chronic airway obstruction. For all 853 patients who gave written informed consent, spirometry was performed by the same clinical laboratory technologist, who was an expert in performing pulmonary function tests and who worked in each facility for 2-3 days. The pulmonary function tests were performed according to the procedures and criteria described in the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] The same spirometer (HI101; Chest, Inc., Tokyo, Japan) was used at all of the facilities. Each pulmonary function test was performed three times. FEV1/FVC was calculated from the maximum FEV1 and maximum FVC, and an FEV1/FVC of <70% was taken as signifying the presence of airflow limitation. In addition, the severity of COPD was determined from the percentage FEV1 relative to the predicted value (mild, ≥80%; moderate, ≥50% but <80%,; severe, ≥30% but <50%; most severe <30%).[1] The institutional Ethics Committee at Jichi Medical University Hospital approved the study protocols and all participants gave written informed consent.

Statistical analyses

Statistical analysis of the relationship between airflow limitation and the demographic characteristics of the patients was performed using the Cochran-Armitage test or Fisher's exact test. The odds ratios for airflow limitation in patients who did or did not

use statins were calculated, with adjustment for smoking history. The odds ratio homogeneity between smokers and non-smokers was determined by the Breslow-Day test. Logistic regression analysis was performed, with airflow limitation as the dependent variable and age, gender, smoking status, pack-years of smoking, the number of current respiratory symptoms, and use or non-use of statin as independent factors. Significance was set at $P < 0.05$. SAS version 9.1.3 software (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

RESULTS

Spirometry was performed on 853 patients (416 males, 437 females, mean age 64.0 ± 11.3 years), who completed the questionnaire and did not have COPD. There were no incomplete or missing data for these 853 patients, and data for all patients was included in the analysis. Airflow limitation was detected in 81 (9.5%) of the 853 patients. Although the prevalence of airflow limitation differed at the 16 facilities participating in the study, there were patients with airflow limitation at all the participating facilities, regardless of the type of medical practice. The prevalence of airflow limitation according to age and gender is shown in Table 1. The prevalence increased significantly with increasing age, and 15.7% of patients 70 years of age or older showed

airflow limitation.

Among patients >60 years old, there were 295 non-smokers, 174 former smokers, and 95 current smokers. In addition, airflow limitation was detected in a significantly higher percentage of men (13.9%) than women (5.3%). The prevalence of airflow limitation according to smoking status and pack-years of smoking is also shown in Table 1. The prevalence of airflow limitation was significantly lower in non-smokers than in former smokers or current smokers, and increased significantly with increasing number of pack-years smoked.

There were no differences in the prevalence of airflow limitation between patients with or without underlying diseases such as hyperlipidaemia, hypertension, or diabetes. However, airflow limitation was detected in only 2.3% (2/89) of the 89 patients who used statins, which was approximately five times lower than the incidence among patients who did not use statins [10.5% (64/609)] (Table 1). There were no significant differences in the prevalence of airflow limitation between patients who did or did not use ARB or ACEI. Table 2 shows a comparison of the demographic characteristics of the patients according to use or non-use of statins. There were no differences in age, respiratory symptoms, or the number of patients using ACEI, between those who used and those who did not use statins. However, the proportions of males, smokers and the

pack-years of smoking were significantly lower in the group of patients who used statins.

The prevalence of airflow limitation in patients who used or did not use statins, according to smoking status, is shown in Table 3. Among the 347 patients with a history of past or current smoking, airflow limitation was not detected in the 30 patients who used statins, but was detected in 47 (14.8%) of the 317 patients who did not use statins. On the other hand, among the 351 non-smokers, the prevalence of airflow limitation was 3.4% in those who used statins and 5.8% in those who did not. Multivariate analysis of the factors associated with airflow limitation showed that age, pack-years of smoking, and the number of current respiratory symptoms were important factors. However, use or non-use of statins was not associated with airflow limitation (Table 4).

DISCUSSION

In order to determine the prevalence of airflow limitation among patients who visited medical facilities that provide primary care, a cross-sectional study based on a questionnaire and spirometry was performed. Airflow limitation was detected in 81 (9.5%) of 853 patients, 40 years of age and older. In a previous epidemiological study

of the prevalence of COPD in Japan [Nippon COPD epidemiology (NICE) study], the prevalence of COPD was 8.5% among those over the age of 40 years.[21] The prevalence of COPD was slightly higher in the present study but the results were similar. Patients were not asked to inhale bronchodilators before the pulmonary function tests. Therefore, the possibility that patients with chronic airway obstruction, such as undiagnosed asthma, were included among those presenting with airflow limitation cannot be ruled out. However, since the prevalence of airflow limitation was about the same as that in the NICE study, it is reasonable to assume that most of the patients with airflow limitation had COPD.

