

Spontaneous Pneumothorax as an Initial Manifestation of Metastatic Papillary Thyroid Carcinoma

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Received : July 3, 2008
Accepted : September 30, 2008

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Spontaneous pneumothorax occurs in a variety of lung diseases. Primary or metastatic lung cancers are rare, but important causes of pneumothorax. We report here on a case of pulmonary metastasis of thyroid papillary carcinoma that initially presented as spontaneous pneumothorax. A 32-year-old male with no history of thyroid disease underwent wedge resection of the lung due to recurrent pneumothorax. Histologically, the pleura and subpleural lung parenchyma revealed several micronodular lesions and randomly scattered glandular structures with mild cytological atypia. The cells were characterized by their overlapped hypochromatic nuclei with longitudinal grooves and inconspicuous nucleoli. On the additional sections, we found a few intranuclear inclusions and colloid-like material in the follicular structures. The glandular cells were immunoreactive for thyroglobulin, TTF-1, CK 7 and HMW-CK and they were focally immunoreactive for EMA, but they were negative for S100, chromogranin and CEA. The Ki-67 labelling index was 4%. Neck ultrasonography revealed an ill-defined hypoechoic nodule in the left lobe of the thyroid. The diagnosis of conventional, classical papillary carcinoma was made by both the cytology and the total thyroidectomy specimen. Pathologists should conduct a through histologic examination for the patients with recurrent spontaneous pneumothorax to search for the underlying causes.

Key Words : Pneumothorax; Cancer; Metastasis; Thyroid; Papillary carcinoma

Primary spontaneous pneumothorax usually affects tall thin young men who don't have any clinically apparent lung disease. Secondary spontaneous pneumothorax occurs in patients with a variety of lung diseases, including airway disease, infections, interstitial lung disease, connective tissue disease and infarction.¹ Primary or metastatic malignant neoplasms are rare but very important underlying cause of spontaneous pneumothorax.²⁻⁹ We report here on a 32-year-old male with microscopic pulmonary metastasis from a clinically undetected thyroid papillary carcinoma, who initially presented with recurrent spontaneous pneumothorax. This case was difficult to diagnose because the metastatic tumor exclusively revealed a follicular growth pattern and mild cytological atypia in an unusual anatomic site. We discuss making the histological differential diagnosis and we include a review of the relevant literature.

CASE REPORT

A 32-year-old male presented with an 11 day history of right

chest pain and dyspnea. For his past medical history, the patient had previously suffered from similar symptoms and he had a chest tube inserted for spontaneous pneumothorax 3 months previously. The chest x-ray and high resolution computed tomography (HR-CT) on admission revealed mild right pneumothorax with no demonstrable abnormalities in both lungs. We performed wedge resection of the right upper lobe. Grossly, the specimen showed a bulla with thickened pleura. The lung parenchyma was grossly unremarkable. Microscopic examination disclosed a bulla with a fibrotic, inflamed wall. An unexpected finding was two tiny nodular lesions in the subpleural lung parenchyma and these measured 2.0 × 1.0 mm and 1.0 × 1.0 mm, respectively. The nodular lesions were composed of small irregular glands (Fig. 1A). Careful histologic examination revealed several tiny cellular aggregates in the alveolar septa and thickened pleura, immediately beneath and near the bulla (Fig. 1B), and these aggregates consisted of one or a few well-formed or abortive glandular structures. The glandular cells were cuboidal or columnar with mild cytologic atypia. The vesicular nuclei were slightly overlapped and the nuclear outlines were irregular. Yet the nuclei were hy-

