Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9714-22
Intern Med 62: 423-429, 2023
http://internmed.jp

【 CASE REPORT 】

Intra-abdominal Hemorrhage Due to Splenic Vein Aneurysm Rupture Caused by Invasive Aspergillosis during Treatment for Advanced Non-small-cell Lung Cancer

Ryutaro Hirama[1], Masato Kono[1], Takeshi Kobayashi[1], Yuiko Oshima[1], Kenichiro Takeda[1], Koichi Miyashita[1], Hideki Miwa[1], Akari Tsutsumi[1], Yoshihiro Miki[1], Dai Hashimoto[1], Yoshiro Otsuki[2] and Hidenori Nakamura[1]

Abstract:

A 71-year-old man was admitted for left-sided chest pain. He had a history of diabetes, treatment with epidermal growth factor receptor-tyrosine kinase inhibitor for advanced non-small-cell lung cancer, and corticosteroid treatment for underlying lung diseases. Chest computed tomography showed consolidations in the bilateral lower lobes, and *Aspergillus fumigatus* was detected by bronchoscopy. Invasive pulmonary aspergillosis was suspected, and antifungal therapy with voriconazole was initiated; however, the patient passed away suddenly. Autopsy revealed disseminated *Aspergillus* infection and intra-abdominal hemorrhage due to the rupture of a splenic vein aneurysm caused by *Aspergillus* necrotizing vasculitis, which was considered the cause of death.

Key words: intra-abdominal hemorrhage, splenic vein aneurysm, invasive aspergillosis, non-small-cell lung cancer

(Intern Med 62: 423-429, 2023)
(DOI: 10.2169/internalmedicine.9714-22)

Introduction

Invasive aspergillosis (IA) is a typical invasive fungal infection that mainly affects highly immunocompromised persons. Patients who are at risk of IA include those with prolonged neutropenia, those with advanced acquired immunodeficiency syndrome or chronic granulomatous disease, and recipients of hematopoietic stem-cell transplants or solid-organ transplants (1). In addition, the presence of solid tumors is a risk factor for IA, not only in neutropenic hosts due to chemotherapy and radiotherapy but also in non-neutropenic hosts with high-dose and/or long-term corticosteroid exposure or underlying lung diseases, such as chronic obstructive pulmonary disease (COPD) (2-4).

The lung is a common portal of entry for *Aspergillus* spores, and invasive pulmonary aspergillosis (IPA) is the most common form of IA in immunocompromised patients (1, 5, 6). The hematogenous dissemination of *Aspergillus* spores induces the extra-pulmonary involvement of IA, affecting the heart, kidneys, central nervous system, gastrointestinal tract, spleen, liver, and other organ systems (7, 8). However, no reports have yet described cases of IA causing the rupture of an infectious splenic vein aneurysm (SVA) (9).

We herein report a case in which IA occurred during the treatment for advanced non-small-cell lung cancer (NSCLC), in which an autopsy revealed intra-abdominal hemorrhage due to SVA rupture as the cause of death. Interestingly, the pathological findings suggested that *Aspergillus* necrotizing vasculitis was involved in the formation and rupture of the SVA. This is the first report of intra-abdominal hemorrhage due to rupture of a SVA caused by IA.

[1]Department of Respiratory Medicine, Seirei Hamamatsu General Hospital, Japan and [2]Department of Pathology, Seirei Hamamatsu General Hospital, Japan
Received: March 7, 2022; Accepted: May 8, 2022; Advance Publication by J-STAGE: June 21, 2022
Correspondence to Dr. Masato Kono, masato.k@sis.seirei.or.jp

Table. Laboratory Data on Admission.

