INTRODUCTION

Hemoptysis is often a life-threatening symptom and may cause severe clinical conditions. Causes of hemoptysis are varied and include bronchiectasis, infection (eg, tuberculosis, pneumonia, and fungal infection), trauma, pulmonary vascular disease, iatrogenic injuries, and airway malignancies. Among them, pulmonary artery pseudoaneurysm (PAP) is a rare cause of hemoptysis, but careful consideration should always be given as it is potentially fatal, especially in patients with primary or metastatic lung cancer. We encountered a 65-year-old male lung cancer patient with hemoptysis due to rupture of PAP induced by thoracic radiation therapy (TRT). An autopsy was performed, and we herein report the detailed clinical, radiological, and pathological findings. Written informed consent was obtained from his relatives.

CASE REPORT

A 65-year-old man presented to our hospital with nausea and vomiting. He was diagnosed with lung squamous cell carcinoma (T1aN2M0, stage IIIA) 1 month before, and TRT at 60 Gy total in 30 daily fractions for primary tumor (Figure 1) was started. Performance status at the time of lung cancer diagnosis was one. His past medical history included hypertension, dyslipidemia, type 2 diabetes mellitus, and old myocardial infarction, and medications were imidapril, atorvastatin, alogliptin, and aspirin. On physical examination, decreased breathing sounds were observed in the upper left side of the chest where TRT had been performed. Chest CT revealed consolidation and cavity in the left upper
lobe. He was thus diagnosed as lung abscess and treated with the intravenous antibiotics, meropenem, for three weeks. No significant bacteria were detected in the sputum culture. His clinical and radiographic findings consequently showed improvement. However, he had hemoptysis after the antibiotic treatment, and intravenous contrasted chest CT revealed left PAP (Figure 2). He coughed up a massive amount of blood before his scheduled PAP embolization and could not be resuscitated due to airway occlusion.

Autopsy was performed on the next day after death. Macroscopic findings showed cavity in the left upper lobe leading to the left pulmonary artery, and whole lung edema was observed (Figure 3A, B). Moreover, blood coagulation was found in the trachea and main bronchus (Figure 3C). Microscopic findings showed that the arterial wall had been damaged with fibrin drainage based on Elastica van Gieson stain (Figure 4A, B). The lung abscess wall included squamous cell carcinoma cells (Figure 4C).

3 | DISCUSSION

Although the rate of PAP occurrence is rare, bronchiectasis, infection, trauma, iatrogenic, vascular disease, and airway malignancy are its major causes. Pseudoaneurysm is defined as focal blood vessel dilation that does not involve all arterial wall layers, while aneurysm is defined as that which involves all three arterial wall layers. The precise mechanism of PAP formation has not yet been elucidated. In our current case, microscopic findings showed arterial wall disruption by inflammation together with invasion of squamous cell carcinoma, which affected the adventitia and the tunica media (Figure 4A). Boerrigter et al recently proposed that the structural changes of elastin and collagen under the influence of an increasing PA pressure may lead to PA dilation and further PAP formation. This disruption and the abnormal formation of the arterial vessel may be further exacerbated by radiation therapy.

Since PAP is a fatal condition, prompt and appropriate diagnosis is essential in the clinical setting. Although pulmonary angiography is the gold standard for PAP diagnosis, contrast-enhanced CT enabled PAP diagnosis with less invasiveness. AP is defined as an upper limit of the main pulmonary artery (PA) diameter (29 mm) and an upper limit of the right interlobar artery (17 mm) measured using CT images. The present case fulfilled these criteria (upper limit of the main PA diameter was 31 mm and upper limit of the right interlobar artery was 19 mm). In past reports, maximum intensity projection (MIP) and multiplanar reconstruction images on CT have been useful for PAP diagnosis.
Previous literature has indicated that lung cancer is associated with PAP formation. In cases with lung cancer-associated PAP, it is possible that tumor invasion to blood vessels may result in PAP formation. To the best of our knowledge, there have been twelve cases of pseudoaneurysm accompanied with lung cancer, and squamous cell carcinoma was the most frequent in the reported cases (Table 1). Six patients survived without any intervention, while four patients died (two were unknown). It is well known that lung squamous cell carcinoma characteristically presents with hemoptysis. Razazi et al reported that 125 patients had hemoptysis related to non-small-cell lung carcinoma, and in those patients, the proportion of squamous cell carcinoma was 52%. Moreover, tumor cavitation during cancer treatment has been suggested as a risk factor for hemoptysis. In the present case, we hypothesize that PAP caused by squamous cell lung carcinoma together with a tumor cavity may be a significant risk factor for massive hemoptysis.