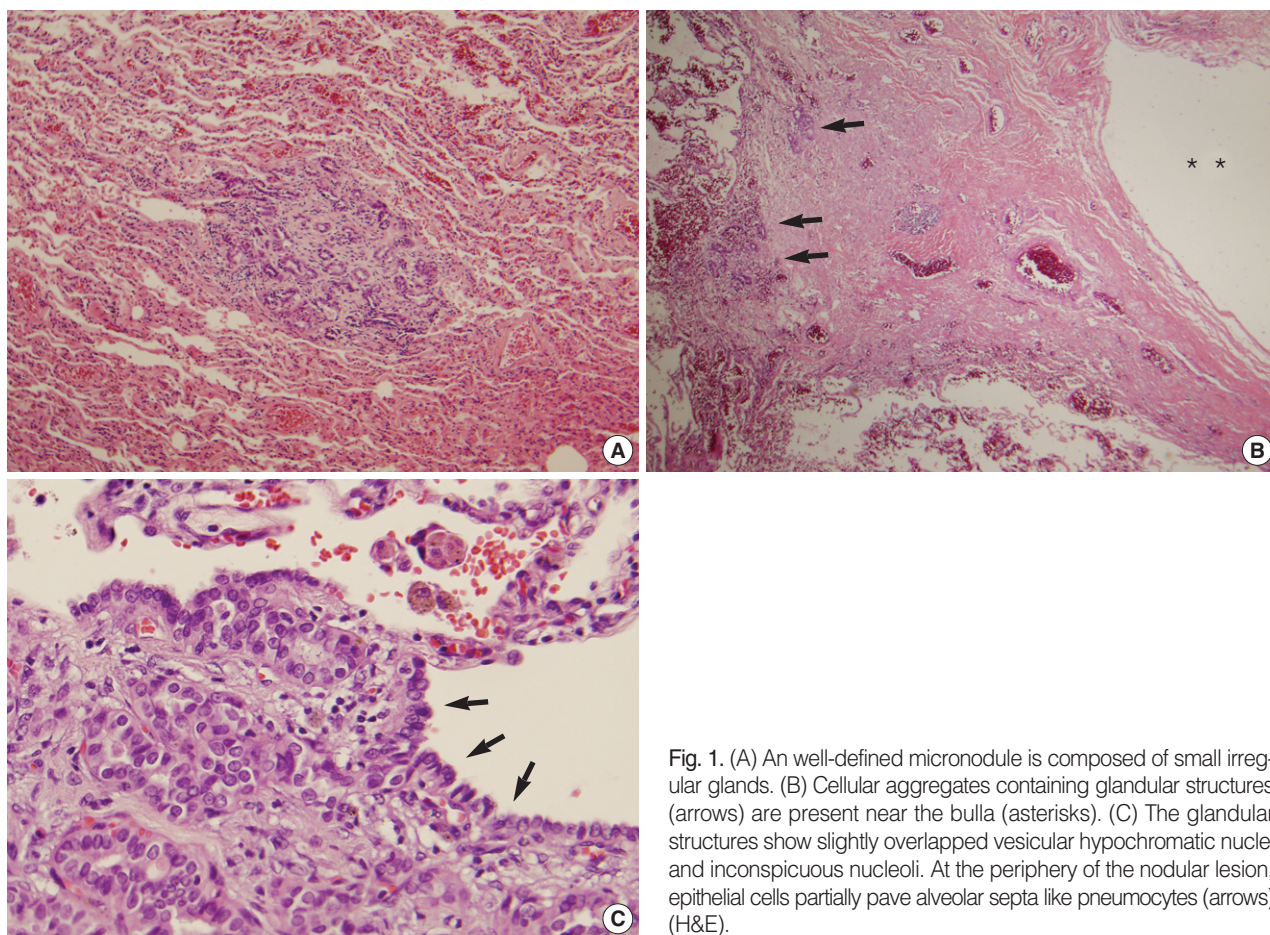


Fig. 1. (A) An well-defined micronodule is composed of small irregular glands. (B) Cellular aggregates containing glandular structures (arrows) are present near the bulla (asterisks). (C) The glandular structures show slightly overlapped vesicular hypocromatic nuclei and inconspicuous nucleoli. At the periphery of the nodular lesion, epithelial cells partially pave alveolar septa like pneumocytes (arrows) (H&E).

pochromatic, even cleared, and the nucleoli were inconspicuous. Nuclear grooves were occasionally found, but mitosis was absent. At the periphery of one nodular lesion, the epithelial cells partially lined the alveolar space in the manner of pneumocytes (Fig. 1C). We initially thought that the lesion was a benign reactive process, including metaplasia, but the histologic and cytologic features were not exactly consistent with those of any specific primary lung lesions or metaplastic epithelium. All the remaining specimen was completely processed for histologic evaluation. An additional 2.0×1.0 mm sized micronodule and multiple randomly scattered glandular structures were found. The lumina of some small glands contained eosinophilic fluid that resembled colloid. A few intranuclear cytoplasmic inclusions were found. Immunohistochemical staining was performed for thyroglobulin (Dako, Glostrup, Denmark), thyroid transcription factor-1 (TTF-1, Dako), cytokeratin (CK) 7 (Neomarkers, Fremont, CA, USA), high molecular weight cytokeratin (HMW-CK, clone 34E1 β 2, Dako), epithelial membrane antigen (EMA, Dako), S100-protein (Dako), chromogranin (Dako), carcinoma embryonic antigen (CEA, Dako), and Ki-67 (Dako). The glandular