Hematology		Biochemistry		Serology	
WBC	12,150 /μL	Na	134 mEq/L	CRP	24.76 mg/dL
Neut	92.6 %	K	3.8 mEq/L	IgE	776.1 U/mL
Lym	1.9 %	Cl	97 mEq/L	CEA	10.8 ng/mL
Mo	4.0 %	TP	7.1 g/dL	SLX	40 U/mL
Eo	1.3 %	Alb	2.1 g/dL		
Ba	0.2 %	AST	29 U/L	**Infection**	
RBC	393 $\times10^4$/μL	ALT	30 U/L	β-D glucan	380 pg/mL
Hb	10.2 g/dL	LD	311 U/L	*Aspergillus* antigen	2.4 (+)
Plt	15.9 $\times10^4$/μL	BUN	15 mg/dL	*Aspergillus* IgG antibody	×128 (+)
		Cre	0.73 mg/dL	PCT	0.19 ng/mL
		eGFR	81 mL/min/1.73m^2		
		Glu	267 mg/dL	**Coagulation**	
		HbA1c	8.4 %	D-dimer	4.4 μg/dL

WBC: white blood cell, Neut: neutrophil, Lym: lymphocyte, Mo: monocyte, Eo: eosinophil, Ba: basophil, RBC: red blood cell, Hb: hemoglobin, Plt: platelet, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactate dehydrogenase, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimated glomerular filtration rate, Glu: glucose, HbA1c: glycated hemoglobin, CRP: C-reactive protein, IgE: immunoglobulin E, CEA: carcinoembryonic antigen, SLX: sialyl Lewis^x, PCT: procalcitonin

Case Report

A 71-year-old Japanese man was admitted to our hospital with left-sided chest pain. He was a former smoker (Brinkman index 4,800) and had a medical history of lung adenocarcinoma (cT3N2M0, cStage IIIA) in the left upper lobe treated with chemoradiation therapy 12 years earlier. In addition, he had been diagnosed with epidermal growth factor receptor (EGFR) mutation-positive (exon19 deletion) lung adenocarcinoma (cT1bN3M1a, cStage IVA) in the right lower lobe a year ago, and the mediastinal lymph nodes had been treated with radiation therapy due to obstruction of the left main bronchus and with the EGFR-tyrosine kinase inhibitor (EGFR-TKI) afatinib to maintain partial remission. He also had diabetes, asthma and COPD overlap that required oral corticosteroids (prednisolone 5 mg/day).

Although there was no fever or evidence of hypoxemia on a physical examination, laboratory tests (Table) revealed an elevated white blood cell count (12,150/μL) and C-reactive protein level (24.76 mg/dL). Tumor markers, including carcinoembryonic antigen (10.8 ng/mL) and Sialyl Lewis^x (40 U/mL), were high but stable.

Compared to the chest radiography findings one month before admission (Fig. 1A), those at admission (Fig. 1B) showed an expanded nodular shadow in the right middle lung field and the appearance of an infiltration shadow in the left lower lung field. Chest computed tomography (CT) revealed consolidation with a cavity in the right lower lung lobe (Fig. 1C), as well as consolidations with emphysematous changes in the left lower lung lobe (Fig. 1D). There were no abnormal findings of intra-abdominal vessels on abdominal CT before admission.

The clinical course after admission of this case is shown in Fig. 2. Considering the possibility of bacterial pneumonia and pleuritis, empiric therapy with ceftriaxone was started after admission, but the treatment response was poor. Bronchoscopy on day 5 showed a large amount of purulent secretion in the left main bronchus, and Gram staining was negative, but the culture test revealed *Aspergillus fumigatus*. Furthermore, a high level of serum β-D glucan (380 pg/mL) and positive anti-*Aspergillus* IgG antibody were revealed. These clinical findings suggested that IPA began as an opportunistic infection during the treatment for advanced NSCLC in this patient. Antifungal therapy with voriconazole (intravenous therapy; 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours) was initiated on day 12, and the inflammatory findings showed a gradual improving trend. Unfortunately, however, the patient died suddenly on day 19.