It was reported that the prevalence of subclinical (undetected) COPD among patients receiving routine clinical check-ups differed according to the demographic characteristics of the patient population, such as male:female ratio and percentage of smokers. Koga *et al.*[22] reported that the prevalence of previously unidentified COPD was 7.4% among patients who received a medical check-up, 16.3% among those who visited a primary care facility, and 25.8% among those who underwent pre-operative pulmonary function tests. In similar studies of patients visiting primary care facilities,[23,24] the reported prevalence of airflow limitation was 27% and 30%, respectively. In the present study, the prevalence of airflow limitation was lower than

that reported in similar previous studies. The low prevalence of COPD in the present study may be explained by the male/female ratio of 416/437 (i.e., almost 1:1), and the relatively low percentage of patients >70 years old (34.3%, 293 patients).

In this study, we also investigated whether the use or non-use of statins influenced the prevalence of airflow limitation. The results showed that the prevalence of airflow limitation among patients who used statins was approximately five times lower than that among patients who did not use statins. Statins play an important role in the prevention and treatment of hyperlipidaemia and atherosclerotic disease. Recent reports indicate that statins have other effects that are independent of their effect in reducing levels of low density lipoprotein cholesterol, such as anti-inflammatory and anti-fibrotic effects, and improvement in endothelial function.[10-12]

Recently, there have been some important reports on the effects of statins in patients with COPD.[13-20] Young *et al.*[6] suggested that the anti-inflammatory effects of statins on both pulmonary and systemic inflammation, through inhibition of guanosine triphosphatase and nuclear factor-κB-mediated activation of inflammatory and matrix remodelling pathways, may result in substantial benefits for patients with COPD. With respect to the effect of statins on airflow limitation, Keddissi *et al.*[25] reported that the annual decline in FEV1 in 215 former and current smoking patients who used statins

(85 ± 171 mL) was significantly less than that in 203 patients who did not use statins (-5 ± 201 mL). Alexeeff *et al.*[26] also reported a follow-up study of elderly men (veterans), including some COPD patients, which showed that statins reduced the rate of decline in FEV1 with age, although there was a difference in the effect with respect to smoking status. Those results support the results from the present study and suggested that the prevalence of airflow limitation was lower in patients who used statins because statin use reduced the annual rate of decline in FEV1.

The limitations of this study include possible bias in the selection of patients. The first bias is the healthy user effect. In this study, the subjects were patients over 40 years of age, who had visited a primary care facility due to lifestyle-related diseases. Therefore, the data analyzed was for a group of people whose health care was managed in medical facilities, and so might not be generalizable to the general population. Second, there were differences in patient demographics with regard to statin use, and the sample size was small. In addition, this was a cross-sectional study, and there is the possibility of reverse causality between statin use and airflow limitation. That is, patients with airflow limitation might have previously experienced limitation in activities of daily living. Therefore, they might have had less opportunity to experience symptoms related to cardiovascular events, such as chest pain on exertion,

with fewer patients therefore using oral statins. Therefore, from the results of this study, it is difficult to determine whether or not statin use directly affects the prevalence of airflow limitation. However, all outpatients attending the selected medical facilities were invited to participate and all patients who consented to participate underwent spirometry. Therefore, we believe that there was no intentional bias in patient selection or exclusion of data.

In conclusion, this cross-sectional study is the first from Japan to demonstrate the potential impact of statin use on the prevalence of airflow limitation. It would appear to be important to accumulate more information on this topic in the future.

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REFERENCES

1. Global strategy for diagnosis, management, and prevention of COPD. Updated 2009. http://www.goldcopd.com/Guidelineitem.asp?l1=2&l2=1&intld=2003. Accessed: 1st July 2010.
2. Sin DD, Man PSF. Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular disease? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 2003; **107**: 1514-19.
3. Gan WQ, Man SFP, Senthilselvan A *et al.* Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax* 2004; **59**: 574-80.
4. Bhowmic A, Seemungal TA, Sapsford RJ *et al.* Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* 2000; **55**: 114-20.
5. Spruit MA, Gosselink R, Troosters T *et al.* Muscle force during an acute exacerbation in hospitalized patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 2003; **58**: 752-6.
6. Young RP, Hopkins R, Eaton TE. Pharmacological actions of statins: potential utility in COPD. *Eur. Respir. Rev.* 2009; **18**: 222-32.
7. Fabbri LM, Rabe KF. From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007; **370**: 797-9.
8. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. *Eur.*

Respir. J. 2009; **33**: 1165-85.

