosis in the aortic arch in a patient without hematologic neoplasms or neutropenia.

2. Case

A 79-year-old man who was a current smoker was admitted to our hospital for hemoptysis in July 2011 (day 0). Before admission, pulmonary emphysema and multiple pulmonary bullae were detected on a chest computed tomography (CT) scan, and we also discovered that the patient had hypertension. He had a history of

lobectomy of the left lower lobe for lung cancer in 1993, with no recurrence; two episodes of bacterial pneumonia; gastrectomy for gastric cancer in August 2010; right spontaneous pneumothorax that required tube drainage in November 2010; and hospitalization for dyspnea in February 2011, at which time chest radiographs showed left lung opacity and a chest CT scan showed consolidation with pleural effusion in the left lung. Several bacterial antibiotics failed to improve the opacity on chest radiographs. A sputum culture was negative for *Aspergillus*. The lack of efficacy of bacterial antibiotics and the presence of multiple bullae and precipitating antibody to *Aspergillus* in the serum (day -163) led to a presumptive diagnosis of chronic necrotizing pulmonary aspergillosis. Voriconazole with a loading dose of 800 mg a day followed by a maintenance dose of 400 mg a day was started on day -155. A switch from intravenous to oral administration of voriconazole at a dose of 400 mg a day was made on day -106. With administration of voriconazole, the opacity on chest radiographs had significantly improved by June 2011. The patient underwent transurethral resection of bladder cancer in March 2011. Oral voriconazole was continued at our outpatient clinic until his admission for hemoptysis. He had no hematologic neoplasm.

On admission, a chest radiograph (Fig. 1a) showed consolidation in the upper field of the left lung and an infiltration shadow in the middle and lower fields of the left lung. A chest CT scan (Fig. 1b) showed consolidation in the pulmonary bullae adjacent to the aortic arch. These shadows were considered to be due to hemorrhage. Bronchoscopy revealed slight bleeding from left B₁₊₂

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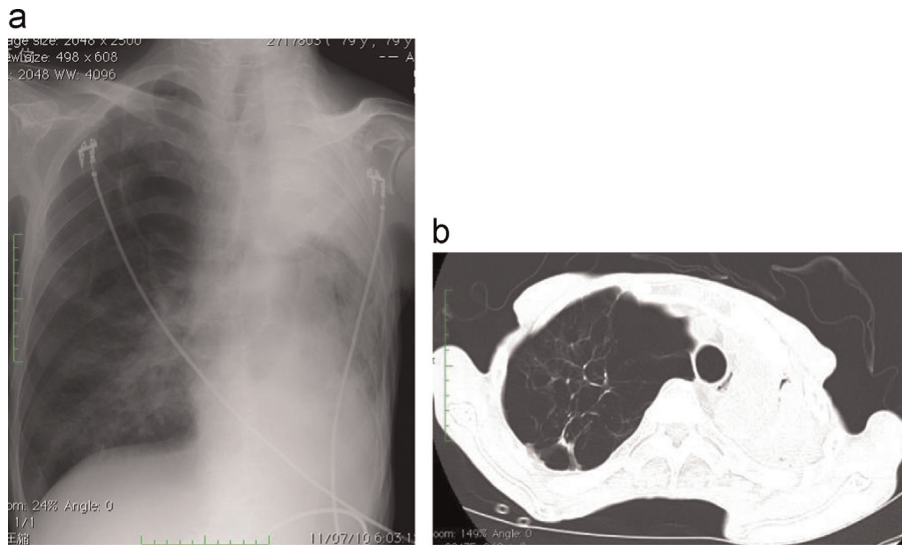


Fig. 1. a. Chest radiograph on admission, showing consolidation in the upper field of the left lung and an infiltration shadow in the middle and lower fields of the left lung. b. Chest CT on admission, showing bullae and emphysema in the right lung and consolidation in pulmonary bullae adjacent to the aortic arch in the left lung.