An autopsy was performed, which revealed approximately 2,000 mL of fresh and partially coagulated blood in the abdominal cavity (Fig. 3A). The bleeding site was confirmed around the spleen (Fig. 3B), and a perforation 3 mm in size was observed in the dilated vessel (Fig. 3C). The cross-sectional surface of the resected specimen of the splenic hilum showed a dilated splenic vein 15 mm in size, which formed the SVA (Fig. 4A). Microscopically, there were some findings concordant with necrotizing vasculitis in the splenic artery and vein, including fibrinoid necrosis and abscess, and partial destruction of elastic fibers in the blood vessels (Fig. 4B, C). Infiltration of multinucleated giant cells and neutrophils was observed in the blood vessel walls (Fig. 4D), and invasion of hyphae suspected to belong to *Aspergillus* was observed at high magnification (Fig. 4E, F). Multiple infarct lesions were found in the spleen (Fig. 4G) and kidneys (Fig. 4H), and infectious thrombi with hyphae were also observed (Fig. 4I). Adenocarcinoma was detected in the right lower lung lobe (Fig. 5A), and degenerated *Aspergillus* hyphae were mainly found inside the cavity of the

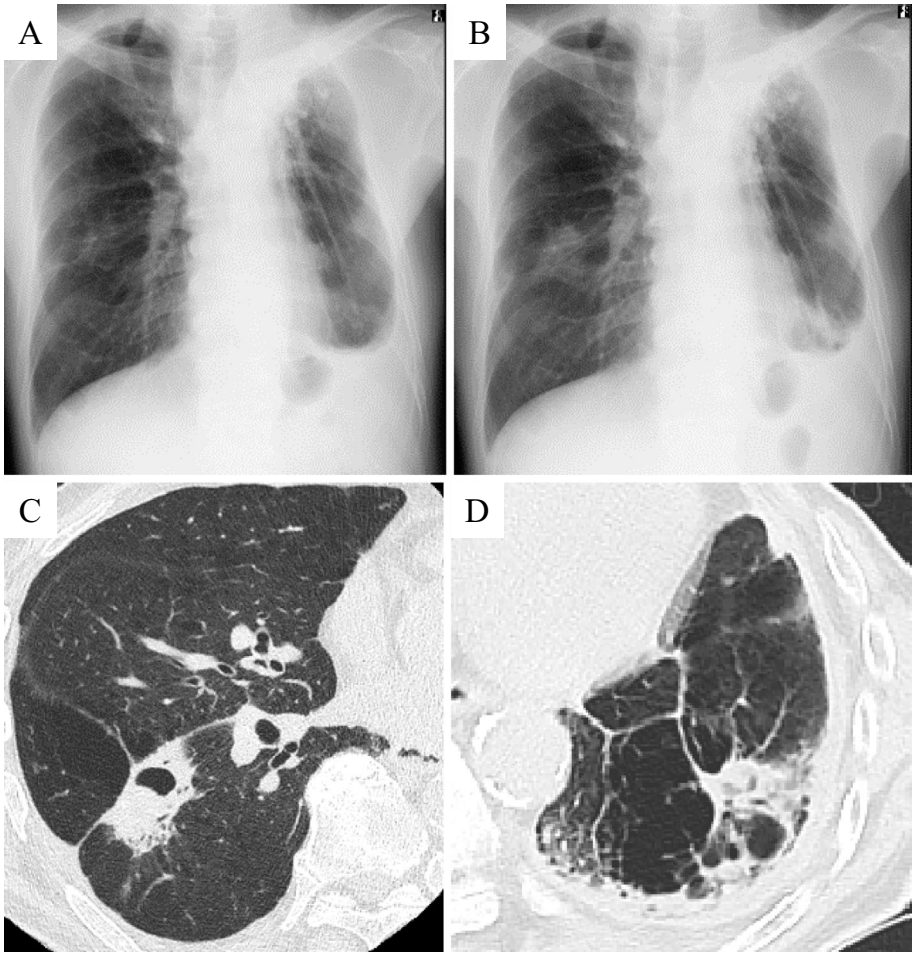

Figure 1. **Compared to the findings of chest radiography 1 month before admission (A), those at admission (B) show an increase in the nodular shadow in the middle right lung field and appearance of an infiltration shadow in the lower left lung field. Chest computed tomography on admission shows consolidation with a cavity in the right lower lobe (C) and emphysematous changes with consolidations in the left lower lobe (D).**

tumor (Fig. 5B, C). A small amount of *Aspergillus* hyphae was also observed in the inflammatory foci of the left upper and lower lung lobes. These findings suggested that the patient had developed IA during treatment for advanced NSCLC, which affected the lungs, spleen, and kidneys. The main cause of death was thus concluded to be intra-abdominal hemorrhage due to rupture of the SVA caused by *Aspergillus* necrotizing vasculitis.