9. Barnes PJ. Chronic obstructive pulmonary disease: Effects beyond the lungs. *PLoS Med.* 2010; **7**: e1000220.
10. Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as anti-inflammatory agents? *Circulation* 2004; **109**: 118-26.
11. Rosenson RS, Tangney CC, Casey LC. Inhibition of proinflammatory cytokine production by pravastatin. *Lancet* 1999; **353**: 983-4.
12. Albert MA, Danielson E, Rifai N *et al.* Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; **286**: 64-70.
13. Blamoun AI, Batty GN, Debari VA *et al.* Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. *Int. J. Clin. Pract.* 2008; **62**: 1373-8.
14. Frost FJ, Petersen H, Tollestrup K *et al.* Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest* 2007; **131**: 1006-12.
15. Ishida W, Kajiwara T, Ishii M *et al.* Decrease in mortality rate of chronic obstructive pulmonary disease (COPD) with statin use: a population-based analysis in Japan. *Tohoku J. Exp. Med.* 2007; **212**: 265-73.
16. Soyseth V, Brekke PH, Smith P *et al.* Statin use is associated with reduced mortality in COPD. *Eur. Respir. J.* 2007; **29**: 279-83.
17. Walsh GM. Statins as emerging treatments for asthma and chronic obstructive

pulmonary disease. *Expert Rev. Respir. Med.* 2008; **2**: 329-35.

18. Janda S, Park K, FitzGerald JM *et al.* Statins in COPD: A systematic review. *Chest* 2009; **136**: 734-43.
19. Young RP, Hopkins R, Eaton TE. Potential benefits of statins on morbidity and mortality in chronic obstructive pulmonary disease: a review of evidence. *Postgrad. Med. J.* 2009; **85**: 414-21.
20. Young RP, Hopkins R, Eaton TE. Comorbidities in COPD. *Eur. Respir. J.* 2009; **34**: 1497-500.
21. Fukuchi Y, Nishimura M, Ichinose M *et al.* COPD in Japan: the Nippon COPD epidemiology study. *Respirology* 2004; **9**: 458-65.
22. Koga T, Tsuda T, Omori H *et al.* Epidemiological survey of unidentified COPD in medical check-up participants, primary care visitors and preoperative patients in the Kyushu area of Japan. *Respiration Research* 2006; **25**: 801-6.
23. Takahashi T, Ichinose M, Inoue H *et al.* Underdiagnosis and undertreatment of COPD in primary care settings. *Respirology* 2003; **8**: 504-8.
24. Geijer RM, Sachs AP, Hoes AW *et al.* Prevalence of undetected persistent airflow obstruction in male smokers 40-65 years old. *Fam. Pract.* 2005; **22**: 485-9.
25. Keddissi JI, Younis WG, Chbeir EA *et al.* The use of statins and lung function in current and former smokers. *Chest* 2007; **132**: 1764-71.
26. Alexeeff SE, Litonjua AA, Sparrow D *et al.* Statin use reduces decline in lung function: VA Normative Aging Study. *Am. J. Respir. Crit. Care Med.* 2007; **176**: 742-7.

Table 1 Prevalence of airflow limitation according to age, gender, smoking status, pack-years of smoking, and use of statins, angiotensin receptor blockers and angiotensin converting enzyme inhibitors

Factor	Category	Number of subjects	Airflow limitation		*P* value
			Number of subjects	%	
Age, years	40-49	114	1	0.88	<0.001
	50-59	175	4	2.29	
	60-69	271	30	11.07	
	70-	293	46	15.70	
Gender	Males	416	58	13.94	<0.001
	Females	437	23	5.26	
Smoking status	Current smokers	174	25	14.37	<0.001
	Former smokers	237	31	13.08	
	Never smokers	442	25	5.66	
Pack-years	0-15	528	28	5.30	<0.001
	15-30	113	9	7.96	
	30-45	103	19	18.45	
	45-	109	25	22.94	
Statin use	Yes	89	2	2.25	0.01
	No	609	64	10.51	
ARB use	Yes	93	10	10.75	0.553
	No	522	45	8.62	
ACEI use	Yes	12	1	8.33	1.000
	No	603	54	8.96	

ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor

Table 2 Comparison of patient characteristics between those who did or did not use statins

