Lung Adenocarcinoma Required the Differentiation from Wegener Granulomatosis

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ABSTRACT. A 68-year-old man was admitted to our hospital for examination of a nodular shadow newly detected in the right middle lung field, and an inhomogeneous shadow in the left lower lung field detected two years earlier. He had a past history of ulcerative colitis of eight years duration. At first, we suspected Wegener granulomatosis because of elevation of cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA) as a laboratory finding on admission. A chest CT scan revealed that the two nodular shadows had cavities, and a bronchoscopic examination was performed. However, because a definite diagnosis could not be made, we carried out video-assisted thoracoscopic surgery (VATS) of the new nodular shadow in the right middle lung field.

Subsequently, it was diagnosed as adenocarcinoma. Afterwards, since his C-ANCA level did not decrease even after repeated measurements, we treated the inhomogeneous shadow in the left lower lung field surgically without excluding the possibility of Wegener granulomatosis. Finally, both nodular shadows were diagnosed as adenocarcinoma because there was no leukocytoclastic vasculitis or necrotizing granulomatosis on the histological finding of VATS suspecting of Wegener granulomatosis and we made a diagnosis of primary adenocarcinoma of the left lower lobe of the lung because no malignant lesions were detected in other organs on radiological examinations. We considered this case in which C-ANCA was elevated due to ulcerative colitis than to Wegener granulomatosis as noteworthy because the C-ANCA level did not change after surgical resection of the lung cancer.

Key words : lung adenocarcinoma — Wegener granulomatosis — C-ANCA, ulcerative colitis

A constellation of extraintestinal manifestations affecting bronchopulmonary lesions has been described in association with ulcerative colitis, including inflammatory tracheal stenosis, panbronchiolitis, bronchiolitis obliterans with organizing pneumonia (BOOP), interstitial pneumonitis, a picture resembling Wegener granulomatosis, and serositis with or without associated myocarditis.[1-5] However, in the present case, we mostly suspected Wegener granulomatosis

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without upper respiratory tract lesions or renal dysfunction because two nodular shadows with cavities appeared and cytoplasmic anti-neutrophil cytoplasmic antigen (C-ANCA) was elevated twice in the laboratory findings on admission. Although bronchoscopic examination and a CT-guided lung biopsy were performed, a definite diagnosis could not be obtained. Finally, a final diagnosis of adenocarcinoma of the lung and intrapulmonary metastasis was made during surgical treatment.

CASE REPORT

A 68-year-old man with a past histroy of ulcerative colitis of eight years duration was admitted to our hospital because of abnormal chest shadows. They consisted of a new nodular shadow with a cavity in the right S^6 and another in the left S^9-S^{10} which had appeared two years before on chest CT. On admission his height was 168 cm and his weight was 57 kg. His radical pulse rate was 72/min and regular. There were no abnormalities in his physical findings.

The main laboratory data on admission are shown in Table 1. Although mild anemia and elevation of the erythrocyte sedimentation rate were observed in the peripheral blood, leukocytosis and elevation of C-reactive protein were not detected. A serological examination showed only C-ANCA to be elevated at 27EU (Normal range : $<$10EU) on admission and to be further elevated to 37EU two weeks later. Aspergillus antigen and antibody were both negative, β-D-glucan was within normal limits and tumor markers were also within normal limits. The results of urinalysis were all normal and renal function was within normal limits.

A chest roentogenogram revealed a nodular shadow (7×5 cm) in the left lower lung field and another nodular shadow (2×2 cm) in the right middle lung field (Fig 1).

A chest CT scan disclosed a nodular shadow with large cavity in the left lower lobe and another nodular shadow with several small cavities and an unclear margin, but without spicula, notches or pleural indentations, in the right S^6. Obvious mediastinal or hilar lymphadenopathy was not detected (Fig 2).

A bronchoscopic examination showed normal macroscopic findings and a transbronchial lung biopsy (TBLB) specimen from the left B^{10} revealed fibrous tissue, but no granuloma. Bronchoalveolar lavage fluid (BALF) findings from the left lower bronchus and the right B^6 were negative for common bacteria including fungus, anti-fast acid bacilli, fungi, and cytology (Table 2). A CT-guided lung biopsy disclosed fibrous thickening without granuloma or malignant disease as well as TBLB for the nodular shadow with a cavity in the left lower lobe. Video-assisted thoracoscopic surgery (VATS) led us to a histological diagnosis of moderately differentiated adenocarcinoma in the right S^6 (Fig 3). Afterwards, we could not comletely exclude the possibility that it could have been Wegener granulomatosis, because the C-ANCA level remained unchanged after surgical resection of the nodular shadow in the right middle lung field. Therefore, we performed VATS for the other nodular shadow in the left lower lobe and it was also diagnosed as a moderately differentiated adenocarcinoma. In addition, to

consider the possibility of intrapulmonary metastasis from other organs, we performed whole body Gallium scintigraphy, abdominal, pelvic, and cervical-head CT scans and upper and lower gastrointestinal endoscopy. Healed ulcerative colitis was recognized, but malignant disease was not detected in any other organs. Finally, we made a diagnosis of primary lung adenocarcinoma of the left lower lobe and intrapulmonary metastasis to the opposite lung field and we denied Wegener granulomatosis because there was no leukocytoclastic vasculitis or necrotizing granulomatosis on the histological finding of VATS.

