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Clinical features of primary lung cancer presenting as pulmonary consolidation mimicking pneumonia

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Abstract

Objectives: It is well recognized that lung cancer can present as parenchymal infiltration mimicking pneumonia on chest X-ray films or computed tomography images. Such cancers can be misdiagnosed as inflammatory lung diseases, delaying accurate diagnosis.

Methods: We retrospectively reviewed nine consecutive lung cancer patients who presented with pulmonary consolidation mimicking pneumonia at their initial examinations between January 2012 and December 2014 and analyzed their clinical courses and radiological and pathological findings.

Results: The nine patients (six men) were aged 47 to 86 years (median 75 years). Four were smokers or ex-smokers. In all cases, radiological findings included parenchymal opacification with air bronchograms; in some cases, parenchymal consolidation was associated with volume loss and traction bronchiectasis and located in the sub-pleural zone. Ground glass opacity or tree-in-bud appearance (suggesting aerogenous metastasis) also sometimes accompanied the consolidation. In all cases, biopsies revealed adenocarcinoma (including three cases of invasive mucinous adenocarcinoma). Neither *EGFR* gene mutation nor *ALK* gene rearrangement were found; however, *KRAS* mutation was identified in five cases. Although lung infiltrations had been recognized for two or more months in some cases, no previous biopsies had been performed. Furthermore, in three cases, initial bronchoscopic examination had failed to diagnose malignancy. None of these patients responded to chemotherapy and four cases died within 6 months of diagnosis.

Conclusion: Diagnosis of lung cancer presenting as lung consolidation mimicking pneumonia is difficult and often delayed. The prognosis is poor because of delayed diagnosis and poor response to chemotherapy.

Keywords: pneumonia shadow, CT finding, invasive mucinous adenocarcinoma, KRAS mutation, diagnostic delay

Introduction

Although the majority of lung cancers (especially adenocarcinomas) present as coin lesions in the lung field, they can present with various other radiological abnormalities such as infiltration, consolidation and, rarely, reticular shadows.[1,2] For example, some patients with lung cancer present with pulmonary consolidation containing air bronchograms, which denote alveolar opacity. Because such cases can be misdiagnosed as bacterial or organizing pneumonia, the clinician should be aware that lung cancer can mimic pneumonia radiologically.[3] In this study, we retrospectively analyzed the clinical features of nine consecutive lung cancer patients who presented with peripheral lung consolidation mimicking pneumonia.

Methods

Study design

This was a single-center retrospective study of consecutive patients with newly-diagnosed lung cancer that had presented as consolidation mimicking pneumonia and been evaluated by chest computed tomography (CT) in our department between January 2012 and December 2014. The study was approved by the Ethics Board of our institution and the requirement for informed consent was waived in view of the retrospective nature of the study.

Data collection

The charts of consecutive patients with lung cancer who had been referred to our department for bronchoscopic diagnosis during the study period were retrospectively reviewed. All patients had undergone chest thin slice (TS)CT (0.5 mm slices) before bronchoscopy. TSCT images that had been generated using a non-enhanced multidetector CT system (Aquilion One Vision Edition; Toshiba Medical Systems, Tokyo, Japan) were retrospectively obtained from our imaging database and patients with lung cancer and radiological findings resembling pneumonia were identified according to the criteria described below. Other clinical data, including age, gender, smoking history, comorbidities, results of pathological examination of lung biopsies, clinical stage, response to chemotherapy, and prognosis, were also collected from the electronic medical file system. As much of the selected patients' medical data as possible were also obtained from referring medical institutions. In all selected cases, the mutational status of gene *EGFR*, *ALK*

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rearrangement and *KRAS* gene mutation analyses (codon 12 and 13) were examined. *EGFR* mutation was analyzed using real-time polymerase chain reaction and *ALK* gene rearrangement by a fluorescent in situ hybridization method (SRL, Tokyo, Japan). *KRAS* mutational analysis was performed using a Scorpion-ARMS method (SRL).

Diagnostic criteria for radiological findings mimicking pneumonia in patients with lung cancer

Images on chest TSCT scans performed on the initial visit to our department were evaluated independently by three respiratory medicine specialists (SM, TO, and KI). Patients with lung cancer and radiological findings that mimicked pneumonia were selected according to the following criteria: peripheral consolidation or infiltration with apparent air bronchograms, more than two of the three pulmonologists including pneumonia in their differential diagnoses of the initial TSCT findings, and histological confirmation of cancer cells in biopsies obtained from the consolidative or infiltrative lesions. Cases with obvious accompanying infection (significant evidence of inflammatory responses such as leukocytosis or increased C-reactive protein concentrations and response to antibiotic treatment) were excluded.