Factor		Categories	Statin use		*P* value
			Yes (n = 89)	No (n = 609)	
Age, years, mean ± SD			63.7±9.1	63.3±12.0	0.946
Gender, n (%)		Males	30 (33.7)	320 (52.5)	<0.001
		Females	59 (66.3)	289 (47.5)	
Smoking status, n (%)		Current smokers	6 (6.7)	136 (22.3)	<0.001
		Former smokers	24 (27.0)	181 (29.7)	
		Never smokers	59 (66.3)	292 (47.9)	
Pack–years, mean ± SD			23.9±16.2	34.8±27.2	0.032
Respiratory symptoms, n (%)	Cough	Yes	19 (21.3)	111 (18.2)	0.468
		No	70 (78.7)	498 (81.8)	
	Sputum	Yes	20 (22.5)	132 (21.7)	0.891
		No	69 (77.5)	477 (78.3)	
	Dyspnoea	Yes	16 (18.0)	145 (23.8)	0.281
		No	73 (82.0)	464 (76.2)	
Drug treatment, n (%)	ARB	Yes	26 (31.7)	63 (13.3)	<0.001
		No	56 (68.3)	412 (86.7)	
	ACEI	Yes	2 (2.4)	10 (2.1)	0.693
		No	80 (97.6)	465 (97.9)	

ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor

Table 3 Association of statin use with airflow limitation according to smoking status

Smoking status	Statin use	Airflow limitation			Odds ratio
		Present	Absent	Total	
Current smokers, *n* (%)	Yes	0 (0.0)	6 (100.0)	6 (100.0)	Point estimate 0.41*
	No	21 (15.4)	115 (84.6)	136 (100.0)	95% CI 0.02, 7.61*
Former smokers, *n* (%)	Yes	0 (0.0)	24 (100.0)	24 (100.0)	Point estimate 0.12*
	No	26 (14.4)	155 (85.6)	181 (100.0)	95% CI 0.01, 2.03*
Never smokers, *n* (%)	Yes	2 (3.4)	57 (96.6)	59 (100.0)	Point estimate 0.57
	No	17 (5.8)	275 (94.2)	292 (100.0)	95% CI 0.13, 2.53
Test for homogeneity of odds ratio (Breslow-Day test)					$P = 0.267$

*Because cell counts included zero, adjustments were made by adding 0.5 to all cells

Table 4 Multivariate analysis of factors associated with airflow limitation

Factor	Categories		Odds ratio (95% CI)	*P* value
Age, years	40-49		Reference	
	50-59	1.23	3.43 (0.32, 36.97)	0.309
	60-69	2.70	14.95 (1.62, 138.0)	0.017
	70-	3.08	21.73 (2.39, 197.7)	0.006
Gender	Males	0.33	1.39 (0.46, 4.18)	0.563
	Females		Reference	
Smoking status	Current/former smoker	-0.87	0.42 (0.10, 1.75)	0.232
	Never smoker		Reference	
Pack–years	0-24		Reference	
	25-49	1.24	3.45 (0.87, 13.70)	0.078
	50-	2.02	7.54 (1.77, 32.05)	0.006
Number of respiratory symptoms	None		Reference	
	One	0.76	2.15 (0.97, 4.74)	0.059
	Two	2.03	7.61 (2.68, 21.61)	<0.001
	Three	2.37	10.66 (2.07, 54.80)	0.005
	Four	3.08	21.67 (2.41, 194.9)	0.006
Statin use	Yes	-1.27	0.28 (0.06, 1.28)	0.101
	No		Reference	
ARB use	Yes	0.58	1.78 (0.75, 4.24)	0.192
	No		Reference	
ACEI use	Yes	-0.17	0.85 (0.09, 8.17)	0.885
	No		Reference	

ARB, angiotensin receptor blocker; ACEI, angiotensin converting enzyme inhibitor

INTERNAL MEDICINE

□ CASE REPORT □

Primary Cardiac Angiosarcoma of the Right Auricle with Difficult-to-Treat Bilateral Pleural Effusion

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Abstract

A 70-year-old woman was admitted to our hospital with pleuritis and pericarditis. Cytological examination of pleural and pericardial effusion, and pleural biopsy specimens under thoracoscopy revealed no specific pathological findings. The pleural effusion was drained continuously; however, she died of circulatory insufficiency at day 45 from admission. At autopsy, a fragile hemorrhagic mass arising from the right auricle had invaded bilateral pleura and the pericardium directly without distant metastasis. Immunohistochemical staining showed that the tumor cells expressed endothelial markers such as CD31 and CD34 antibodies, and factor VIII-related protein. These findings supported the diagnosis of a poorly differentiated angiosarcoma.

Key words: primary cardiac angiosarcoma, pleural effusion, pericardial effusion, immunohistochemical staining

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Introduction

In some cases, it is difficult to diagnose the underlying disease that causes pleural effusion. The cause of pleural effusion is not evident in diagnostic thoracentesis in up to 25% of all cases, and false negatives occur in approximately 8%, even with thoracoscopic biopsy (1).