Discussion

This report describes a case of intra-abdominal hemorrhage on autopsy due to the rupture of an SVA, which showed *Aspergillus* necrotizing vasculitis on a histological analysis. The patient had a history of advanced NSCLC treated with EGFR-TKI, chest radiotherapy, diabetes, asthma and COPD overlap, and long-term use of oral corticosteroids; these were suspected risk factors for IA. Thus, IPA occurred in this case and progressed to disseminated *Aspergillus* infection that affected the kidneys and spleen, resulting in a poor prognosis despite treatment with voriconazole. To our knowledge, this is the first report of intra-abdominal hemorrhage due to the rupture of an SVA caused by IA.

A previous report demonstrated that the risk factors of IPA in patients with lung cancer are stage IV disease, recent chemotherapy, and corticosteroid use (2). Compared to IPA patients with hematologic malignancy, those with solid tumors were are likely to have had COPD, other underlying lung diseases (e.g. cavitated lesions, scars, bronchiectasis, or pneumonitis), or prior lung surgeries and have received radiotherapy prior to the IPA diagnosis (4). These factors affect the local defensive action of the lungs and have been hypothesized to be risk factors for invasive fungal infection (4, 5). In addition, Park et al. reported a case of IPA in NSCLC without neutropenia, wherein the involvement of the immune function through the inhibition of T cell proliferation and activation of EGFR-TKI treatment was suggested in the development of invasive *Aspergillus* infection (10). Therefore, although our patient did not have neutropenia, the presence and involvement of these multiple risk factors in the development of IA were speculated.