Results

Patient characteristics

During the study period, nine patients with lung cancer who presented with pulmonary radiological findings mimicking pneumonia were identified. Table 1 shows their characteristics. Their median age was 75 years (range 47-86 years). Three of them had never smoked. Six of the nine cases were asymptomatic at the initial visit to our hospital. Among these asymptomatic patients, chest X-ray abnormalities had been identified incidentally: during follow-up of comorbidities in four patients and at an annual health check in two patients. All patients had advanced stage diseases (T4N0M1a stage IV) without distant metastases on their first visits to our department.

Chest CT characteristics of the tumors

Chest CT features of the nine cases on their first visits to our department were investigated. Representative CT features are shown in Figure 1. All cases exhibited bilateral multiple consolidation accompanied by air bronchograms (Fig. 1A). Some specific findings within areas of consolidation, such as traction bronchiectasis (Fig. 1B), loss of volume (Fig. 1C), and location in the sub-pleural zone (Fig. 1D), were also identified. Characteristics of each patient's CT findings are summarized in Table 2. In addition to consolidation, extensive ground glass

Table 1. Summary of patient characteristics

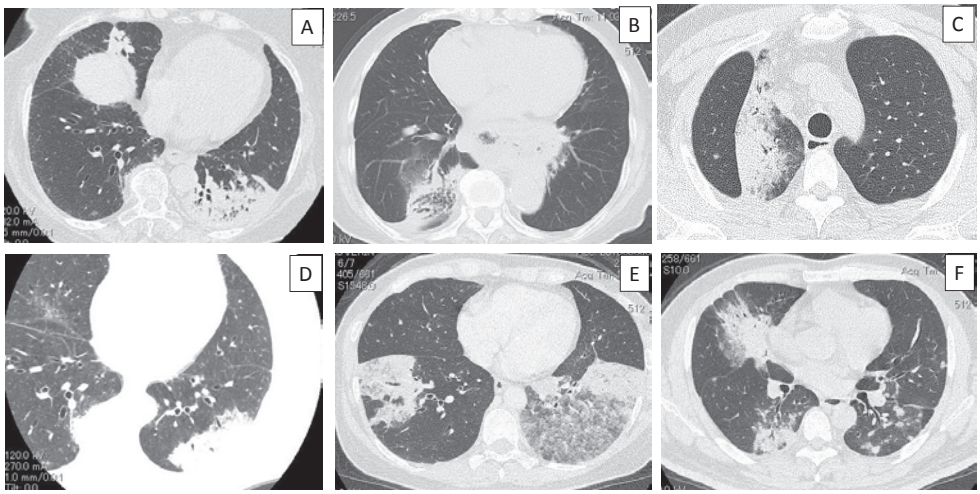
	Age (years)	Sex	Smoking status (BI)	Occupation	Past history	Comorbidities	Detection of lung cancer
1	57	M	Ex (400)	Sales	None	None	Routine health check
2	47	F	Current (600)	Factory worker	Uterine myoma	None	Routine health check
3	68	F	Never	Driver	None	HT	Incidental chest X-ray finding
4	86	M	Current (3600)	Iron work	None	COPD	Symptom (cough)
5	62	M	Never	Town councilor	None	None	Symptom (cough)
6	81	F	Never	Clerk	None	RA	Incidental chest X-ray finding
7	76	M	Ex (1200)	Sales	None	HT	Incidental chest X-ray finding
8	78	M	Ex (450)	Welder	Colon cancer	DM	Symptom (sputum)
9	75	M	Ex (100)	Clerk	Gastric and prostate cancer	HT, CKD	Incidental chest X-ray finding

BI. Brinkman index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; Current, current smoker; DM, diabetes mellitus; Ex, ex-smoker; HT, hypertension; Never, never-smoker; RA, rheumatoid arthritis.