Primary cardiac angiosarcoma is extremely rare. Most cases of cardiac angiosarcoma have metastasis to multiple organs at the time of diagnosis (2, 3); therefore, they have a poor prognosis. We present a rare case that had dyspnea on effort with difficult-to-treat bilateral pleural effusion, and we diagnosed the patient with primary cardiac angiosarcoma, which occurred from the right auricle that had invaded the bilateral pleura without distant metastasis at autopsy.

Case Report

A 70-year-old Japanese woman was admitted to the cardiology division at Jichi Medical University Hospital with a diagnosis of acute pericarditis with unidentified underlying disease. Her pericardial effusion was controlled after drainage. However, she was re-admitted to the pulmonary medicine division with dyspnea on effort 3 months later.

A physical examination upon admission revealed the following: height, 152 cm tall; weight, 44 kg; arterial blood pressure, 142/98 mmHg; pulse rate, 108/min; and temperature, 36.5℃. Respiratory sounds were remarkably diminished on the left side of the chest. Lymphadenopathy was absent. Laboratory findings revealed the following: white blood cell counts were 7,700/mm^3 with 77.5% neutrophils; C-reactive protein levels were slightly elevated to 0.35 mg/dL; and brain natriuretic peptide levels were 92.1 ng/mL. A purified protein derivative skin test and QuantiFERON TB-2G were negative. Other tests, including antinuclear antibody, rheumatoid factor, human immunodeficiency virus antibody, and thyroid-stimulating hormone were negative. Tumor markers relevant to carcinoma were also negative: carcinoembryonic antigen (CEA) was 1.7 ng/mL, cytokeratin-19 fragment was 1.2 ng/mL, neuron-specific enolase was 16.6 ng/mL, and ProGRP was 45.8 pg/mL. An electrocar-

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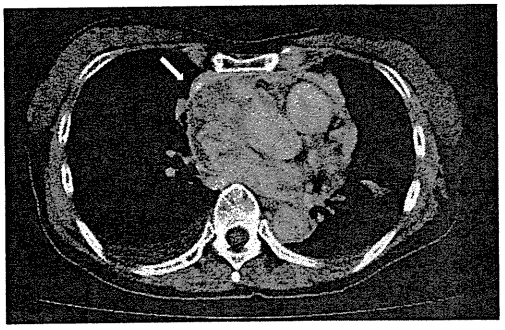

Figure 1. Chest computed tomography after left thoracic drainage demonstrated pericardial and pleural effusion, and a lesion with irregular heterogeneous density and ill-defined margins (arrow) in front of the right atrium.

diogram showed normal sinus rhythm and it was within the normal limits including the ST-T changes. Chest X-ray on admission revealed left pleural effusion. The findings of the patient's pleural effusion were as follows: bloody and exudative, pH, 8.0; protein, 4.9 g/dL (serum protein, 5.9 g/dL); glucose, 0.11 g/dL; lactate dehydrogenase (LDH), 295 IU/L (serum LDH, 292 IU/L); CEA, 0.9 ng/mL; adenosine deaminase, 11.6 IU/L; and a positive Rivalta reaction. Cytological examination of pleural effusion showed 88.0% lymphocytes and no malignant or abnormal cells. Cultures and PCR using Amplicor *Mycobacterium* of the pleural effusion showed negative results.

To make a definitive diagnosis, we performed a biopsy from the left parietal pleura under thoracoscopy. Thoracoscopic findings of the visceral and parietal pleura included no abnormal findings, and there were no specific pathological findings without a reactive mesothelium. Chest computed tomography (CT) after left thoracic drainage revealed a lesion with irregular heterogenous density with ill-defined margins, which was not identified on transthoracic echocardiography, in front of the right atrium (Fig. 1). A transthoracic echocardiogram only demonstrated normal left ventricular contraction, mild pericardial effusion, and right pleural effusion. Pericardial effusion revealed characteristics similar to those of the pleural effusion. Abdominal CT, upper gastrointestinal endoscopy, colonoscopy, cervical echography, and gynecological examination showed no specific findings.

Pleural effusion had to be drained continuously because it was produced at approximately 700 ml per day. At day 18 after admission, right pleural effusion, which had similar characteristics to those of left pleural effusion, was suddenly increased. The patient gradually weakened with hypoalbuminemia, and her blood pressure was not controlled with suddenly worsened respiratory failure at day 45 from admission. Unfortunately, the patient died of circulatory insufficiency without identification of the underlying disease.

