

## A Case of Bronchial Squamous Cell Carcinoma *In Situ* Detected by Sputum Cytology

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### ABSTRACT

A 64-year-old man underwent a medical checkup in May 1996 and was evaluated as class V using sputum cytology. Chest X-ray examination, bronchoscopy and chest computed tomography (CT) demonstrated no abnormalities. Thereafter, the patient was followed up with chest X-ray, bronchoscopy and chest CT at 3-month intervals. In December 1996, chest CT showed an increased density at the mediastinal side of the left upper bronchus, B<sup>1+2</sup>. There were no findings on bronchoscopy, but subsequent exfoliative cytology demonstrated keratinized malignant cells in samples obtained from left upper bronchus, B<sup>1+2</sup>. Although, it was difficult to identify localization of the tumor, left upper lobectomy was performed and the diagnosis of squamous cell carcinoma *in situ* was finally made. Here, we report on the course of this patient and discuss the diagnostic usefulness of sputum cytology as well as the pathogenesis of lung squamous cell carcinoma.

**Key words:** *Sputum cytology, Thin section CT, De novo carcinogenesis, Squamous cell carcinoma*

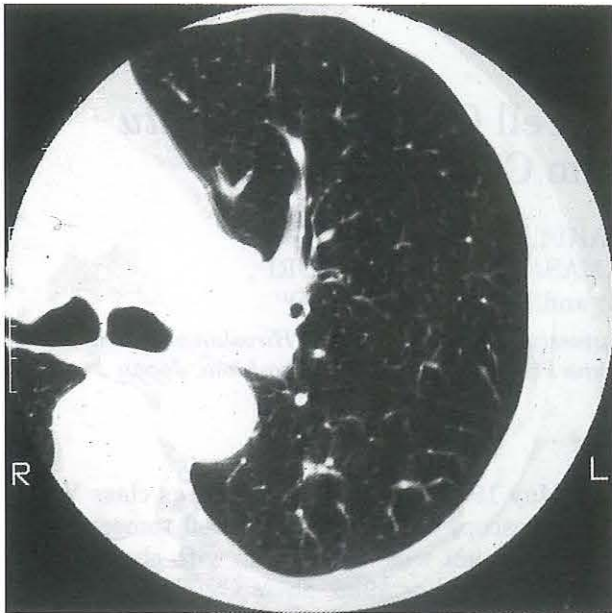
Sputum cytology is considered a useful method for detecting lung squamous cell carcinoma when no abnormalities are found on chest X-ray examination. However, when tumorous findings are not observed by bronchoscopy, it is difficult to diagnose such cases. In the present case, bronchial squamous cell carcinoma was detected using sputum cytology although localization of the tumor was difficult to ascertain using chest X-ray examination or bronchoscopy. Here, the clinical course of this patient is reported and the diagnostic usefulness of sputum cytology as well as the pathogenesis of bronchial squamous cell carcinoma is discussed.

### CASE REPORT

A 64-year-old man with a smoking history of 20 cigarettes/day for 44 years underwent a medical screening for lung cancer in May 1996. Chest X-ray examination did not demonstrate any abnormalities but the patient was diagnosed as class V on subsequent sputum cytology. On examination by bronchoscopy and chest computed tomography (CT), performed during the medical examination, abnormalities were not detected. Thereafter, this

patient was followed up with chest X-ray, bronchoscopy and chest CT at 3-month intervals. In October 1996, various examinations revealed no abnormal findings except sputum cytology after bronchoscopy in which the patient was diagnosed as class IV. In December 1996, the patient was admitted to our hospital for re-examination and total bronchial brushing.

There were no abnormal findings in physical or laboratory examinations on admission. Chest X-ray examination also showed no abnormalities. Compared with the findings of the previous two chest CT scans, the chest CT on admission demonstrated increased density at the mediastinal side of left upper bronchus, B<sup>1+2</sup> without apparent swelling of the mediastinal lymph node (Fig. 1). Thin section CT was performed centering around the left superior segmental bronchi. However, abnormal findings such as apparent hypertrophy of the bronchial wall were not detected. There were no abnormal findings on the mucosal surface of any bronchi (Fig. 2). Based on the findings of the chest CT described above, it was considered that abnormality would most likely exist in the left superior segmental bronchi. Therefore, exfolia-