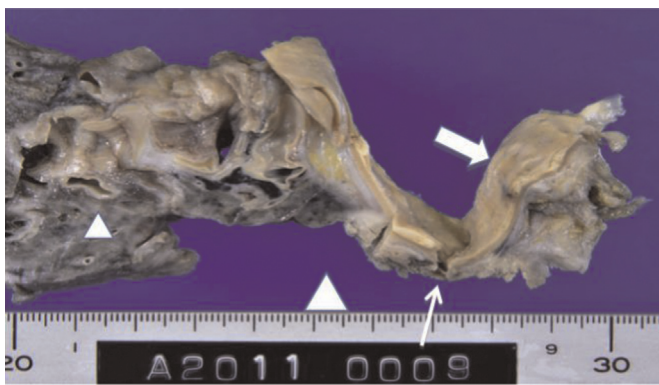


Fig. 2. Macroscopic view of the aortic wall and the lung. The bold arrow shows the aortic wall, the thin arrow indicates the hole in the aortic wall into the bullae, the large triangle shows the space within the bullae, and the small triangle shows the lung parenchyma.

without evidence of a tumor. Laboratory tests showed a normal count of polymorphonuclear leukocytes. Serological human immunodeficiency virus (HIV) testing was not performed, but the patient had no obvious risk factors for HIV infection. Serum precipitating antibody to *Aspergillus* was positive on day 2. The amount of expectorated blood decreased with rest, but massive hemoptysis occurred on day 16. Despite bronchial artery embolization, a second massive hemoptysis occurred and the patient died on day 21. The final day of voriconazole administration was day 20.

At autopsy, the pulmonary bullae were filled with blood. A macroscopic examination showed a hole in the aortic wall into the bullae (Fig. 2). This hole was unlikely to have been a consequence of the autopsy procedure because a microscopic examination of the tissue around the hole showed extensive accumulation of inflammatory cells (Fig. 3a–c). This microscopic examination also revealed small fungal lesions in the pulmonary bullae adjacent to

the aortic wall (Fig. 4a–c). The diameters of these lesions were approximately 4 mm. The fungal hyphae were 5–10 μm in width, with septae and a dichotomous pattern of branching at 45° . These features are consistent with those of *Aspergillus* species. Microscopically, extensive necrotic lesions with *Aspergillus* hyphae were found in the media of the aortic wall (Fig. 5a and b). Immunohistochemical analysis with an anti-*Aspergillus* antibody (rabbit polyclonal antibody, anti-*Aspergillus* antibody ab20419; Abcam plc, Cambridge, UK) identified *Aspergillus* hyphae in lesions in pulmonary bullae (Fig. 6a and b) and in the necrotic media of the aortic wall (Fig. 7a and b). This established the diagnosis of aspergillosis. There was no other histopathologic evidence for aspergillosis elsewhere in the body, but we note that autopsy was not performed on the brain. There was no histopathological evidence for recurrence of gastric cancer, lung cancer, or bladder cancer. Prostate cancer was also found at autopsy.

3. Discussion

Aortic infection by *Aspergillus* has been described in patients with hematologic disorders, including mycotic aneurysm of the thoracic aorta [1], rupture of a sinus of Valsalva aneurysm [2], occlusion of the aortic arch [3], a polypoid mass within the lumen of the descending aorta [4], and a mycotic sinus of Valsalva pseudoaneurysm [6]. In cases with a mycotic aneurysm of the thoracic aorta, occlusion of the aortic arch, and a polypoid mass within the lumen of the descending aorta, patients had neutropenia and developed pulmonary *Aspergillus* infection [1, 3, 4], and the pulmonary lesions invaded the aorta directly. In cases with a sinus of Valsalva aneurysm or pseudoaneurysm, the preceding disease was *Aspergillus* endocarditis or *Aspergillus* pericarditis due to an immunocompromised state [2, 6].

Aortic infection has also been described after cardiovascular surgery for valvular replacement [9, 14, 16], aortocoronary bypass [9, 12, 13], and replacement of the aorta for aortic dissection [15].