Table 2. Summary of chest CT findings

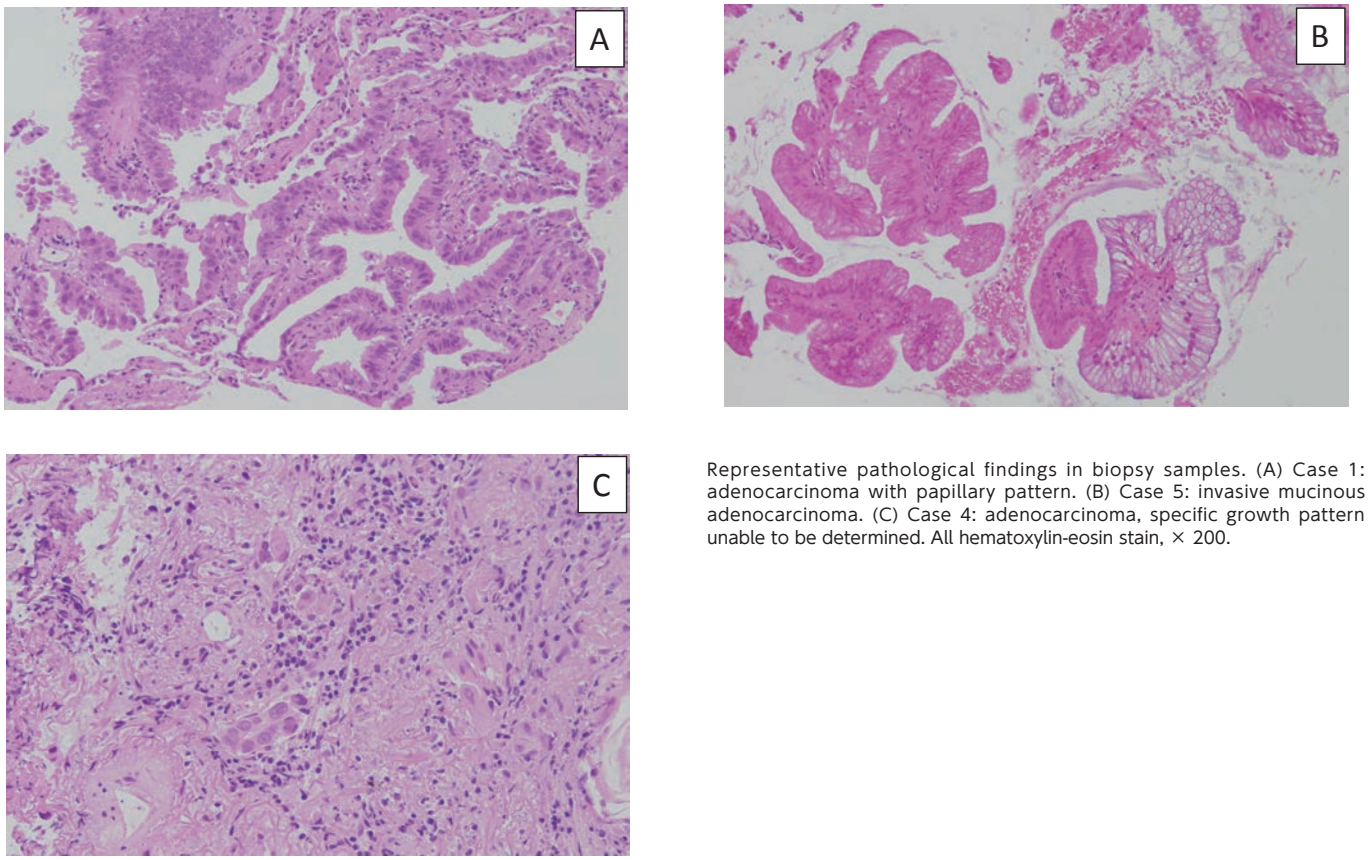
Radiologic findings \ Case	1	2	3	4	5	6	7	8	9
Bilateral consolidation with air bronchogram	■	■	■	■	■	■	■	■	■
Traction bronchiectasis within consolidation			■			■	■		
Consolidation with associated loss of volume			■						■
Consolidation located in subpleural zone			■				■		
Extensive ground glass opacities		■		■	■	■			
Nodular shadows with centrilobular distribution	■			■					

Figure 1



Representative chest CT features of lung cancer with pulmonary consolidation mimicking pneumonia. (A) Case 3: bilateral consolidations with marked air bronchogram. (B) Case 6: traction bronchiectasis within area of consolidation. (C) Case 1: consolidation associated with loss of volume. (D) Case 3: consolidation located in subpleural zone. (E) Case 2: extensive ground glass opacities. (F) Case 1: nodular shadows with centrilobular distribution.

