SHORT COMMUNICATION

Clinical implication of atypical cells from sputum in patients without lung cancer

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Clinical implication of atypical cells from sputum in patients without lung cancer

Objective and background: Atypical—but not definitely malignant—cells in cytological examinations of sputum are usually associated with lung cancers. However, atypical cells are occasionally identified in patients without lung cancer. The aim of this study was to determine the clinical implication of the atypical cells from sputum in patients without lung cancer or other malignancies.

Methodology: All patients with atypical cells observed following cytological examination of sputum on one or more occasion over a 2-year period in Seoul National University Hospital were enrolled. After exclusion of patients followed up for less than 6 months, their clinical data were reviewed retrospectively.

Results: Among 601 enrolled patients with atypical cells, lung cancers were diagnosed within 30 days of identification of atypical cells in 542 (90.2%) patients. Five out of 59 patients who had no evidence of lung cancer, were subsequently diagnosed with lung cancer or other malignancies following a mean observation of 164 days. In the other 54 patients without subsequent malignancies, the most common respiratory diseases were pneumonia including tuberculosis.

Conclusions: The subsequent development of malignancy in patients with atypical cells in sputum despite a thorough evaluation was rare, and close observation without invasive diagnostic procedures might be simply required in these patients.

Key words: atypical cell, lung cancer diagnosis, sputum cytology.

INTRODUCTION

Since Menetrier introduced the cytological examination of sputum for the diagnosis of lung cancer in 1866,1 it has been a cornerstone in the diagnosis of lung cancer2 because of its low cost, lack of discomfort for patients and low invasiveness. Although the sensitivity of this examination is 36–69%, its specificity reaches 97–99.5%.3–5 Especially in the diagnosis of early lung cancers, sputum cytology is superior to simple CXR.6–8

Because several steps are involved in the pathogenesis of lung cancer, going from hyperplasia to dysplasia to carcinoma in situ to invasive carcinoma,9 the presence of atypical cells without evidence of definite malignant change has been believed to be a high risk for the future development of invasive lung cancer.10–14 However, many benign disease processes involving pulmonary inflammation or injury may lead to false positive cytological changes,15 and atypical type II pneumocytes are thought to be the primary cells causing such results.16

The widespread use of radiographic or invasive procedures, including CT of the chest and flexible bronchoscopy, may now be detecting lung cancers more frequently in patients with atypical cells from their sputa; thus the prevalence of subsequent lung...

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cancer in patients with atypical cells may be declining. In addition, there has been no systematic study on patients with atypical cells in sputum cytology without evidence of lung cancer or other malignancy. The aim of this study was to determine the clinical implication of the presence of atypical cells from cytological examinations of sputum in patients without lung cancer or other malignant disease.

**MATERIALS AND METHODS**

**Patient recruitment**

All patients presenting with atypical cells in cytological examinations of sputum on one or more occasion over a 2-year period, in Seoul National University Hospital were included. The criteria for atypical cells we used were ‘squamous cells with mild nuclear atypia’ and ‘squamous metaplasia with atypia’. Patients with atypical cells, but without lung cancer of other malignant diseases, followed up for less than 6 months were excluded. We retrospectively reviewed the clinical records, the results of laboratory, bacteriological and pathology examinations and serial radiographs of the patients. Every follow-up period in this study was defined as the period from the day of first observation of atypical cells from patients’ sputa.

**Sputum sampling and cytopreparatory technique**

Sputum sampling and cytopreparatory techniques are performed in Seoul National University Hospital as follows. Patients are asked to expectorate sputum from a deep spontaneous cough. If necessary, sputum production is helped with an inhalation of 3% hypertonic saline aerosol. Specimens are collected in wide-mouthed jars. An aliquot of the sputum is placed on a glass slide using a cotton tip, and it is then smeared with a new slide. The two slides are fixed immediately in 95% ethyl alcohol for 10 min, and then stained using Papanicolau’s method.17 If there are too few alveolar macrophages or bronchial epithelial cells on the slides, the sputum sample is classified as unsatisfactory.

**RESULTS**

**Clinical characteristics and evolution of patients with atypical cells without evidence of malignant disease**

A total of 639 patients were identified and 38 had a follow up of less than 6 months and were excluded from further analysis. Among the 601 enrolled patients, primary or metastatic lung cancers were diagnosed within 30 days of identification of atypical cells in 542 (90.2%; Fig. 1). Fifty-nine patients with atypical cells from sputum cytological examinations and without evidence of lung cancer or other malignancies were followed up for a mean of 702 ± 317 days. The most common complaints were coughing (14 patients, 23.7%) and dyspnoea (10 patients, 16.9%). Table 1 shows the distribution of demographic features and chief complaint in these patients.