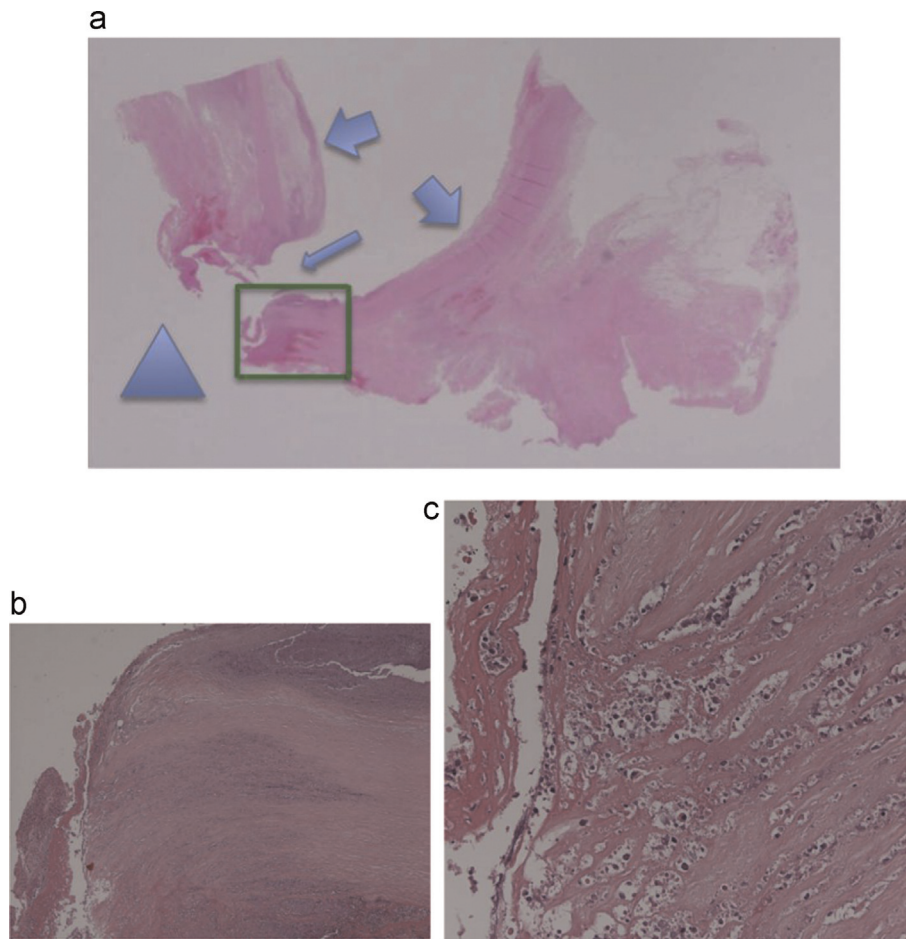


Fig. 3. a. The aortic wall (bold arrows), hole in the aortic wall (thin arrow), tissue around the hole in the aortic wall (area indicated by the green rectangle), and space within the bullae (triangle) (hematoxylin-eosin (H-E) stain, original magnification $\times 1$). b. Magnified view of the tissue around the hole of the aortic wall. All layers of the aortic wall are extensively necrotic (H-E stain, original magnification $\times 40$). c. Further magnification, showing extensive accumulation of inflammatory cells in the tissue around the hole (H-E stain, original magnification $\times 200$).

Aspergillus aortitis includes ascending aortic pseudoaneurysm [9], aortic aspergilloma with supravalvular aortic stenosis [12], and fungal ascending aortic aneurysm [14].

A histopathological study of aortic lesions in aspergillosis in immunologically compromised patients with hematological disorders showed formation of a mural thrombus in the intima, complete necrosis of smooth muscle cells in the media, and granulomatous chronic inflammatory change in the adventia [5]. Extensive necrotic lesions in the media of the aortic wall with *Aspergillus* hyphae were also observed in our case.

Our patient had no hematological disorder and we did not detect any *Aspergillus* lesions such as a fungus ball in a CT scan. The presence of infectious *Aspergillus* lesions in pulmonary bullae and aortic infection by *Aspergillus* became evident microscopically for the first time in the postmortem examination. *Aspergillus* may have been inhaled into pulmonary bullae and colonized the bullae to produce more infectious lesions. We speculated that *Aspergillus* in the lesions in pulmonary bullae had also invaded the aorta and made extensive necrotic lesions in the media of the aortic wall, including making a hole in the wall. This led to a diagnosis of invasive aspergillosis in the aortic arch. This case was particularly unusual because the patient was immunocompetent and had neither hematologic disorder nor neutropenia.

Scedosporium apiospermum is a difficult fungus to differentiate from *Aspergillus* in tissues [17] and has been reported as a cause of mycotic aortic aneurysm in an immunocompromised patient [18]. Thus, without immunohistochemical evidence, fungal aortitis (as observed in our case) might be due to a non *Aspergillus* spp. such as *S. apiospermum*. However, in our case, immunohistochemical results established the diagnosis of invasive aspergillosis in the aortic arch.