Infection such as lung abscess is also known as an important factor for PAP, but the detailed mechanism of PAP formation by lung abscesses is unknown. Several decades ago, syphilis and tuberculosis infection frequently caused PAP, but
those causes dramatically decreased nowadays.\(^9\) The cause of PAP formation was primarily thought to be structural destruction of the vessel wall by granulation tissue.\(^7\) Likewise, it is presumed that the spillover of inflammation to the pulmonary arteries due to bacterial infections may be a significant factor. In this case, we diagnosed clinically pulmonary abscesses by blood tests and imaging examinations, although no obvious causative organism could be identified, and autopsy findings were consistent with pulmonary abscesses.

Additionally, radiation therapy is known to cause vascular diseases including PAP.\(^24\) Schultz et al reported that radiation therapy causes acute upregulation of pro-inflammatory cytokines and adhesion molecules in the endothelium that recruits inflammatory cells to the sites of vascular injury.\(^25\) Martin et al subsequently proposed a mechanism of radiation-induced vascular disease whereby resultant oxidative stress causes nuclear factor-kappa B (NF-κB) activation that in turn causes inflammatory cytokine upregulation.\(^26\) Moreover, preexisting cardiac disease has been significantly associated with development of cardiac events in patients with lung cancer who have received radiation therapy. In the Netherlands, 23% of patients with lung cancer had developed cardiovascular disease.\(^27\) In Table 1, four patients had received radiation therapy for lung cancer treatment before PAP diagnosis (two had received combined chemotherapy with radiation therapy, and two including our case had received radiation therapy alone). As with these cases, there was a possibility that PAP development was accelerated by radiation therapy in our case.

Endovascular and percutaneous interventional procedures are often used for PAP treatment. Percutaneous intervention is a less invasive option than surgical treatment. While the primary intervention is the embolization of systemic arteries, other therapeutic options may be considered depending on the size and location of the PAP.\(^12\) Unfortunately, the current case had died from massive hemoptysis before receiving intervention therapy.

### 4 CONCLUSIONS

In summary, we encountered a lethal clinical course of pulmonary artery pseudoaneurysm after thoracic radiation therapy against lung squamous cell carcinoma. In this case, there was no evidence of PAP prior to radiation therapy. Therefore, it was possible that a combination of factors, such as infection and squamous cell carcinoma, were involved in addition to radiation therapy. Although rare, lung cancer can be associated with a pseudoaneurysm of the pulmonary artery, which can be exacerbated and fatal, especially after radiation therapy, so prompt intervention should be done if diagnosed.

### ETHICS STATEMENT

The study complied with the principles of the Declaration of Helsinki. The Showa University Ethics Committee approved this study (approval number: 2659).

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CONFLICT OF INTEREST
None declared.

AUTHOR CONTRIBUTIONS
Yosuke Fukuda: Conceptualization and writing (original draft); Tetsuya Homma: Supervision and writing (review and editing); Tomoki Uno, Yasunori Murata, and Shintaro Suzuki: Investigation; Eisuke Shiozawa and Masafumi Takimoto: Supervision. Hironori Sagara: Writing (review and editing).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author, YF. The data are not publicly available due to restrictions that their containing information could compromise the privacy of research participants.

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