The lung is a common portal of entry for *Aspergillus*

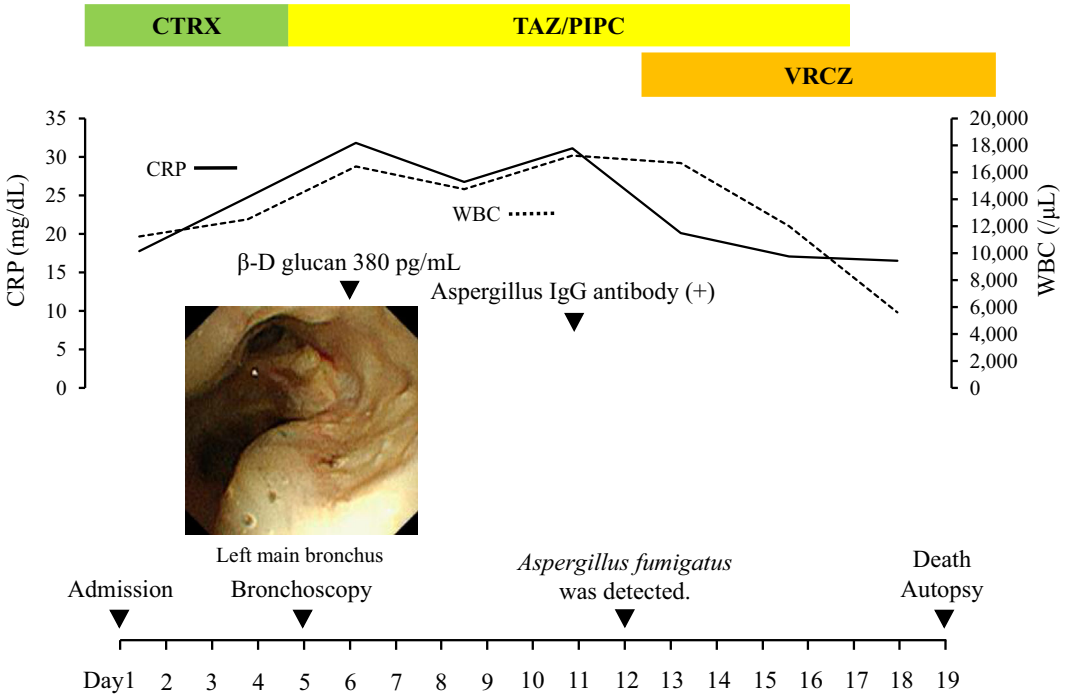

Figure 2. **Clinical course after admission. Bronchoscopy at day 5 showed a large amount of purulent secretion in the left main bronchus. CRP: C-reactive protein, CTRX: ceftriaxone, IgG: immunoglobulin G, TAZ/PIPC: tazobactam piperacillin, VRCZ: voriconazole, WBC: white blood cell**

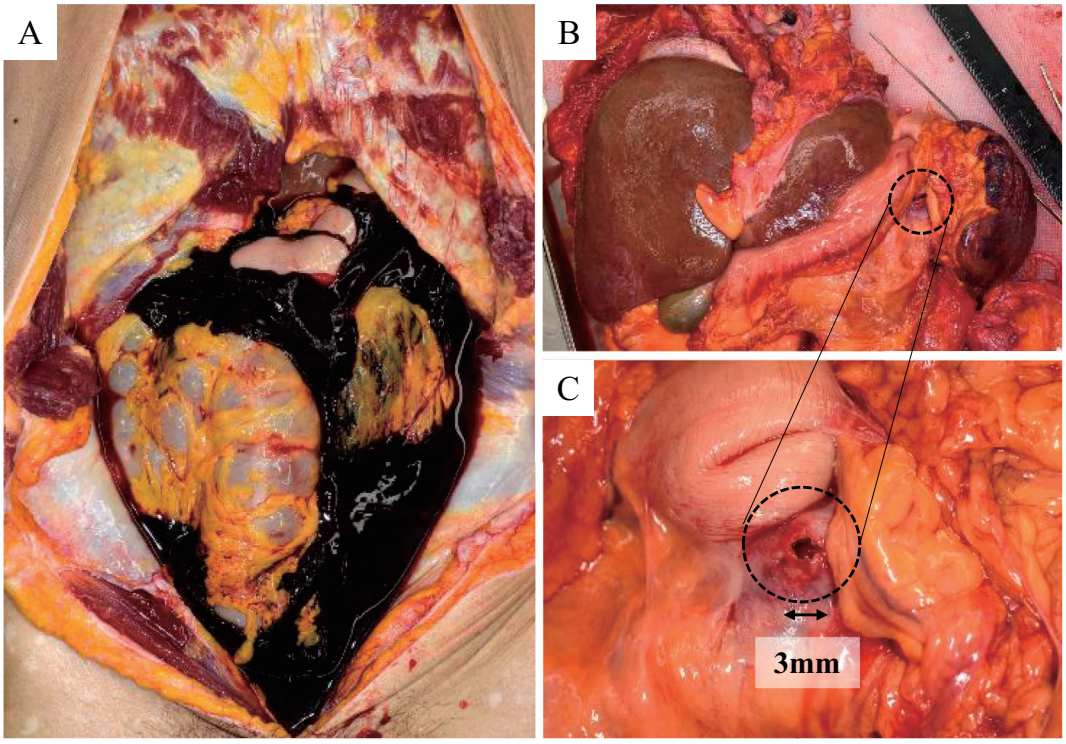

Figure 3. **Approximately 2,000 mL of fresh and partially coagulated blood is observed in the abdominal cavity (A). The bleeding site is confirmed around the spleen (B), and a perforation 3 mm in size is observed in the dilated vessel (C).**

spores, and IPA is the most common form of IA in immunocompromised patients (1, 5, 6). Autopsy studies have reported that the frequency of extra-pulmonary involvement in IA is 37.5% to 51.4%, and this includes the involvement of the heart, kidneys, central nervous system, gastrointestinal tract, spleen, liver, and other organ systems (7, 8). Extra-pulmonary involvement occurs at an advanced stage of IA, has poor response to anti-fungal treatment, and has a higher