At autopsy, hemorrhagic fibrinous adhesions were found over both lungs. On opening the pericardium, there was similar hemorrhagic fibrinous material. The hemorrhagic fibrinous material over the epicardium was considered to be fibrinous pericardium at a glance, but after sectioning, we observed that a fragile hemorrhagic mass approximately 5 cm in diameter arose outwardly from the muscle layer of the right auricle (Fig. 2A). This tumor proliferated to under the endocardium of the atrium without invasion to the inside. Microscopically, the tumor cells had oval to spindle-shaped nuclei and were diffusely proliferated (Fig. 2B, C). Although a vascular lake or hemorrhage was formed, there were no vascular structures lined by endothelial-like atypical cells. Immunohistochemical staining showed that the tumor cells expressed endothelial markers such as CD31 and CD34 antibodies, and factor VIII-related protein (Fig. 3). These findings supported the diagnosis of a poorly differentiated angiosarcoma.

Discussion

We report an autopsy case of primary cardiac angiosarcoma with bilateral pleural effusion that was difficult to treat. Primary cardiac tumors are rare with an incidence ranging from 0.0017% to 0.0033% in reported autopsy series, and the majority of them are benign (4). Although angiosarcoma is the most common primary cardiac malignant tumor, it is extremely rare. Approximately 80% of primary cardiac angiosarcomas occur from the right atrium and pericardium or another chamber around the right atrium (5). Clinical symptoms and signs include (a) a tumor mass that obstructs intracardiac blood flow or interferes with valve function, (b) arrhythmias or pericardial effusion with tamponade, (c) tumor embolism, and (d) systemic or constitutional symptoms (6). Most cases of cardiac angiosarcoma metastasize to multiple organs such as the lungs, liver, and bones; some cases are diagnosed by secondary symptoms derived from metastatic lesions. As a result, they have a poor prognosis of 2-24 months from the time of diagnosis (2, 3).

Meng et al reported that the sensitivities of transthoracic echocardiogram (TTE) and transesophageal echocardiogram to detect these primary masses are 93% and 97%, respectively (6). On the other hand, magnetic resonance imaging (MRI) currently appears to be the imaging modality of choice in the assessment of a patient with known cardiac mass (7). Flurorine-18 fluorodeoxyglucose positron emission tomography imaging (FDG-PET) might also add additional information on the tumor and result in an early diagnosis (8). In the present case, the tumor, which arose from the right auricle and was not identified by TTE, invaded the pericardia, and therefore, she was found to have cardiac tamponade with pericarditis at the last hospitalization. In addition, while pericardial effusion did not increase, the left pleural effusion increased due to invasion of the left pleura. It then invaded the right pleura without invasion of the atrial endocardium or distant metastasis, and as a result, right pleural effusion was increased. This resulted in respiratory failure with no other symptoms of metastatic lesions, which

