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Letters

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Bronchioloalveolar Carcinoma Presenting Aerogenous Metastasis to the Upper Airway

N. Hidaka,[1] Y. Hidaka,[1] Y. Tajima,[2] I. Sugano[2] and K. Nagao[2]

[1]Department of Internal Medicine and [2]Department of Surgical Pathology, Teikyo University School of Medicine, 3426-3 Anesaki, Ichihara, Chiba 299-01, Japan

A UNIQUE feature of bronchioloalveolar carcinoma (BAC) is aerogenous metastasis within the lungs [1–7], which has been suggested by gross pathological examination and radiological findings. Although many investigators favour aerogenous spread as the cause for intrapulmonary dissemination [2, 6], it has not yet been proven by histological evidence.

Tumour cells of BAC in the primary lesion exhibit a characteristic spreading pattern, growing along intact alveolar walls [1–3, 6–8]. However, the structure of aerogenous metastasis of BAC has not ever been precisely documented.

The purpose of this letter is to present histological evidence of aerogenous metastasis by describing extrapulmonary spread of our BAC case, and to reveal unique structural features of the metastasis distinctive from those of hematogenous and lymphangitic metastases.

The patient was a 49-year-old non-smoking woman who complained of a considerable amount of serous sputum. A chest radiograph showed diffuse pulmonary lesions. The diagnosis of BAC was established by the histology of specimens obtained from transbronchial lung biopsy. Several months after a small tumour mass was expectorated, the patient reported impaired hearing, tinnitus, epistaxis, nasal obstruction and discharge from the left ear and right nose. Computerised tomography indicated multiple metastatic tumours in the nasal cavity and middle ear, some of which were visible.

The patient was subsequently treated with multiple systemic therapies and eventually died of progressive lung cancer. The autopsy revealed extensive involvement of both lungs. The expectorated mass, biopsy samples of the nasal cavity and middle ear, and autopsy materials of the lungs were investigated. Tumours were fixed and examined with stains including Periodic acid-methenamine silver (PAM) stain to make pre-existing basement membranes distinct.

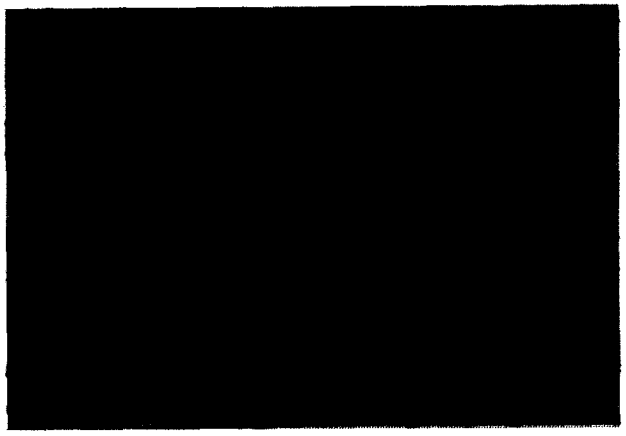

Figure 1. The aerogenous metastasis of the nasal cavity. Note that tall columnar tumour cells are lined up on intact alveolar basement membranes shown as continuous line with PAM stain (original magnification ×50).

The metastatic lesions of the nasal cavity and middle ear maintained a characteristic BAC growth pattern similar to that of the primary tumour, composed of a single layer of tall columnar tumour cells lining intact alveolar walls (Figure 1). The histological appearance of the expectorated tumour was also notably similar to that of the lung primary. These specimens manifested a mucinous subtype with basally located bland nuclei and abundant mucin.

The present BAC case was classified as a mucinous subtype, which is considered to have a higher rate of aerogenous spread than the other two subtypes: non-mucinous and sclerosing [4]. Our results were compatible with the unique behaviour of BAC, including the incohesive nature and the formation of papillary structures in alveolar spaces [2, 3, 7].

Since the arrangement of the metastasis was markedly similar to that of the primary tumour, tumour cells appeared to be transferred together with supporting structures during aerogenous spread. However, lymph node metastasis of lung cancer does not maintain alveolar walls as is observed in the primary tumours [3].

Our hypothesis for the mechanism of aerogenous metastasis in this case is as follows: the primary tumour was forced into papillary folds, broke off and migrated toward the upper airway. They became implanted in the nasal cavity. Possibly one of these tumour masses was found in the sputum. Tumour cells passed along the auditory tube and lodged in the middle ear. The similar mode of metastasis has been described as transtubal implantation metastasis from the paranasal sinus to the middle ear [9, 10].

The present case is the first documented case of lung cancer with aerogenous metastasis to other organs, which is a new aspect of biological behaviour of BAC.

Correspondence to N. Hidaka.
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1. Grigioni WF, Biagini G, Carbisa S, *et al.* Immunohistochemical study of basement membrane antigens in bronchioloalveolar carcinoma. *Am J Pathol* 1987, **128**, 217–224.
2. Axiotis CA, Jennings TA. Observations on bronchiolo-alveolar carcinomas with special emphasis on localized lesions. *Am J Surg Pathol* 1988, **12**, 918–931.
3. Clayton F. Bronchioloalveolar carcinomas. Cell types, patterns of growth, and prognostic correlates. *Cancer* 1986, **57**, 1555–1564.