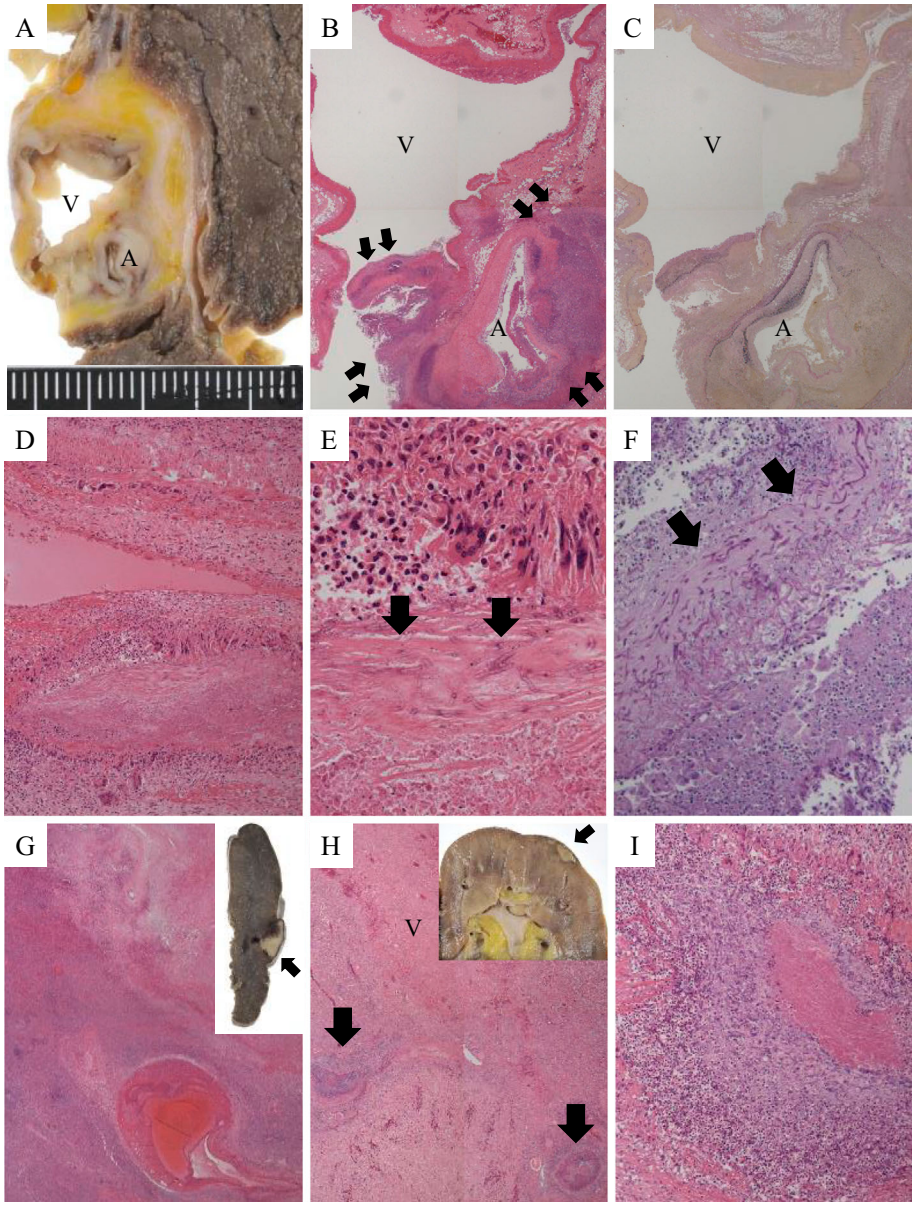

Figure 4. **The cross-sectional surface of the resected specimen of splenic hilum at autopsy shows a dilated splenic vein 15 mm in size forming the splenic vein aneurysm (A). Microscopic findings show necrotizing vasculitis in the splenic artery and vein, including fibrinoid necrosis and abscess (arrows), and partial destruction of the elastic fibers in the blood vessels. B: Hematoxylin and Eosin (H&E) staining, ×2; C: EVG staining, ×2. Infiltration of multinucleated giant cells and neutrophils (arrows) is observed in the blood vessels (D: H&E staining, ×10), and the invasion of hyphae (arrows) suspected to belong to *Aspergillus* is confirmed (E: H&E staining, ×40; F: PAS staining, ×20). Multiple infarcts (inset; arrow) are found in the spleen, which shows necrosis with hemorrhage (G: H&E staining, ×4). The kidneys also show infarctions (inset: arrow) (H: H&E staining, ×2), and infectious thrombi with hyphae (arrows in H) are observed (I: H&E staining, ×20). A: splenic artery, EVG: Elastica van Gieson, V: splenic vein**

fatality in disseminated IA than in localized IA (7). In our case, IA was histologically observed in multiple organs, including the lungs, kidneys, and spleen. Regarding splenic involvement of IA, a previous report demonstrated that infarction and abscess were observed pathologically (7). Notably, the present case had an SVA with *Aspergillus* necrotizing vasculitis