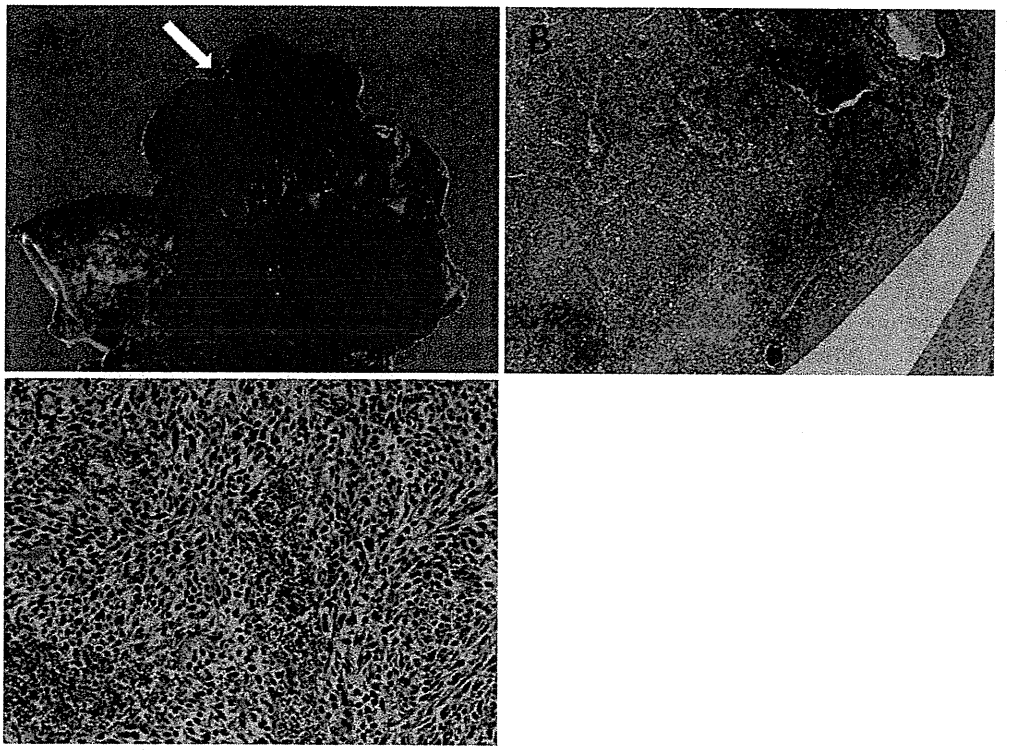

Figure 2. Macroscopic and microscopic features of the tumor. (A) Macroscopic features include a fragile hemorrhagic mass approximately 5 cm in diameter (arrow) arising from the right auricle. (B) Hematoxylin and Eosin staining, ×40. (C) Hematoxylin and Eosin staining, ×200. Microscopic features include tumor cells that have oval to spindle-shaped nuclei and are diffusely proliferated. Although a vascular lake or hemorrhage was formed, there were no vascular structures lined by endothelial-like atypical cells.

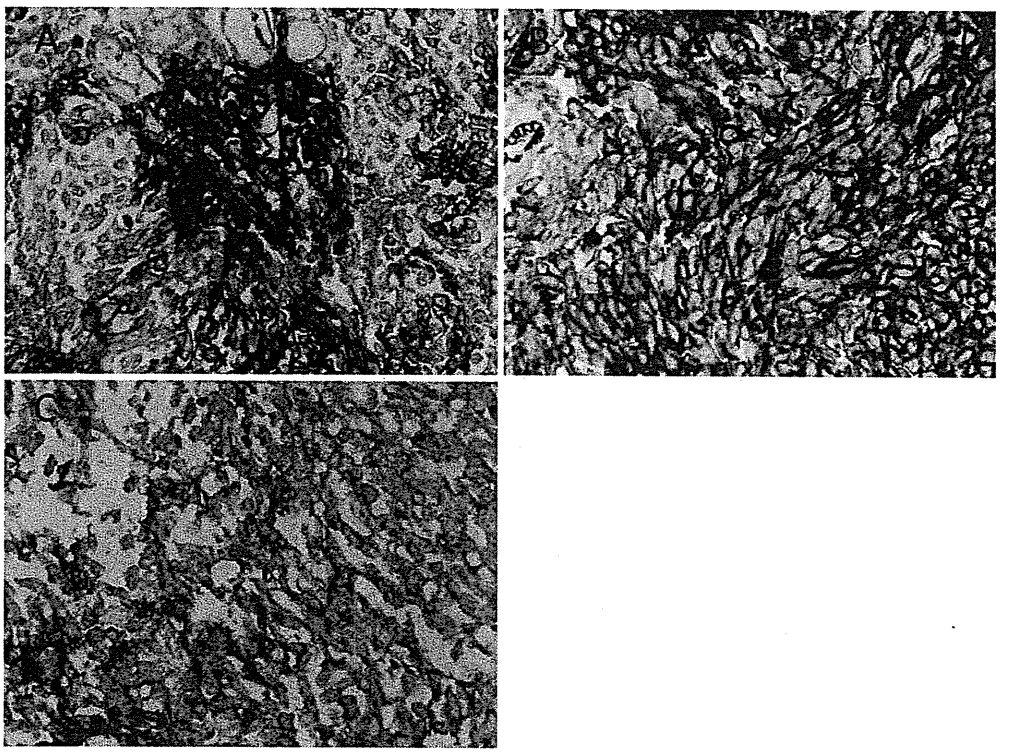

Figure 3. Immunohistochemical staining shows that the tumor cells express endothelial markers such as (A) CD34 and (B) CD31 antibodies, and (C) factor VIII-related protein (×400).

is a rare finding according to the literature. We did not take into consideration primary heart disease because pericardial effusion did not increase. In addition, we did not find distant metastasis with other systemic symptoms, and therefore, we did not perform MRI or FDG-PET.

In the pathological findings, typically, small clusters of anisocytotic spindle-shaped tumor cells appear as vascular-like structures and hemosiderin-laden macrophages in many erythrocyte-rich environments (9). They vary from well-differentiated tumors that are composed of anastomosing vascular channels to undifferentiated tumors arranged as solid sheets of anaplastic cells. Histopathological variations of cardiac angiosarcoma make them difficult to recognize, and some lesions including metastasis may appear benign or may even be mistaken for "benign hemangioma" (5). Since the histopathology of angiosarcoma can show various findings, most cases of primary cardiac angiosarcoma are diagnosed by surgical biopsy. In the present case, it was difficult to diagnose from the biopsy specimens under thoracoscopy; therefore, primary cardiac angiosarcoma may be difficult to diagnose from tiny specimens. Immunohistochemical staining is recommended if possible, because factor VIII-related antigen, CD31, and CD34 are strongly positive throughout the cytoplasm for the tumor cells. In our case, we did not perform immunohistochemical staining in the biopsy specimens under thoracoscopy because we did not take into consideration angiosarcoma. Therefore, we consider that immunohistochemical staining should be performed, while taking into consideration primary cardiac angiosarcoma, which develops with this pattern.

