

Metachronous adenocarcinoma of lung mimicking metastatic papillary thyroid carcinoma: A case report

Lei Zhang, Abbey Johnston, Natalya Shlyakhova, Fritz Lin,
Richard M. DeMay, Di Lu

ABSTRACT

Introduction: We report an unusual case of adenocarcinoma of lung metachronous with stage IVA papillary thyroid carcinoma. The two tumors are morphologically similar; and the later presence of lung mass could clinically masquerade as metastatic thyroid carcinoma. We discuss the challenges in clinical, imaging and pathologic diagnosis. **Case Report:** A 64-year-old non-smoking female had a thyroidectomy and neck lymph node dissection for a stage IVA tumor with pathologic findings of one 2 mm microcarcinoma of left thyroid and six positive cervical lymph nodes. The post-surgical I¹³¹ whole body scan was negative and thyroglobulin is suppressed and stable (<1 ng/ml). One year later, she developed a ground glass and part-solid mass in the superior segment of left lower lobe of lung. The mass slowly grew increasing in size from 2.4 cm to 3.3 cm over 3 years. Biopsy of the lung lesion reveals morphologic features of nuclear inclusions and papillae similar to the previously diagnosed thyroid carcinoma. However, the spectrum of atypia, coarse chromatin and lepidic like growth pattern of tumor cells raise suspicion of adenocarcinoma from lung

primary. Immunohistochemical study further confirmed that the lung and thyroid lesions were two different tumors. **Conclusion:** Despite the history of advanced papillary thyroid carcinoma, secondary lung cancer should be considered when the postoperative serum thyroglobulin levels are consistently low. Appreciation of cytopathologic details helps differentiating lung primary cancer from thyroid metastasis.

Keywords: Lymph node metastasis, Metachronous adenocarcinoma of lung, Papillary thyroid carcinoma, Thyroglobulin,

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Lei Zhang¹, Abbey Johnston¹, Natalya Shlyakhova¹, Fritz Lin¹, Richard M. DeMay², Di Lu¹

Affiliations: ¹Department of Pathology, University of California at Irvine, Orange county, CA, USA; ²Department of Pathology, University of Chicago, Cytology division, Chicago, IL, USA.

Corresponding Author: Lei Zhang MD PhD, 1200 Oppenheimer Tower, Los Angeles, CA 90024; Ph: 310-562-1181; Fax: 310-983-3263; Email: lei_248@hotmail.com

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INTRODUCTION

Up to 8% of papillary thyroid carcinoma (PTC) metastasizes to lung, and lung is the most frequent site for PTC metastasis [1]. Therefore, metastasis is an imperative differentiation for a lung mass in a patient with history of thyroid cancer. Even for the PTC at advanced stage, the reported death is extremely rare and many patients benefit from iodine ablation [2]. On the other hand, lung cancer has a five-year survival of 15.6% compared to that of 97.8% in the thyroid cancer per the SEER (surveillance, epidemiology and end results) program; this has made

early diagnosis of lung cancer and timely surgery crucial. The accurate identification of thyroid extension versus new lung primary is of utmost importance.

The incidence of secondary primary tumor after thyroid cancer is 7%, with most of them being in the kidney (3.16%) and breast (1.19%); however, there is no statistics about thyroid and lung primary combination [3]. There are only five cases of metachronous thyroid and lung cancer reported in English literature, one associated with a third primary of larynx squamous cell carcinoma [4] and the other four presenting as thyroid papillary carcinoma metastasis to lung adenocarcinoma [5]. We present an unusual case of metachronous adenocarcinoma of lung clinically masquerading as and morphologically mimicking previously diagnosed papillary thyroid carcinoma, and discuss the overlapping and distinguishing features of these two diseases.