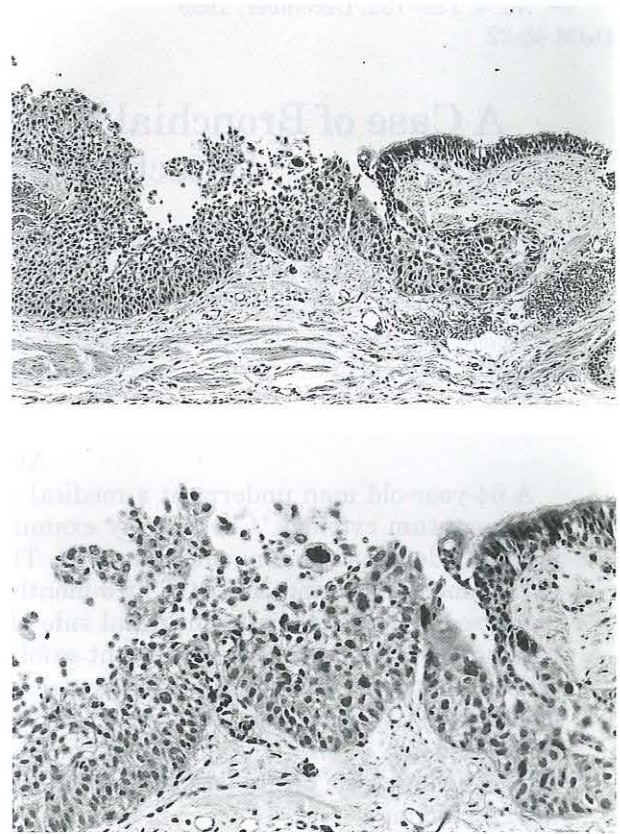


**Fig. 1.** Chest computed tomography on admission demonstrated increased density at the mediastinal side of the left B<sup>1+2</sup> without apparent swelling of the mediastinal lymph node.



**Fig. 2.** In bronchoscopic examination on admission, there were no abnormal findings in the mucous membrane of any bronchi.

tive cytology obtained by washing the left superior segment, B<sup>1+2</sup> or B<sup>3</sup>, and brushing each of the other lobar bronchi, was performed. As a result, atypical cells with keratinization were detected in cytology samples obtained from left B<sup>1+2</sup> but not from other segments of the lobar bronchi. Abdominal CT, brain magnetic resonance imaging (MRI), or bone scintigraphy did not demonstrate any abnormalities. Moreover, bronchoscopic examinations, performed three times preoperatively, demonstrated no abnormalities in luminal findings.



**Fig. 3.** Proliferation of atypical squamous cells substituting for all layers of the existing bronchial epithelium without apparent infiltrative proliferation beyond the basement membrane was observed in an area immediately before the bifurcation of the B<sup>1+2b</sup> and B<sup>1+2c</sup> in the resected tissue specimens. (HE stain. A: low power view, B: high power view.)

As described above, although the location of the tumor was not macroscopically identified, the patient was diagnosed as having squamous cell carcinoma (TxN0M0, clinical stage: 0) at the B<sup>1+2</sup> of the superior lobe of the left lung. On February 13, 1997, left upper lobectomy was performed together with mediastinal lymph node dissection. A hemorrhagic gastric ulcer developed postoperatively. It was successfully managed and the course of the patient was uneventful thereafter. In addition, sputum cytology performed 18 months after surgery demonstrated a negative result.

Although apparent protruding or excavated lesions were not macroscopically observed on the bronchial mucosa in the resected tissue specimens, slight sequential disarray was observed in the bronchial cartilage around the B<sup>3</sup>. Proliferation of atypical squamous cells substituting for all layers of the existing bronchial epithelium in an area measuring 4 × 2 × 1 mm was observed immediately before the bifurcation of the B<sup>1+2b</sup> and B<sup>1+2c</sup>. Since there was no apparent infiltrative proliferation beyond the basement membrane, a diagnosis of squamous cell carcinoma *in situ* was finally established (Fig. 3).

## DISCUSSION

Three institutions in the United States performed prevalence studies and have reported that lung cancer was detected in 37 (0.18%) of 21,127 subjects employing sputum cytology, and 35 (95%) of the 37 lung cancer patients were pathohistologically classified as having squamous cell carcinoma<sup>2</sup>. Considering the usefulness for detecting lung cancer demonstrating no abnormalities on chest X-ray examination<sup>6</sup>, sputum cytology is the most useful procedure for detecting early lung squamous cell carcinoma. However, in addition to the low positive rate using sputum cytology, the location of the malignant tumor could not be identified in approximately half of the patients detected using sputum cytology.

In the present case, despite the positive findings from sputum cytology, repeated examination of bronchoscopy did not demonstrate any abnormalities in the mucosal surface. Therefore, it was difficult to ascertain localization of the tumor in this patient. Although changes observed on chest CT performed at 3-month intervals did not directly contribute to detection of the tumor in this patient, these scans provided support for the diagnosis. A careful retrospective review of chest CT in the present case revealed that sequential disarray of the bronchial cartilage detected at the B<sup>3</sup> in the resected tissue specimen was also suggested on thin section CT. Although disarray of the cartilage was not considered to be related to the presence of cancer in this case, these observations suggested that sufficient and careful follow-up study employing chest CT may be important for accurate diagnosis and to ascertain the location of lung cancer. Since more than six months elapsed from the patient's first visit to our hospital to the establishment of diagnosis in the present case, it was considered that total bronchial brushing cytology should be introduced at the early stages in such cases together with sufficient otolaryngological examinations.