The main treatment strategy in cardiac angiosarcoma is surgical resection with or without chemotherapy and radiation. However, Truong et al reported that patients treated with complete resection had improved overall survival compared with those with incompletely resected disease (25 months vs. 6 months, p=0.042) (10). The high rates of disease progression and mortality highlight the need for more effective local and systemic treatments that may be used in conjunction with surgery to improve patient outcomes. Chemotherapy for cardiac angiosarcoma with doxorubicin-based chemotherapy, paclitaxel, docetaxel, or cyclophosphamide has been reported (11-13). IL-2 therapy has been reported to be effective for angiosarcoma of the skin, and it has also been performed for cardiac angiosarcoma. The combination of chemotherapy and immunotherapy has been reported to be effective for cardiac angiosarcoma (14). Although the numbers of patients are too small to draw conclusions, the long-term benefits from systemic chemotherapy should be determined using a larger population. Data on the role of radiation in cardiac sarcoma management are also sparse. High doses of radiation to local tumors improve control, but they increase the chances of severe events such as pericarditis, cardiomyopathy, and vascular injury (15, 16). The most effective method to improve the outcome of cancer radiation therapy is to concentrate the dose of radiation only on the tumor. The present patient could not be treated with complete surgical resection and high doses of radiation, and therefore, she might have had a poor prognosis even if we had been able to diagnose her. In conclusion, it may be necessary to consider primary cardiac angiosarcoma in cases where it is difficult to treat pericarditis and pleuritis of unknown origin.

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

References

1. Venekamp LN, Velkeniers B, Noppen M. Does 'idiopathic pleuritis' exist? Natural history of non-specific pleuritis diagnosed after thoracoscopy. Respiration **72**: 74-78, 2005.
2. Whorton CM. Primary malignant tumors of the heart. Cancer **2**: 245, 1949.
3. Sorlie DAG, Myhre ESP, Stalsberg H. Angiosarcoma of the heart: unusual presentation and survival after treatment. Br Heart J **51**: 94-97, 1984.
4. Silverman NA. Primary cardiac tumor. Ann Surg **191**: 127-138, 1980.
5. Janigan DT, Husain A, Robinson NA. Cardiac angiosarcomas: A Review and a case report. Cancer **57**: 852-859, 1986.
6. Meng Q, Lai H, Lima J, Tong W, Qian Y, Lai S. Echocardiographic and pathologic characteristics of primary cardiac tumor; a study of 149 patients. Int J Cardiol **84**: 69-75, 2002.
7. Mader MT, Poulton TB, White RD. Malignant tumors of the heart and great vessels: MR imaging appearance. Radiographics **17**: 145-153, 1997.
8. Freudenberg LS, Rosenbaum SJ, Schulte-Herbrüggen J, et al. Diagnosis of cardiac angiosarcoma by fluorine-18 fluorodeoxyglucose positron emission tomography. Eur Radiol **12**: S158-S161, 2002.
9. Iwa N, Masuda K, Yutani C, Kobayashi TK. Imprint cytology of primary cardiac sarcomas: a report of 3 cases. Ann Diagn Pathol **13**: 239-245, 2009.
10. Truong PT, Jones SO, Martens B, et al. Treatment and outcomes in adult patients with primary cardiac sarcoma: the British Columbia Cancer Agency Experience. Ann Surg Oncol **16**: 3358-3365, 2009.
11. Llombart-Cussac A, Pivot X, Contesso G, et al. Adjuvant chemotherapy for primary cardiac sarcoma: the IGR experience. Br J Cancer **78**: 1624-1628, 1998.
12. Simpson L, Kumar SK, Okuno SH, et al. Malignant primary cardiac tumors: review of a single institution experience. Cancer **112**: 2440-2446, 2008.
13. Nakamura-Horigome M, Koyama J, Eizawa T, et al. Successful treatment of primary cardiac angiosarcoma with docetaxel and radiotherapy. Angiology **59**: 368-371, 2008.
14. Kakizaki S, Tagari H, Hosaka Y. Cardiac angiosarcoma responding to multidisciplinary treatment. Int J Cardiol **62**: 273-275, 1997.
15. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. Lancet Oncol **6**: 219-228, 2005.
16. Prosnitz RG, Chen YH, Marks LB. Cardiac toxicity following thoracic radiation. Semin Oncol **32**: 71-80, 2005.