TABLE 1. Laboratory data on admission

Hamatology		Serology	
RBC	$396\times10^4/\mu l$ ↓	GRP	0.09 mg/dl
Hb	12.6 g/dl ↓	lgG	1082 mg/dl
Ht	38.4% ↓	lgA	429 mg/dl
WBC	$4400/\mu l$	lgM	90 mg/dl
Neutro	36.6% ↓	lgD	0.6 mg/dl
Tzosino	5.0%	lgE	110 U/ml
Baso	1.4%	ANA	(−)
Mono	9.3% ↑	CH50	37.8 U/ml
Lym	47.7% ↑	CHA	×64
Plt	$19.7\times10^4/\mu l$	RA	(−)
ESR	36 mm/hr ↑	C-ANCA	27EU ↑
Biochemistry		P-ANCA	(−)
TP	7.0 g/dl	Candida antigen	(−)
BS	96 mg/dl	Cryptococcus antigen	(−)
Bil(T)	0.5 mg/dl	Aspergillus antigen	(−)
ALP	236 IU/l	β-D-glucan	<6.0 pg/ml
Cho	180 mg/dl	CEA	2.4 ng/ml
γ-GTP	21 IU/l	CA19-9	<5.0 U/ml
LDH	170 IU/l	ProGRP	15.5 pg/ml
Alb	4.4 g/dl	SCC	1.0 ng/ml
Glb	2.6 g/dl	SLX	24.9 U/ml
chE	311 IU/l	NSE	5.7 ng/ml
GPT	14 IU/l	CYFRA	1.0 ng/ml
GOT	27 IU/l	Urinalysis	
Crn	0.70 mg/dl	Protein	(−)
BUN	14 mg/dl	Blood	(−)
UA	3.9 mg/dl	Glucose	(−)
Amy	62 IU/l	RBC	0/HPF
Na	141 mEq/l	WBC	0/HPF
K	4.2 mEq/l	Cast	(−)
Cl	104 mEq/l	β_2-microglobulin	$110\mu g/l$
Ca	9.0 mg/dl	NAG	1.2 U/ml

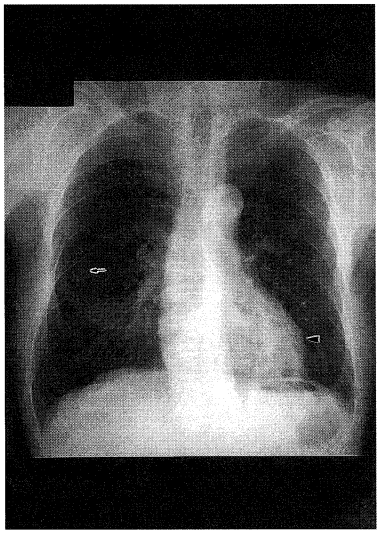

Fig 1. Chest roentogenogram on admission revealed a nodular-like shadow (7×5 cm) in the left lower lung field (arrowhead) and another nodular shadow (2×2 cm) in the right middle lung field (arrow).

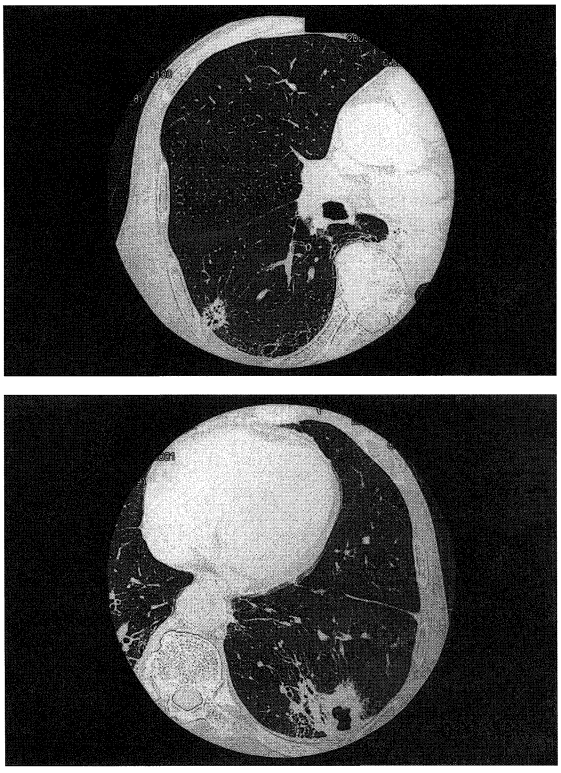

Fig 2. Chest tomography on admission disclosed a nodular-like shadow with a large cavity in the left lower lobe (left) and another nodular shadow with several small cavities in the right S^6 (right).