The lung cancer in the present patient was characterized by squamous cell carcinoma *in situ*. Such cases of lung cancer could provide an insight into the pathogenesis of squamous cell carcinoma but there have been few reports to date. Concerning the etiology of squamous cell carcinoma, attention has generally been paid to the carcinogenic pathway in which carcinoma develops from dysplasia (theory of multi-step carcinogenesis). Among smokers and lung cancer patients, Auerbach et al<sup>1</sup> examined numerous tissue sections obtained from the non-cancerous region of the bronchi and reported that frequencies of atypical epithelium and carcinoma *in situ* were markedly high. Moreover, Kobayashi et al<sup>3</sup> succeeded in inducing squamous cell carcinoma by administering methylcholanthrene and benzpyrene to the lumen of implanted bronchial autograft in dogs. During

the developmental process of squamous cell carcinoma, they confirmed that mucous cell metaplasia and basal cell proliferation appeared over time<sup>3</sup>. They also confirmed that the atypia of these cells increased with time, resulting in the development of infiltrative squamous cell carcinoma<sup>3</sup>.

Although the possibility remains that precancerous lesion was excluded by the neoplastic process, since dysplasia was not observed around the tumor in the present case, it suggests the possibility of *de novo* carcinogenesis. Shimozato et al<sup>5</sup> reported that they could detect 7 bronchial carcinoma *in situ* (including micro-infiltration) in 5 lung cancer patients. They also noted that the size of tumors in 6 of 7 carcinoma *in situ* were small (2–7 mm in diameter) and adjacent to the seemingly normal ciliated columnar epithelium or slightly hyperplastic ciliated columnar epithelium without bordering, and adjacent metaplasia or atypical epithelium<sup>5</sup>. This observation was consistent with the findings in our patient. Moreover, Melamed et al<sup>4</sup> also reported the possibility of *de novo* carcinogenesis noting that the tumor develops regardless of the presence or absence of basal cell hyperplasia or squamous metaplasia. They suggested that these hyperplastic changes and metaplasia are non-specific reactions induced by carcinogenesis<sup>4</sup>. Further studies are necessary in order to clarify the pathogenesis of squamous cell carcinoma.

In conclusion, sputum cytology is suggested to be a useful procedure for early detection of lung squamous cell carcinoma. However, it is not easy to establish a diagnosis in cases with positive findings from sputum cytology. In such cases, it is suggested that sufficient, careful follow-up study using chest CT may be important to establish a diagnosis and/or a location of lung cancer. Moreover, total bronchial brushing cytology in the early stage together with sufficient otolaryngological examinations is considered necessary in undiagnosed patients with positive findings from sputum cytology.

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## REFERENCES

1. Auerbach, O., Stout, A.P., Hammond, E.C. and Garfinkel, L. 1961. Changes in bronchial epithelium in relation to cigarette smoking and in relation to lung cancer. *N. Engl. J. Med.* **265**: 253–267.
2. Berlin, N.I., Buncher, C.R., Fontana, R.S., Frost, J.K. and Melamed, M.R. 1984. The National Cancer Institute Cooperative Early Lung Cancer Detection Program. Results of the initial screen (prevalence). Early lung cancer detection: Introduction. *Am. Rev. Respir. Dis.* **130**: 545–549.
3. Kobayashi, N., Kanisawa, M., Okamoto, T., Okita, M. and Katsuki, H. 1978. Sequential cytologic study of the development of squamous cell car-

- cinoma induced in subcutaneously implanted bronchial autograft of dog. *Acta Cytol.* **22**: 99–104.
4. **Melamed, M.R., Zaman, M.B., Flehinger, B.J. and Martini, N.** 1977. Radiologically occult *in situ* and incipient invasive epidermoid lung cancer: detection by sputum cytology in a survey of asymptomatic cigarette smokers. *Am. J. Surg. Pathol.* **1**: 5–16.
  5. **Shimozato, Y.** 1980. Growth characteristics, prognoses and functions of lung cancer in relation to its morphology. *Jpn. J. Lung Cancer* **20**: 3–19. (in Japanese)
  6. **Strauss, G.M., Gleason, R.E. and Sugarbaker, D.J.** 1997. Screening for lung cancer. Another look; a different view. *Chest* **111**: 754–768.