CASE REPORT

A 64-year-old non-smoking Asian female with no known family or cancer history had a total thyroidectomy and lymph node dissection for neck mass lesion. One 2-mm papillary microcarcinoma was identified in the left inferior pole. Six out of thirty lymph nodes are positive for metastasis (6/30). The positive nodes are located in the pre-tracheal, and bilateral neck compartments. The largest positive node measures up to 2.7 cm with extranodal tumor extension present. The pathologic stage is IVA, pT1a, N1b. She had iodine ablation and received thyrotropin suppressive treatment with L-thyroxine. The postoperative I¹³¹ whole body scan (WBS) performed three months after surgery was negative. One year later, a ground glass part-solid mass in the superior segment of left lower lobe of lung was identified during the X-ray surveillance follow-up. She remained asymptomatic. The mass slowly grew increasing in size from 2.4 cm to 3.3 cm over three years (Figure 1). Meanwhile, thyroglobulin has been suppressed and stable (less than 1 ng/ml) with negative anti-thyroglobulin antibody in the serum. The neck ultrasound was unremarkable. Concerning for malignancy, computed tomography (CT) guided core needle biopsy of lung mass was performed.

The touch preparations reveal abundant non-mucinous tumor cells with nuclear inclusions showing spectral change in atypia: round cells with fine chromatin lacking definitive cytoplasmic border, and irregularly shaped cells with coarser chromatin and prominent cell border (Figure 2). Correspondingly, the histology shows the same spectral cells configuring lepidic (hobnail like tumor cells growing along pre-existing alveolar septum) and papillary pattern, which further suggests invasive adenocarcinoma (papillae) arising from in situ component (lepidic architecture) (Figure 3 A–B). Comparative immunohistochemical studies (Figure 4) were performed because of the small size of primary thyroid papillary carcinoma in contrast with

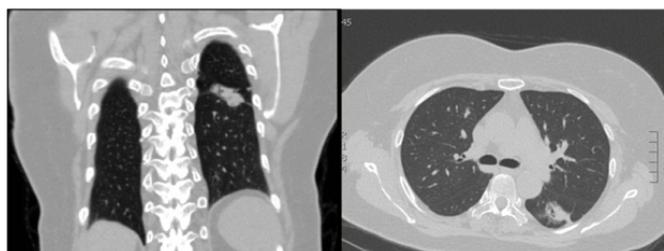


Figure 1: Computed tomography scan of chest without contrast. A part-solid mass in the superior segment of left lower lobe of lung with air bronchogram and peripheral ground glass density (left, coronal section; right, axial section)

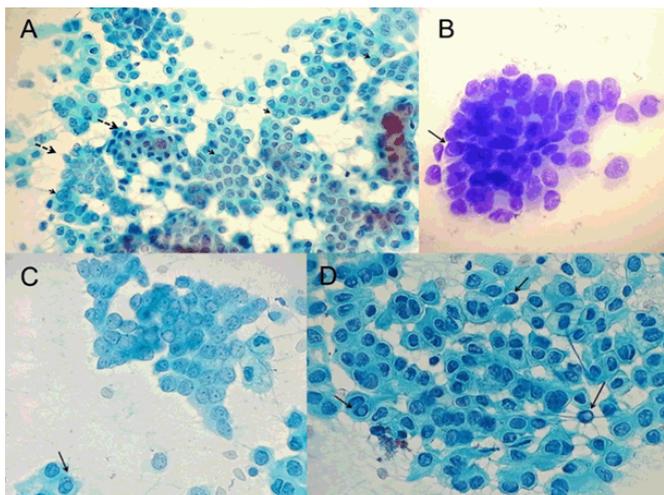


Figure 2: Cytomorphology of touch preparations of CT guided core biopsy of lung lesion showing mosaic of atypical cells with spectrum changes (A, Pap stain): mild atypical round cells with fine chromatin lacking definitive cytoplasmic border (dashed arrow, lower), to more atypical irregularly shaped cells with coarser chromatin and prominent cell border (dashed arrow, upper) and cells showing transition between the two types. High power of cells showing mild atypia is illustrated in C (Pap stain), and moderate atypia in D (Pap stain). Papillary architecture is demonstrated in B (Diff Quik stain). Numerous intranuclear inclusions are indicated by solid arrows in A through D.