cells revealed diffuse strong reactivity for thyroglobulin, TTF-1, CK 7 and HMW-CK and they showed focal reactivity for EMA (Fig. 2). The S100-protein, chromogranin and CEA stains were negative. The Ki-67 labelling index was 4%. We strongly suspected that the pathology was hematogenous pulmonary metastasis of thyroid papillary carcinoma. Neck ultrasonography revealed a 2.0×1.5 cm sized, ill-defined hypoechoic nodule with microcalcifications in the left lobe of the thyroid. Multiple enlarged lymph nodes with microcalcifications were also noted along both internal jugular chains. The subsequent fine needle aspiration cytology (FNAC) showed the typical cytologic features of papillary carcinoma. The patient was then discharged. A whole body positron emission tomography-computed tomography (PET-CT) scan performed in another hospital revealed only a hypermetabolic nodule in the thyroid without any abnormal findings in other organs. The patient underwent total thyroidectomy along with neck lymph node dissection. The gross examination exhibited an ill defined, yellowish white sclerotic lesion in the left lobe, and the lesion measured 2.0 cm at the maximal diameter. Microscopically, the primary tumor was confirmed to be conventional clas-

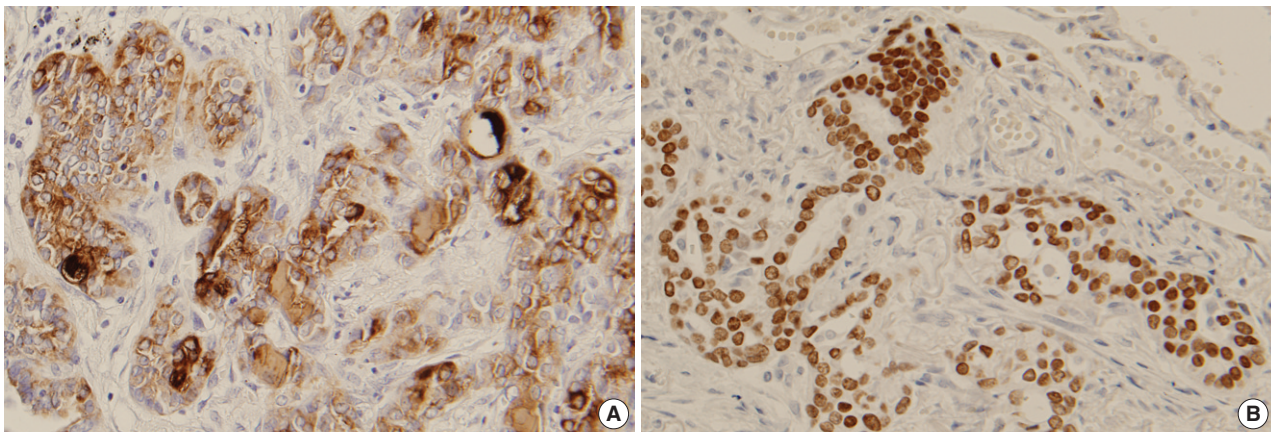


Fig. 2. In immunohistochemical stains, the glandular cells reveal strong positive reaction for thyroglobulin (A), and thyroid transcription factor-1 (TTF-1) (B).

sical papillary carcinoma with multiple, microscopic intrathyroidal metastases in both lobes and multiple lymph node involvement (10 out of 27). The tumor extended into the perithyroidal soft tissue, but any definite vascular invasion was absent. He has undergone one session of radioiodine ablation therapy.