Although positive immunohistochemistry using an anti-*Aspergillus* antiserum favors *Aspergillus* spp. as causative agents, potential cross-reactivity of this serum cannot be excluded.

The observation that the pulmonary bullae were filled with blood at autopsy suggested that the source of bleeding in our case was the hole in the aortic wall, through which massive hemoptysis occurred due to the connection between the systemic circulation and the airway. A previous report has also described massive hemoptysis due to a thoracic aorta infected with *Aspergillus* [4]. However, a case with bleeding other than massive hemoptysis due to a hole in the descending aorta invaded by *Aspergillus fumigatus* has also been described [19]. Our case with invasive aspergillosis in the aortic arch is particularly rare because most cases of aspergillosis in the aorta occur with accompanying hematologic neoplasms and neutropenia.

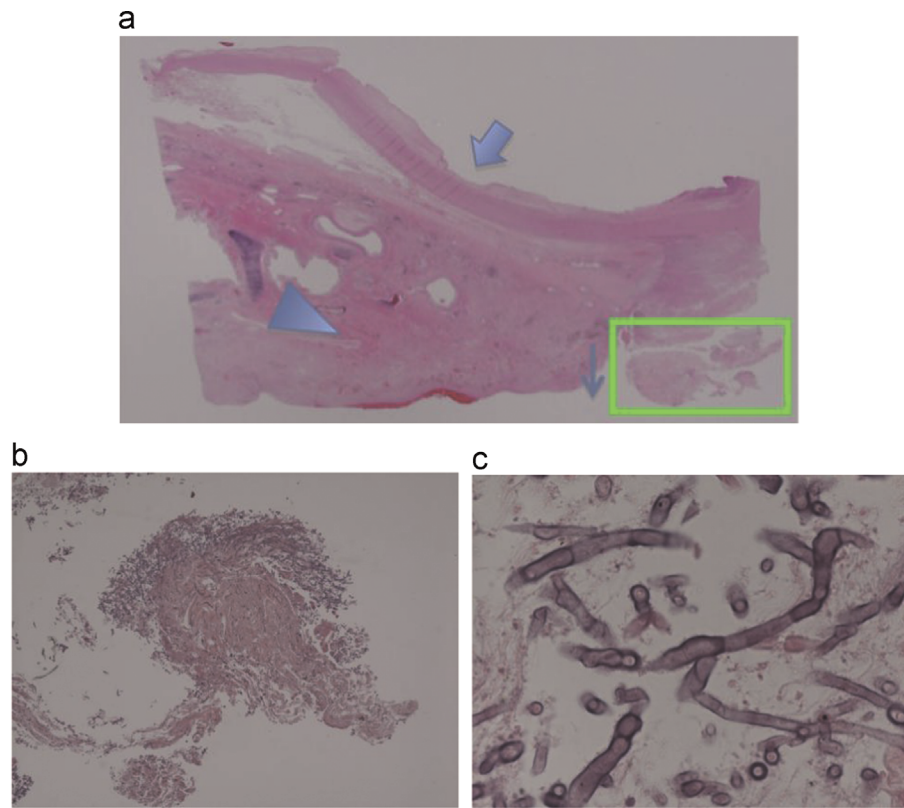


Fig. 4. a. The aortic wall (bold arrow), pulmonary parenchyma (triangle), pulmonary bullae (thin arrow), and fungal lesions in pulmonary bullae (area indicated by the green rectangle) (hematoxylin-eosin (H-E) stain, original magnification $\times 1$). b. Magnified view of the fungal lesions in pulmonary bullae (H-E stain, original magnification $\times 40$). c. Further magnification, showing that the fungal hyphae were 5–10 μm in width, with septae and a dichotomous pattern of branching at 45° . These findings are consistent with *Aspergillus* species (H-E stain, original magnification $\times 600$).