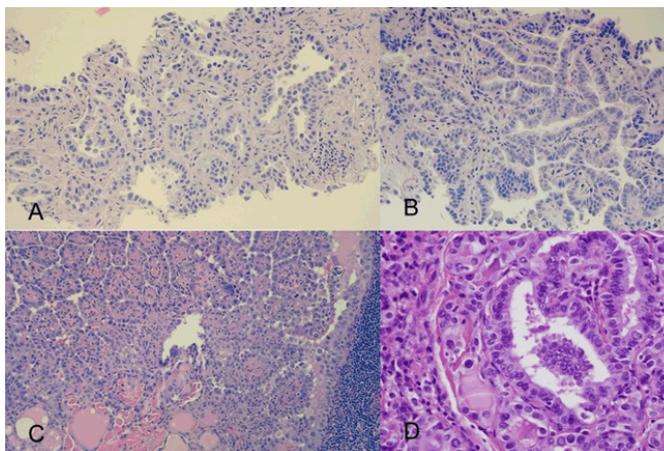


Figure 3: Histology of adenocarcinoma of lung and papillary carcinoma of thyroid. Lung adenocarcinoma shows lepidic growth (A) and papillary architecture (B). Thyroid papillary carcinoma metastasis to the cervical lymph node showing papillae and follicles with colloid (C, D). Nuclear inclusions are seen in both tumors.

extensive neck node metastasis, and similar morphology of lung (Figure 3 A–B) and thyroid lesions. The tumor in lung is positive for surfactant proteins including surfactant protein A (SP-A) and Napsin A, as well as carcinoembryonic antigen (CEA), and negative for thyroglobulin; in contrast, the thyroid lesion is negative for SP-A, CEA and positive for thyroglobulin (Figure 4). The immunophenotype supports metachronous thyroid and lung tumors.

Diagnosis: Metachronous adenocarcinoma of lung

The patient has an elective lung lobectomy in outside hospital and the surgical pathology confirmed the cytology and biopsy interpretation. The patient is followed-up free of disease for six months.

DISCUSSION

Combination of intranuclear pseudoinclusion, fine chromatin and papillary architecture are typical for papillary thyroid carcinoma (PTC). However, these features have also been variably seen in formerly known bronchioloalveolar carcinoma (BAC) non-mucinous type, and papillary adenocarcinoma of lung. Of note, based on prognostic significance, the BAC is relinquished and replaced by subgroups of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma, and lepidic predominant invasive adenocarcinoma per the 2011 new classification system for lung adenocarcinoma [6]. Adapting this classification, uniform round nuclei with fine chromatin are uniquely seen in AIS but not in invasive adenocarcinoma; On the other hand, coarse/dark chromatin seems to be associated with invasive lung adenocarcinoma [6], and has not been described in either AIS of lung or PTC [7]. The spectrum change, e.g., from round nuclei to irregular nuclei, fine chromatin to coarse

chromatin strongly suggests invasive adenocarcinoma of lung arising from in situ.

Histologically, lepidic growth is diagnostic of AIS; all other architectures including papillary, acinar, solid and micropapillary are by themselves indicative of invasion [6]. The mixed patterns of lepidic and papillary subtypes which are positive for surfactant protein SP-A, Napsin A and negative for thyroglobulin are concordant with the cytological impression of in situ and invasive adenocarcinoma of lung, arguing against thyroid metastasis.

Lung adenocarcinoma is believed to proceed from AIS to minimally invasive with predominant lepidic growth, then to fully invasive adenocarcinoma. This prospectation has been recently recapitulated in a mouse model [8]. Following the processes of hyperplasia→ atypical adenomatoid hyperplasia→adenocarcinoma, type II pneumocytes give rise to papillary carcinoma and Clara cells develop lepidic predominant adenocarcinoma [8]. Taking these together and considering that intranuclear pseudoinclusion may occur in type II pneumocytes, it is no surprise that the cytohistological features of nuclear inclusion, lepidic growth and papillary architecture come together in this case. Cytology, histology and molecular pathogenesis are united.

In thin section CT radiographic imaging, AIS is more often seen in the left lobe as a single or multiple nodules, and reflected by ground glass nodule (GGN) with vessels and lung architecture seen through. Solid, part-solid nodule with bubble like appearance or air bronchogram is not excluded from AIS [6, 9]. The presentation of minimal invasive adenocarcinoma is variable, but typically as a GGN with central solid or part-solid consolidation. The appearance of invasive adenocarcinoma can be any patterns described above, and thick coarse speculation has been associated with lymph node metastasis and vascular invasion [6, 9]. The imaging findings of metastatic papillary carcinoma in the lung are most often multiple small nodules which could be indistinguishable from AIS; and rarely, metastatic thyroid carcinoma could present as large solitary nodule which masqueraded as lung primary carcinoma [9]. Overall, the CT findings are diagnostically suggestive but not definitive for lung primary or thyroid metastasis.