TABLE 2. BALF findings

(1) Left lower bronchus		
	Total cell count	3×10^5/ml
	Neutrophils	90.4%
	Lymphocytes	0.2%
	Eosinophils	0.4%
	Macrophages	9.0%
	Bacteria	Normal flora
	Tbc	Smear (−), Culture (−)
	Gytology	Class II
(2) Right B^6 bronchus		
	Total cell count	2×10^5/ml
	Neutrophils	56.4%
	Lymphocytes	6.2%
	Eosinophils	0.2%
	Macrophages	37.0%
	Bacteria	Normal flora
	Tbc	Smear (−), Culture (−)
	Cytology	Class II

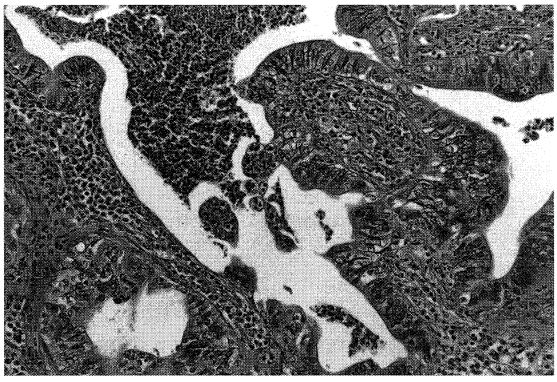

Fig 3. The histological findings show a moderately differentiated adenocarcinoma with a broncheoalveolar architecture of malignant cells (arrow) in the right S^6 (HE staining, ×100).

DISCUSSION

Anti-neutrophil cytoplasmic antibody (ANCA) was an autoantidoby first detected in patients with acute progressive glomerulonephrities by Davis *et al* in 1982.[6] Afterwards, ANCA was classified into cytoplasmic ANCA (C-ANCA), which diffusely stains the cytoplasm of neutrophils, and perinuclear ANCA (P-ANCA) which strongly stains the perinuclear portion of neutrophils with a fluorescent staining pattern. C-ANCA showed high specificity for Wegener granulomatosis, with a specificity of 95%.[7] In addition, C-ANCA antibody has correlated with the activity of pulmonary

lesions (multiple nodular shadows with cavities, infiltration shadows) and has been useful as an index of activity.[8] However, it has been reported to show rare false positives for infectious diseases (such as mycobacterial infection and HIV infection), malignant diseases (such as lung cancer, cardiac myxoedema, colon cancer and malignant lymphoma) and gastrointestinal diseases (such as ulcerative colitis and Crohn's disease).[9] Lower gastrointestinal endoscopy of this patient revealed no signs of colon cancer, with only healing of his ulcerative colitis being detected. Therefore, it is unknown to what, if any, degree the elevation of C-ANCA was related to his ulcerative colitis. Although it is difficult to conclude what the cause for C-ANCA elevation is in patients with lung cancer, the elevation of C-ANCA may have been related to his ulcerative colitis since it did not change after surgical resection of the lung cancer in the bilateral lungs. Elzouski *et al*,[10] in fact, mentioned that C-ANCA was significantly elevated in 12% of 141 patients with ulcerative colitis.

Regarding the pulmonary lesions occurring with inflammatory bowel diseases such as ulcerative colitis or Crohn's disease, Camus classified them into four types; airway disease, interstitial disease, necrotic parenchymal nodules, and serositis. They noted that necrotic parenchymal nodules showed radiological and histological findings resembling Wegener granulomatosis.[1,2] In our case, because of the elevation of C-ANCA and the radiological findings of two nodular shadows with cavities resembling each other in the two lungs, we at first considered the possibility of Wegener granulomatosis on admission and then of differentiated intrapulmonary lesions with ulcerative colitis, pulmonary aspergillosis, metastatic lung cancer, or peripheral lung cancer.

Although we performed a bronchoscopic examination and a CT-guided lung biopsy after admission as diagnostic methods, we could not obtain a histological finding of fibrous connective tissue. We considered the reason that the biopsy specimen was limited to the area around the cavitary lesions.

Although squamous cell carcinoma has been previously reported to most frequently form cavities among lung cancers with cavities,[11-13] the frequency for both adenocarcinoma and squamous cell carcinoma has been almost the same with the progress in radiological findings in recent reports.[14,15] In this case, the final diagnosis was primary lung adenocarcinoma in the lower lobe and intrapulmonary metastasis in the opposite Lung as determined by the surgical treatment. The mechanism of the cavity formation was suspected to be as follows: the central portion of the lung cancer became necrotic and the necrotic tissue became detached from the responsible bronchus; the so-called check valve mechanism. The cavity had thickened and deviated, and there was an irregular wall as a result of central ischemic change in the tumor.[16] Regarding other organs, we carried out upper and lower gastrointestinal endoscopy, whole body gallium scintigraphy, and abdominal, pelvic, and cervical-head CT scans and detected no malignant findings. Therefore, we made a diagnosis of primary adenocarcinoma in the left lower lobe of the lung and intrapulmonary metastasis to the right lower lobe. The adenocarcinoma in the left lower lobe, which had detected as an inhomogeneous shadow two years earlier, was bigger than that in the right

one.

Finally, attention should be paid to the possibility of other diseases that include transitional change because it has recently been reported that C-ANCA is elevated in various other diseases.

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