in addition to these findings. Although mycotic aneurysm due to *Aspergillus* species is rare, it has been reported in various vessels, including the aorta and cerebrovascular vessels (11, 12); however, SVA caused by IA has not been reported.

Vascular diseases of the spleen are uncommon. SVA is extremely rare and may be congenital or acquired (9). The most common etiology of an acquired SVA is portal hypertension, but it can also be caused by other factors (9, 13). Shimoda et al. reported a case of intra-abdominal hemor-

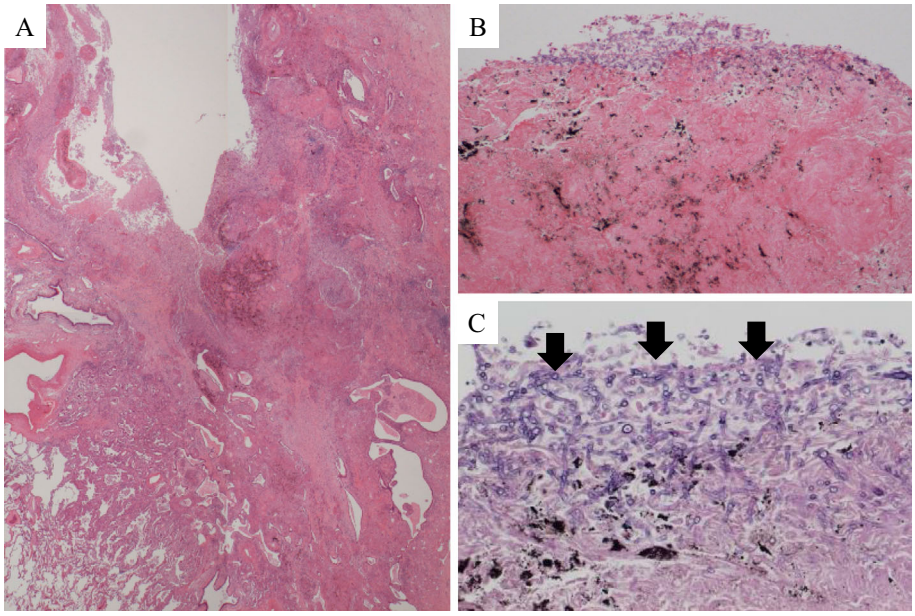

Figure 5. Signs indicative of adenocarcinoma seen in the right lower lung lobe. A: Hematoxylin and Eosin (H&E) staining, ×4. Degenerated hyphae suspected of *Aspergillus* (arrows) are mainly found inside the cavity of the tumor. B: H&E staining, ×20; C: PAS staining, ×40. PAS: periodic-acid Schiff

rhage due to rupture of an SVA without any evidence of portal hypertension, and the histological findings showed that the cause of SVA was associated with pancreatitis (14). Regarding the formation of the SVA in this case, the absence of any abnormal findings of splenic vessels before admission was confirmed. The presence of pathological findings on autopsy thus suggested that disseminated *Aspergillus* infection in the spleen had caused necrotizing vasculitis and abnormal dilation of the splenic vessels, thereby forming an SVA and subsequently leading to rupture.