Diagnostic or therapeutic dose I¹³¹ can accumulate in the thyroid remnant or thyroid cancer, but variety of unusual lesions including aspergilloma can also trap I¹³¹. Thus, interpretation of I¹³¹ based WBS requires caution to avoid false positivity.

Clinically, the timing of thyroid cancer metastasis to lung can be variable from concurrent, 17 years after thyroidectomy, or before the identification of thyroid lesion [1, 2, 9]. It is usually indolent, same as low grade adenocarcinoma in situ of lung. For thyroid tumor, small tumor size alone is not a reliable prognostic marker. Papillary thyroid microcarcinoma (≤ 10 mm) may have aggressive behavior or be metastatic as are large, differentiated thyroid cancers [2]. In PTC, the odds ratio

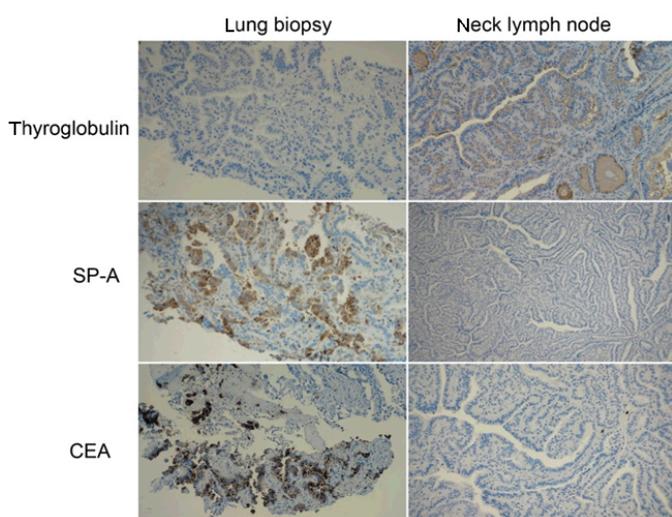


Figure 4: Comparison of immunohistochemical stains of lung biopsy and neck lymph node lesion. The lung nodule showing absence of thyroglobulin and expression of SP-A, CEA (left). The opposite pattern is observed in neck lymph node lesion (right).

for lung metastasis are 9.9, 10.6, 13.8 and 25 respectively for 1-5, 6-10, 11-20 and >20 involved lymph nodes. Categories of 0, 1–20 and >20 lymph nodes metastases correlate better with lung metastasis than current Tumor Node Metastasis (TNM) N categories No, N1a and N1b [1]. Nonetheless, >20 lymph node metastases have a low positive predictive value (22.9%) compared to high negative predictive value (92.7%), which means that despite being classified as high risk in TNM system, the likelihood of being disease free after surgery is still high [1].

TNM system is important for prognosis. However, successful ablation which is established by negative serum thyroglobulin level and negative diagnostic I-131 WBS leads to higher probabilities of favorable outcome regardless of the initial risk. Therefore, several new risk stratification systems have been developed to complement TNM system. Among them, the response to initial therapy of differentiated thyroid cancer predicts the long-term outcome better than other classical systems [10]. In one study, all 176 patients with suppressed thyroglobulin <1 ng/ml, negative neck ultrasound and negative I¹³¹ WBS had no persistent or recurrent disease in the mean follow up of 7 years [10]. Our patient would be at low risk for thyroid disease recurrence based on suppressed thyroglobulin and unremarkable neck ultrasound. The three months post-surgery I¹³¹ WBS was negative. Although I¹³¹ WBS was not performed in the following three years, the non-expression of thyroglobulin in the lung biopsy would portend a negative result.

CONCLUSION

In summary, despite a history of thyroid papillary carcinoma, secondary lung cancer should be considered when serum thyroglobulin level is low. The spectrum of atypia, coarse chromatin and lepidic like growth pattern helps differentiating lung primary cancer from thyroid metastasis morphologically.

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Author Contributions

Lei Zhang – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Abbey Johnston – Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published

Natalya Shlyakhova – Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published

Fritz Lin – Acquisition of data, Analysis and interpretation of data, Final approval of the version to be published

Richard M. DeMay – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Di Lu – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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