4. Manning JT, Spjut HJ, Tschen JA. Bronchioloalveolar carcinoma: the significance of two histopathologic types. *Cancer* 1984, **54**, 525–534.
5. Clayton F. The spectrum and significance of bronchioloalveolar carcinomas. *Pathol Ann* 1988, 361–394.
6. Edwards CW. Alveolar carcinoma: a review. *Thorax* 1984, **39**, 166–174.
7. Ohori NP, Yousem SA, Griffin J, *et al.* Comparison of extracellular matrix antigens in subtypes of bronchioloalveolar carcinoma and conventional pulmonary adenocarcinoma. An immunohistochemical study. *Am J Surg Pathol* 1992, **16**, 675–686.
8. Pääkkö P, Risteli J, Risteli L, Autio-Harmainen H. Immunohistochemical evidence that lung carcinomas grow on alveolar basement membranes. *Am J Surg Pathol* 1990, **14**, 464–473.
9. Abrams J, Hüttenbrink KB. Die Implantationsmetastase eines Adenokarzinoms der Nebenhöhlen im Mittelohr. *Laryngo Rhino Otol* 1992, **71**, 86–90.
10. Willis RA. Secondary tumours in sundry unusual situations. In *The Spread of Tumors in the Human Body*, 3rd. ed. London, Butterworths, 1973.

Table 1. Thyroglobulin levels versus scintigraphic findings after treatment with iodine-131 (^{131}I)

Tg level (ng/ml)	Number of patients with ^{131}I uptake: Thyroid remnants only	Lymph nodes	Distant metastases
< 1 ng/ml ($n = 34$)	28	6	0
1–< 5 ng/ml ($n = 36$)	34	2	0
> 5–< 15 ng/ml ($n = 17$)	13	2	2
> 15 ng/ml ($n = 26$)	14	5	7

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Thyroglobulin Measurement and Postablative Iodine-131 Total Body Scan After Total Thyroidectomy for Differentiated Thyroid Carcinoma in Patients with No Evidence of Disease

F. Tenenbaum, C. Corone, M. Schlumberger and C. Parmentier

Service de Médecine Nucléaire, Institut Gustave Roussy, 94805 Villejuif Cedex, France

During the follow-up of patients with differentiated thyroid carcinoma, measurement of serum thyroglobulin (Tg) can lead to the early discovery of neoplastic foci [1,2] and an iodine-131 total body scan (^{131}I-TBS) post therapy is the most sensitive tool for their imaging [3]. This study was undertaken in patients with no evidence of disease after total thyroidectomy to evaluate the accuracy of the ^{131}I-TBS performed after an ablative dose of radioiodine and of Tg measurement after thyroxine withdrawal.

Over the last 3 years, 135 patients with no evidence of disease were given an ablative dose of 3.7 GBq (100 mCi) ^{131}I, 1–3 months after total thyroidectomy. Treatment with thyroxine was withdrawn for 5 weeks and T3 treatment for 2 weeks before the dose. On the day of ^{131}I administration, serum TSH (Behring kit) was above 20 mU/ml in all patients; serum Tg was measured using an IRMA method (Dynotest Tg, Henning, Berlin); 22 patients with Tg auto-antibodies were excluded, and the recovery test was above 80% in all of the remaining 113 patients. Four days after treatment with ^{131}I, a TBS was performed with a nuclear rectilinear scan (Ohio Nuclear, Mentor, Ohio, U.S.A.) and a neck scintigraph was taken with a rectilinear scan.

^{131}I uptake in the remnants of the thyroid was below 2% in all patients, thus confirming that a total thyroidectomy had been performed.

^{131}I-TBS disclosed ectopic uptake in 11% of the patients with a Tg level below 5 ng/ml and in 37% of those with a Tg level above 5 ng/ml (Table 1). Of the 12 patients with a Tg level below 15 ng/ml and who had ectopic uptake, all were cured after further treatments, with surgery in the 10 patients with lymph node metastases and with radioiodine treatments in the 2 patients with lung metastases. At subsequent TBS, no radioiodine uptake was found and the Tg level after thyroxine withdrawal was undetectable.

Of the 26 patients with a Tg level above 15 ng/ml, 12 patients had ectopic iodine uptake and were treated with surgery, radioiodine or external radiotherapy. The remaining 14 patients had only thyroid remnants: 6 months later, serum Tg was still elevated after thyroxine withdrawal in 11 of the 14 patients, suggesting the presence of non-functional neoplastic foci.

In conclusion, this study advocates the combined use of both tools in patients with unfavourable prognostic indicators, even in those with a low Tg level after thyroxine withdrawal. The Tg level appears to be of major value both for the diagnosis of neoplastic foci after apparently complete initial surgery and for prognosis.

Correspondence to F. Tenenbaum at Service de Médecine Nucléaire, Hôpital Cochin, 27 rue du faubourg Saint-Jacques, 75014, Paris, France.
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1. Schlumberger M, Fragu P, Gardet P, Lumbroso J, Violot D, Parmentier C. A new immunoradiometric assay (IRMA) system for thyroglobulin measurement in the follow-up of thyroid cancer patients. *Eur J Nucl Med* 1991, **18**, 153–157.
2. Schlumberger M, Arcangioli O, Piekarski JD, Tubiana M, Parmentier C. Detection and treatment of lung metastases of differentiated thyroid carcinoma in patients with normal chest X-rays. *J Nucl Med* 1988, **29**, 1790–1794.
3. Pacini F, Lippi F, Formica N, *et al.* Therapeutic doses of iodine-131 reveal undiagnosed metastases in thyroid cancer patients with detectable serum thyroglobulin levels. *J Nucl Med* 1987, **28**, 1888–1891.