DISCUSSION

In patients with spontaneous pneumothorax, it is very important to find the underlying cause to administer appropriate management and predict the overall prognosis. Secondary spontaneous pneumothorax is associated with a number of lung diseases, including such airway disease as chronic obstructive pulmonary disease (COPD), infectious diseases, interstitial lung disease and connective tissue disease.¹ Among them, the most common two causes are COPD and pneumocystis carinii pneumonia. On rare occasion, patients with primary or metastatic lung cancer present with spontaneous pneumothorax.²⁻⁹ In the general population, 10 of 1,143 cases with spontaneous pneumothorax are attributed to a malignancy.³ The most common malignant tumors are metastatic sarcomas,³⁻⁵ including osteosarcoma and angiosarcoma, germ cell tumors² and primary lung cancers.^{6,7} We found two cases of spontaneous pneumothorax associated with metastatic thyroid carcinomas in the English medical literature.^{8,9}

Various mechanisms have been proposed as possible causes of spontaneous pneumothorax in patients with malignancy. Necrosis within a tumor itself, mechanical airway obstruction by tumor, chemotherapy-related tumor shrinkage and direct tumor invasion of the pleura may predispose a person to the development of pneumothorax.^{2,3} In the present case, three micronodules of

metastatic thyroid papillary carcinoma in the subpleural areas may have acted as a check valve, causing air accumulation in the distal alveolar space and eventual rupture. The many randomly scattered tiny foci of metastatic carcinoma may have induced weakness of the alveolar wall and irritation to the pleura.

In addition to the rarity, the present case draws our interest because making the diagnosis of small metastatic thyroid papillary carcinoma with a follicular pattern was not as easy as diagnosing the tumor in the primary site. Although the primary tumor of the present case was classical papillary carcinoma, the tumor cells in the metastatic foci exclusively showed a follicular growth pattern and this caused diagnostic difficulty. On the histologic examination, we considered a wide range of lesions from benign reactive processes to low grade malignant epithelial tumors. At first, we thought the lesion was a benign reactive process, including metaplasia as Vermeer-Mens *et al.* have described.¹⁰ However, epithelial nests were randomly scattered without any relationship to the inflammation and we could not find any causative agents or lesions. The histologic differential diagnosis included multifocal micronodular pneumocyte hyperplasia (MNPH), atypical adenomatous hyperplasia, bronchioloalveolar carcinoma (BAC), thyroid inclusions in the lung, and metastatic papillary carcinoma of the thyroid.

Multifocal MNPH is a rare, but distinctive hamartomatous process of the lung, and this occurs exclusively in patients with tuberous sclerosis.^{11,12} Multiple discrete small nodules are composed of a proliferation of type II pneumocytes, and there are dense aggregations of macrophages in the alveolar space. Pneumocytes pave the thickened alveolar septa and their ingrowth forms papillary and trabecular structures in the alveolar wall. The pneumocytes vary in size and shape, but they lack marked

nuclear atypia or mitotic figures. Some crowded pneumocytes show eosinophilic intranuclear inclusions.¹² In the present case, a portion of the epithelial cells lined the alveolar space as pneumocytes. The multifocality of the lesions and some of the cytologic features of the epithelial cells, including intranuclear inclusions, raised the possibility of MNPH. However, MNPH lacks a true glandular structure with secretory material, the ground-glass like hypochromatic nuclei and the nuclear grooves that are characteristic features of the present case.

Because the epithelial cells of our case showed mild cytological atypia and some of them lined the alveolar space, we considered them to be primary precancerous or cancerous lesions of the lung. However, the present case lacked predominant lepidic growth, which is the most characteristic histologic feature of atypical adenomatous hyperplasia and bronchioloalveolar carcinoma (BAC). Primary pulmonary adenocarcinomas, including the usual type and BAC, could be excluded due to the absence of frank nuclear atypia.

We identified some follicular structures that contained deep eosinophilic colloid-like fluid on the additional sections. This finding was a very valuable clue, pointing to the thyroid origin of the epithelial cells and prompting us to thoroughly review the histologic features. The origin of epithelial cells was confirmed by a panel of immunohistochemical stains, including thyroglobulin. When we encounter thyroid tissue in the lung, we should consider two entities: heterotopic thyroid tissue and metastatic thyroid carcinoma. Heterotopic thyroid tissue can be found in the midline from the tongue to the diaphragm, in the abdominal or thoracic cavity and rarely in the lung.^{13,14} Heterotopic thyroid tissue consists of morphologically normal thyroid tissue and it has a very low Ki-67 labelling index close to zero.¹⁵ In this case, the glandular cells had the characteristic nuclear features of papillary carcinoma. The Ki-67 labelling index was 4%, which was similar to that of primary papillary carcinoma of the thyroid.^{13,15}

The overall incidence of distant metastasis in patient with papillary carcinoma is 10%.¹⁶ The most common sites are the lungs and bones. The follicular variant of papillary carcinoma was noted to have a higher incidence of pulmonary metastasis, but many authors have still reported that there was no significant difference in the rate of distant metastasis between the follicular variant and the classical type of papillary carcinoma.¹⁷ Although its prognosis is adversely affected by distant metastasis, thyroid papillary carcinomas with distant metastasis show a more favorable survival than other tumors if appropriate treatments are performed, especially in young patients with microscopic metastasis.^{10,16} This fact emphasizes the importance of making an early, accurate diag-

nosis of this unique tumor and even for its metastatic foci.