Among 59 patients without evidence of lung cancer, five were diagnosed as having malignant disease after

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**Figure 1** Evolution of the 639 patients with atypical cells from their sputa.
were found in six out of 19 cytological examinations and a pleural effusion on the right side. Atypical cells purulent sputum and his CXR revealed consolidation (Table 2).

3Ex-smokers who had stopped smoking for more than 1 year.

more than 6 months of follow up (162 ± 209 days). In the remaining 54 patients, sputum cytological examinations were repeated for a median of two times (range: 0–27 times) over a median of 9.5 days (range: 0–1720 days) after the initial cytological examination with atypical cells. In these 54 patients, primary or metastatic lung cancers or other malignancies were not detected during a mean of 712 ± 323 days of observation (Fig. 1).

Clinical course of the five patients with atypical cells subsequently diagnosed as having a malignancy

During the period of close observation, five out of 59 patients with atypical cells in their sputa were diagnosed as having lung cancer (four patients) or nasopharyngeal cancer (one patient) at a mean of 162 ± 209 days after the identification of atypical cells (Table 2).

Patient 1 was admitted because of high fever and purulent sputum and his CXR revealed consolidation and a pleural effusion on the right side. Atypical cells were found in six out of 19 cytological examinations of sputa performed at the first admission; however, the patient’s fever and radiographic abnormalities cleared with antibiotic treatment. Almost 18 months after the initial admission, he was readmitted for evaluation of a new mass in left upper lobe of the lung and was subsequently diagnosed with a squamous cell carcinoma.

Patient 2 was admitted because of increasing dyspnoea, and a chest CT scan showed a cavitory mass with an air-meniscus sign in the right upper lobe, a small fuzzy nodule in left lower lobe, and moderate degree of honeycombing in both lower lobes. His sputum cytology showed atypical cells in three out of 11 samples; however, bronchoscopy revealed no intra-bronchial lesion. Nine months later, his right supraclavicular lymph node became enlarged and he was readmitted for evaluation. A chest CT scan showed that the nodule in the left lower lobe had increased. Cytology of aspirates from the right supraclavicular lymph node revealed an undifferentiated carcinoma. The patient was diagnosed as having a lung cancer with metastasis to lymph nodes.

Patient 3 visited our hospital because of supraclavicular lymph node enlargement. Diagnosis could not be made despite CT scans of the chest and aspiration cytology of the enlarged lymph nodes. Four months later, the patient developed discomfort on swallowing. A nasopharyngeal mass was detected and a diagnosis of nasopharyngeal cancer was made by biopsy.

In both patients 4 and 5, bronchoscopy was needed, but was delayed because of evaluation and treatment of ischaemic heart disease. The diagnosis of lung cancer was delayed by 34 days in patient 4 and 31 days in patient 5.

Underlying diseases in the 54 patients who had not developed a subsequent lung cancer or other malignancy during the period of observation

The most common underlying respiratory diseases were pneumonia (11 patients, 20.4%) and pulmonary tuberculosis (10 patients, 18.5%). Other frequent conditions included sequelae of previous tuberculosis (eight patients, 14.8%), COPD (six patients, 11.1%), bronchiectasis (four patients, 7.4%) and bronchial anthracofibrosis (three patients, 5.6%).

DISCUSSION

Because lung cancer is the end-stage of multiple steps in carcinogenesis involving hyperplasia, dysplasia, carcinoma in situ and eventually invasive carcinoma,9 the presence of atypical cells might be used to foretell the future development of invasive lung cancer. In fact, the presence of atypical or dysplastic cells without evidence of definite malignant change is indeed a high-risk factor for later developing invasive lung cancers.10–14

However, atypical cells found in cytological examinations of sputum could be the regenerating or hyperplastic type II pneumocytes from the alveoli in patients without lung cancer.15 These regenerating or hyperplastic type II pneumocytes, mimicking malignant cells, have been reported from patients with tuberculosis,16 thermal injuries,17 thromboembolisms,18 lung infarctions,19 anthracosis,20 interstitial pneumonia21 and bronchiectasis.22 To differentiate these type II pneumocytes from well-differentiated bronchioloalveolar carcinoma has been a challenge for the correct diagnosis of lung diseases.16

In this study, among the 59 patients without evidence of lung cancer, only five (8.5%) were diagnosed with lung cancers (four patients) or nasopharyngeal cancer (one patient) at a mean of 164 days after the