In patients with IPA, the early initiation of antifungal therapy, particularly voriconazole as the primary treatment, is recommended (15). A previous report described high odds of successful treatment of IPA with voriconazole in patients with IPA and solid tumors (3). In the present case, voriconazole treatment was started immediately after the suspected diagnosis of IPA and was clinically effective, but the prognosis was poor because of intra-abdominal hemorrhage due to the SVA rupture as a complication of IA. This case had severe inflammatory findings on laboratory data despite corticosteroid administration, and the findings persisted after antifungal treatment, suggesting the presence of a serious *Aspergillus* infection. The chief complaint of left-sided chest pain on admission in this case probably reflects splenic infarction due to disseminated *Aspergillus* infection, and earlier treatment may have been successful.

In conclusion, our patient developed intra-abdominal hemorrhage caused by the rupture of an SVA associated with disseminated *Aspergillus* infection during treatment for advanced NSCLC, as seen histologically. This was an extremely rare and fatal complication of IA. The occurrence of IA should be considered in patients with advanced NSCLC, especially in those with multiple risk factors for IA, even in the absence of neutropenia.

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

References

1. Segal BH. Aspergillosis. N Engl J Med **360**: 1870-1884, 2009.
2. Yan X, Li M, Jiang M, Zou LQ, Luo F, Jiang Y. Clinical characteristics of 45 patients with invasive pulmonary aspergillosis: retrospective analysis of 1711 lung cancer cases. Cancer **115**: 5018-5025, 2009.
3. Dandachi D, Wilson Dib R, Fernández-Cruz A, et al. Invasive pulmonary aspergillosis in patients with solid tumours: risk factors and predictors of clinical outcomes. Ann Med **50**: 713-720, 2018.
4. Dib RW, Khalil M, Fares J, et al. Invasive pulmonary aspergillosis: comparative analysis in cancer patients with underlying haematologic malignancies versus solid tumours. J Hosp Infect **104**: 358-364, 2020.
5. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. Eur Respir Rev **20**: 156-174, 2011.
6. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax **70**: 270-277, 2015.
7. Hori A, Kami M, Kishi Y, Machida U, Matsumura T, Kashima T. Clinical significance of extra-pulmonary involvement of invasive aspergillosis: a retrospective autopsy-based study of 107 patients. J Hosp Infect **50**: 175-182, 2002.
8. Lehrnbecher T, Frank C, Engels K, Kriener S, Groll AH, Schwabe D. Trends in the postmortem epidemiology of invasive fungal infections at a university hospital. J Infect **61**: 259-265, 2010.
9. Uy PPD, Francisco DM, Trivedi A, O'Loughlin M, Wu GY. Vascular diseases of the spleen: a review. J Clin Transl Hepatol **5**: 152-164, 2017.
10. Park S, Park S, Choi H, et al. Invasive pulmonary aspergillosis in a patient with metastatic non-small cell lung cancer after treatment with gefitinib. Korean J Intern Med **33**: 211-213, 2018.
11. Silva ME, Malogolowkin MH, Hall TR, Sadeghi AM, Krogstad P. Mycotic aneurysm of the thoracic aorta due to Aspergillus terreus: case report and review. Clin Infect Dis **31**: 1144-1148, 2000.

12. Sundaram C, Goel D, Uppin SG, Seethajayalakshmi S, Borgohain R. Intracranial mycotic aneurysm due to *Aspergillus* species. J Clin Neurosci **14**: 882-886, 2007.
13. Sfyroeras GS, Antoniou GA, Drakou AA, Karathanos C, Giannoukas AD. Visceral venous aneurysms: clinical presentation, natural history and their management: a systematic review. Eur J Vasc Endovasc Surg **38**: 498-505, 2009.
14. Shimoda M, Kubota K, Sakuma A, Hogami T, Yamaguchi H, Tagaya N. Intra-abdominal hemorrhage due to rupture of a splenic vein aneurysm: a case report. J Gastrointest Surg **7**: 683-686, 2003.
15. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis **63**: e1-e60, 2016.