Figure 2



Representative pathological findings in biopsy samples. (A) Case 1: adenocarcinoma with papillary pattern. (B) Case 5: invasive mucinous adenocarcinoma. (C) Case 4: adenocarcinoma, specific growth pattern unable to be determined. All hematoxylin-eosin stain, × 200.

opacity (Fig. 1E) and nodular shadows with centrilobular distribution (Fig. 1F) were also noted. These features may represent early phase aerogenous metastases along alveolar walls or via the bronchial tree, respectively. Notably, although all cases presented with broad areas of consolidation in both lungs, pulmonary or systemic symptoms such as dyspnea, fever, and productive cough were absent or minimal on their first visits to our department.

Pathological findings and analyses of gene mutations in the tumors

Pathological findings in the nine cases are shown in Table 3. All pathological analyses were based on examination of transbronchial biopsy or CT-guided needle aspiration biopsy samples. Adenocarcinoma was diagnosed in all cases. Three cases had mucinous adenocarcinoma clearly presenting in a lepidic pattern (Fig. 2a) and were diagnosed as having invasive mucinous adenocarcinoma. In four cases, mainly papillary patterns were recognized, and in the remaining two, no specific

Table 3. Pathological diagnoses and outcome

Case	Pathological diagnosis (Biopsy)	Gene analysis			Delay in referral (days) [a]	Delay in diagnosis (days) [b]	Outcome (days after diagnosis)
		EGFR	*ALK*	*KRAS*			
1	Adenocarcinoma (papillary pattern)	−	−	−	445[c]	26	Alive
2	Adenocarcinoma (papillary pattern)	−	−	−	162	20	Alive
3	Adenocarcinoma (papillary pattern)	−	−	+	369[c]	15	Alive
4	Adenocarcinoma (no specific pattern)	−	−	+	315	60	Dead (30)
5	Invasive mucinous adenocarcinoma	−	−	+	168[c]	91	Dead (122)
6	Adenocarcinoma (papillary pattern)	−	−	+	60	193	Alive
7	Invasive mucinous adenocarcinoma	−	−	−	202	56	Alive
8	Adenocarcinoma (no specific pattern)	−	−	−	392	18	Dead (26)
9	Invasive mucinous adenocarcinoma	−	−	+	1055	23	Dead (149)

[a], Days from first identification of radiological pulmonary abnormality to first visit to respiratory specialist

[b], Days from the first visit to respiratory specialist to confirmation of diagnosis

[c], Diagnosis of lung cancer not made on first transbronchial biopsy

patterns of growth were identified in the small biopsy samples (Fig. 2b, 2c). However, importantly, mucin production by the cancer cells was apparent in these cases. Gene mutational analyses revealed no case harboring *EGFR* mutation or *ALK* rearrangement. On the other hand, *KRAS* mutation was detected in four cases including two with confirmed invasive mucinous adenocarcinoma (Table 3).

Delays in diagnosis and prognosis

Evaluation of the clinical courses of the nine cases revealed surprisingly long delays between initial radiological detection of pulmonary abnormalities and referral to pulmonologists (our department) in most cases (Table 3). The median delay was 315 days (60-1075 days). Most patients had visited general physicians or medical practitioners and been diagnosed as having inflammatory changes or organizing pneumonia over a long period of observation. Furthermore, in some cases not even respiratory medicine specialists made the final diagnosis on their initial assessments. The reasons for delayed diagnosis by specialists included misdiagnoses as inflammation, deterioration in the patient's condition because of comorbidities, and patients' refusal to undergo further examination. In three cases (Cases 1, 3, and 5), diagnoses of lung cancer were not made on the first transbronchial biopsy (Table 3). In case 5, both first and second trans-bronchial biopsies were misdiagnosed as showing inflammatory changes or a benign tumor; the correct diagnosis was made only after further consultation with a specialized lung cancer pathologist. At the time of first visit to our institute, serum carcinoembryonic antigen (CEA) concentration was high in only one case. Some patients received cytotoxic chemotherapies (platinum-based regimens with pemetrexed and bevacizumab, carboplatin with paclitaxel, S1 or gemcitabine monotherapy) with no detectable benefit. Four patients died within six months of their diagnoses.