In conclusion, pathologists should conduct an extensive histologic examination for patients with recurrent spontaneous pneumothorax to search for the underlying causes. Although it is rare, metastatic carcinoma should be included in the differential diagnosis of spontaneous pneumothorax.

REFERENCES

1. Sahn SA, Heffner JE. Spontaneous pneumothorax. *N Engl J Med* 2000; 342: 868-74.
2. Srinivas S, Varadhachary G. Spontaneous pneumothorax in malignancy: a case report and review of the literature. *Ann Oncol* 2000; 11: 887-9.
3. Dines DE, Cortese DA, Brennan MD, Hahn RG, Payne WS. Malignant pulmonary neoplasms predisposing to spontaneous pneumothorax. *Mayo Clin Proc* 1973; 48: 541-4.
4. Seo JB, Im JG, Goo JM, Chung MJ, Kim MY. Atypical pulmonary metastases: spectrum of radiologic findings. *Radiographics* 2001; 21: 403-17.
5. Kim MK, Shin BK, Oh WE, Kim AR, Won NH, Choi JS. Spontaneous pneumothorax as a complication of pulmonary metastasis of osteosarcoma: A case report. *Korean J Pathol* 1999; 33: 281-4.
6. Steinhauslin CA, Cuttat JF. Spontaneous pneumothorax. A complication of lung cancer? *Chest* 1985; 88: 709-13.
7. Lee HW, Choi PJ, Roh MS. Peripheral micronodular squamous cell carcinoma of the lung unexpectedly discovered after an operation for spontaneous pneumothorax: A case report. *Korean J Pathol* 2005; 39: 424-7.
8. Lee MJ, Kim EK, Kim MJ, Kwak JY, Hong S, Park CS. Spontaneous pneumothorax in metastatic thyroid papillary carcinoma. *J Clin Oncol* 2007; 25: 2616-8.
9. Nenkov R, Radev R, Christosov K, Sechanov T. Hurthle cell carcinoma of the thyroid with bilateral pneumothorax. *Thyroid* 2005; 15: 627-8.
10. Vermeer-Mens JC, Goemaere NN, Kuenen-Boumeester V, et al. Childhood papillary thyroid carcinoma with miliary pulmonary metastases. *J Clin Oncol* 2006; 24: 5788-9.
11. Muir TE, Leslie KO, Popper H, et al. Micronodular pneumocyte hyperplasia. *Am J Surg Pathol* 1998; 22: 465-72.
12. Maruyama H, Ohbayashi C, Hino O, Tsutsumi M, Konishi Y. Pathogenesis of multifocal micronodular pneumocyte hyperplasia and lymphangioleiomyomatosis in tuberous sclerosis and association with tuberous sclerosis genes TSC1 and TSC2. *Pathol Int* 2001; 51: 585-94.

13. Hwang I, Lee SK, Cho KJ, Kim KR. Heterotopic intrathymic thyroid tissue. *Pathol Int* 2006; 56: 629-32.
14. Simon M, Baczako K. Thyroid inclusion in the lung. Metastasis of an occult papillary carcinoma or ectopia? *Pathol Res Pract* 1989; 184: 263-7.
15. Letsas KP, Frangou-Lazaridis M, Skyrlas A, Tsatsoulis A, Malamou-Mitsi V. Transcription factor-mediated proliferation and apoptosis in benign and malignant thyroid lesions. *Pathol Int* 2005; 55: 694-702.
16. Shaha AR, Ferlito A, Rinaldo A. Distant metastases from thyroid and parathyroid cancer. *ORL J Otorhinolaryngol Relat Spec* 2001; 63: 243-9.
17. Lang BH, Lo CY, Chan WF, Lam AK, Wan KY. Classical and follicular variant of papillary thyroid carcinoma: a comparative study on clinicopathologic features and long-term outcome. *World J Surg* 2006; 30: 752-8.