Table 1 Clinical characteristics of 59 patients with atypical cells in the sputum without evidence of malignant disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>61 ± 13</td>
</tr>
<tr>
<td>History of smoking</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>19 (32.2%)</td>
</tr>
<tr>
<td>Ex-smoker†</td>
<td>17 (28.8%)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>23 (40.0%)</td>
</tr>
<tr>
<td>Mean duration of follow up (days)</td>
<td>702 ± 317</td>
</tr>
<tr>
<td>Chief complaint</td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>14 (23.7%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>10 (16.9%)</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>9 (15.2%)</td>
</tr>
<tr>
<td>Abnormal CXR</td>
<td>8 (13.5%)</td>
</tr>
<tr>
<td>Cervical lymph node enlargement</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Sputum</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Routine check-up</td>
<td>2 (3.4%)</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>12 (20.3%)</td>
</tr>
</tbody>
</table>

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Table 2  Clinical course of five patients finally diagnosed as having lung cancer or other malignancy

<table>
<thead>
<tr>
<th>Patient (age/gender)</th>
<th>Chief complaint</th>
<th>CXR findings</th>
<th>Initial impression</th>
<th>Number of atypical cells/total sputum samples tested</th>
<th>Initial work up for diagnosis</th>
<th>Final diagnosis</th>
<th>Interval to diagnosis$^1$ (days)</th>
<th>Method of final diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (77/M) Dyspnoea</td>
<td></td>
<td>• Consolidation in the right lower lobe$^1$ • Right pleural effusion$^1$ • Mass in right upper lobe • Increased interstitial marking in lower lobe</td>
<td>Pneumonia with parapneumonic effusion</td>
<td>6/19</td>
<td>• Chest CT$^5$ • Bronchoscopy</td>
<td>Lung cancer (squamous cell carcinoma)</td>
<td>528</td>
<td>Percutaneous needle aspiration for a newly appeared mass in the left upper lobe</td>
</tr>
<tr>
<td>2 (66/M) Dyspnoea</td>
<td></td>
<td>• Mass in right upper lobe • Fungus ball • Possible idiopathic interstitial fibrosis</td>
<td></td>
<td>3/11</td>
<td>• Chest CT • Bronchoscopy</td>
<td>Lung cancer (undifferentiated carcinoma)</td>
<td>267</td>
<td>Biopsy of newly appeared right supraclavicular lymph node in the setting of a growing nodule in the left lower lobe</td>
</tr>
<tr>
<td>3 (79/M) Right cervical lymph node enlargement</td>
<td>Streaky density in right upper lobe</td>
<td>Lymphoma</td>
<td>1/3</td>
<td>• Chest CT • Aspiration cytology of cervical lymph node</td>
<td>Nasopharyngeal Cancer (Undifferentiated carcinoma)</td>
<td>138</td>
<td>Nasopharyngeal biopsy</td>
<td></td>
</tr>
<tr>
<td>4$^*$ (45/M) Blood-tinged sputum</td>
<td>No abnormal finding</td>
<td>Haemoptysis of unknown origin</td>
<td>1/1</td>
<td>• Chest CT</td>
<td>Lung cancer (squamous cell carcinoma)</td>
<td>34</td>
<td>Bronchoscopic biopsy</td>
<td></td>
</tr>
<tr>
<td>5$^*$ (78/M) Blood-tinged sputum</td>
<td>Increased opacity in left infra hilar area</td>
<td>Lung cancer</td>
<td>4/9</td>
<td>• Chest CT</td>
<td>Lung cancer (squamous cell carcinoma)</td>
<td>31</td>
<td>Cytological examination of bronchoscopic washing fluid</td>
<td></td>
</tr>
</tbody>
</table>

$^1$Interval from the initial detection of atypical cell to final diagnosis.
$^1$These lesions improved completely following antibiotic treatment.
$^1$CT of chest.
$^1$Bronchoscopy was delayed because of cardiac problems.
$^1$M, male.
identification of atypical cells. In the other 54 patients, lung cancers or malignancies were not detected during the period of observation. Furthermore, atypical cells might not be related to the lung cancer detected almost 2 years later in patient 1, and of the lung cancers whose detection was delayed because of heart problems in patients 4 and 5. In this context, atypical cells foretold malignancies in only two out of the 59 patients. Given that 40–83% of patients with atypical cells in their sputa subsequently develop lung cancer in previous case series,10–13 the rate of developing subsequent lung cancers or other malignancies was very low in this series. This might reflect the introduction and more widespread use of chest CT scans and bronchoscopy.

As lung cancers developed in only a few of the patients with atypical cells, and as atypical cells tend to disappear with the resolution of underlying benign conditions,13 patients with atypical cells in their sputa subsequently develop lung cancer despite a thorough evaluation including chest CT scans and bronchoscopy could simply be observed carefully without the need for further invasive diagnostic procedures.

REFERENCES