Discussion

We here report that lung cancer can present as pulmonary consolidation mimicking bacterial or organizing pneumonia. It is well recognized that lepidic predominant adenocarcinoma, a unique form of adenocarcinoma formerly called bronchoalveolar carcinoma, can present as pulmonary ground glass opacities.[2,4] Recently, pathological criteria for diagnosing invasive mucinous adenocarcinoma, formerly mucinous bronchoalveolar carcinoma, have been defined.[5] Miyata et al. have reported that even early stage invasive mucinous adenocarcinoma can exhibit parenchymal consolidation with apparent air bronchograms on high resolution CT; additionally, these tumors may also show lobular margins or vaguely defined ground glass shadows that are difficult to differentiate from inflammatory consolidation.[6] Invasive mucinous adenocarcinoma is associated with *KRAS*, but not with *EGFR* mutation.[5] In agreement with this, four of our cases had KRAS mutation; however, none showed *EGFR* mutation or *ALK* rearrangement.

In the present study, because all patients had stage IV disease by the time of diagnosis, none of them underwent surgical resection. The only tissues available for pathological evaluation were therefore from small biopsy samples. In some cases, we identified other growth patterns besides that of mucinous adenocarcinoma, such as a papillary pattern. However, invasive mucinous adenocarcinoma may show a heterogeneous mixture of lepidic, acinar, papillary, micropapillary, and solid growth.[5] Because small biopsy specimens may not be representative of the whole tumor, we could not ascertain whether other types of adenocarcinoma, such as papillary pattern dominant adenocarcinoma, can also present as pulmonary consolidation. This is one of the major limitations of this study.

The incidence of lung cancer has been increasing in parallel with the increasing proportion of older persons.[7] Older persons may have serious comorbidities such as chronic obstructive pulmonary disease, pulmonary fibrosis, or cerebrovascular

diseases and often develop pulmonary bacterial infections such as aspiration pneumonia.[8] These pulmonary diseases can be refractory and organized consolidation may persist long after cure of the infection. Many physicians determine whether pulmonary consolidation is active (requiring treatment) by evaluating their patients' symptoms (fever, cough, or dyspnea) and laboratory tests that indicate inflammation such as leukocyte count and C reactive protein concentration. In cases with no evidence of inflammation, physicians may consider persistent pulmonary consolidation to represent organizing pneumonia or inflammatory sequelae.[3,9] Our study indicates that lung cancer with radiological pulmonary abnormalities mimicking pneumonia is frequently misdiagnosed. We believe that it is very important for us to be aware that, in patients with persistent asymptomatic radiological changes suggestive of active or unresolved pneumonia in spite of appropriate antibiotic treatment, a differential diagnosis of lung cancer should always be considered. One international guideline for the management of community-acquired pneumonia recommends a repeat radiograph 4 to 6 weeks after hospital discharge to exclude the possibility of other diseases, including malignancy.[10] We recommend that patients with radiologic evidence suggestive of pneumonia that persists for more than four weeks should be referred to chest physicians for further investigation. Importantly, it should be noted that lung cancer presenting as pneumonia is difficult to diagnose pathologically because the tumor cells may exhibit minimal atypia and biopsy specimens obtained by bronchoscopy are sometimes too small to allow accurate determination of the degree of cellular atypia. The diagnosis of lung cancer was not made on the first transbronchial biopsy in three of our cases. Additionally, CEA, a marker of lung cancer, may not be useful for the diagnosis of this type of lung cancer. Furthermore, none of our study subjects had *EGFR* mutation or *ALK* rearrangement.

Although one study has reported a favorable effect of platinum-based chemotherapy, systemic chemotherapy is generally ineffective for these tumors.[11] Because surgical resection at an early stage is the only means of achieving a cure, it is critical to diagnose lung cancer mimicking pneumonia correctly at such a stage.[12]

This retrospective study included only patients who had been referred to a department of respiratory medicine in a university hospital. All patients had advanced stage (stage IV) disease. Thus, this study cannot elucidate the clinical features of these tumors at an earlier stage or assess prognosis after surgery. In addition, we cannot definitively conclude that earlier detection of lung adenocarcinoma presenting to general physicians as pneumonia would improve the prognosis. Further prospective study may be warranted.

Conclusions

Lung cancer can present as pulmonary consolidation mimicking pneumonia. When a patient has radiological evidence of pneumonia without evidence of inflammation, the clinician should include lung cancer in the differential diagnosis. Early biopsy and careful assessment could lead to early therapeutic intervention.

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Competing interests

The authors declared no potential conflict of interest.

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