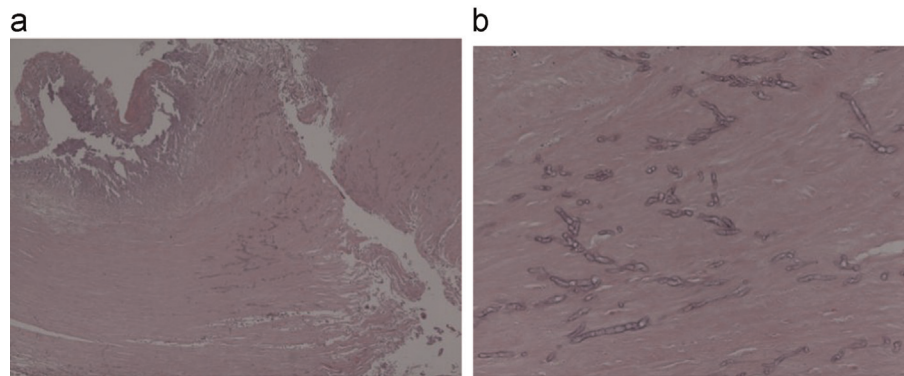


Fig. 5. Photographs show a microscopic view of the aortic wall. a. The media of the aortic wall was extensively necrotic (hematoxylin-eosin (H-E) stain, original magnification $\times 40$). b. *Aspergillus* hyphae were present in the necrotic media of the aortic wall (H-E stain, original magnification $\times 200$).

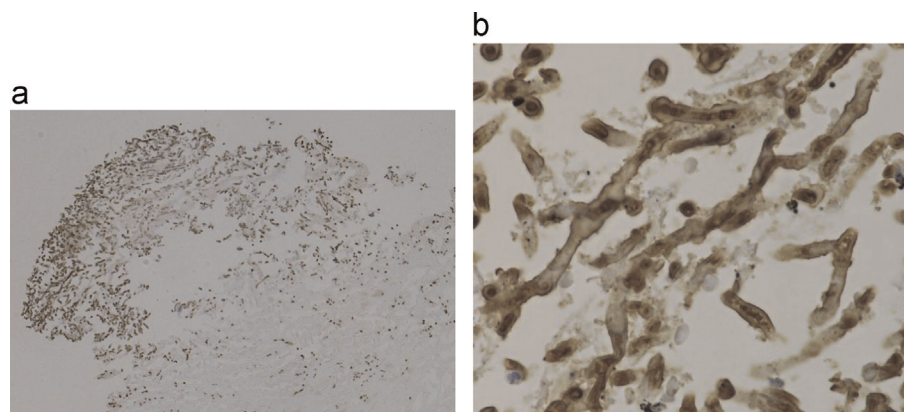


Fig. 6. Immunohistochemical analysis with anti-*Aspergillus* antibody. a. *Aspergillus* hyphae were identified in lesions in pulmonary bullae (immunostaining, original magnification $\times 40$). b. Magnified view of the identified *Aspergillus* hyphae in lesions in pulmonary bullae (immunostaining, original magnification $\times 600$).

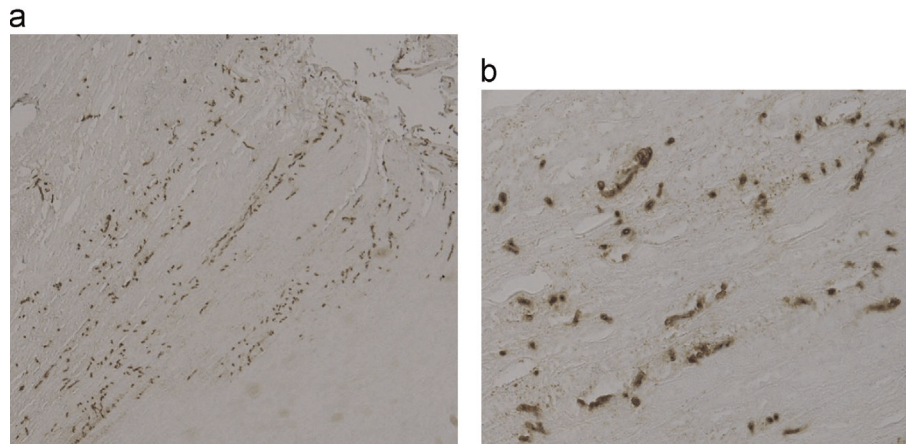


Fig. 7. Immunohistochemical analysis with anti-*Aspergillus* antibody. a. *Aspergillus* hyphae were identified in the necrotic media of the aortic wall (immunostaining, original magnification $\times 40$). b. Magnified view of the identified *Aspergillus* hyphae in the necrotic media of the aortic wall (immunostaining, original magnification $\times 200$).

Conflict of interest

There are none.

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