

Primary Signet Ring Adenocarcinoma of the Lung in a 34-Year-Old Nonsmoking Man

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ABSTRACT

Background: Pulmonary carcinoma is a burdensome malignancy that has the third rank in prevalence among other cancers and is the leading cause of death in patients with cancer diagnosis. Signet ring morphology is encountered commonly in many sites like stomach, bladder, gallbladder and etc. Primary signet ring adenocarcinoma of the lung is a rare phenomenon, including about 5% of all surgically removed pulmonary adenocarcinoma. It should be distinguished from metastatic tumors.

Case presentation: a 34-year-old nonsmoker man who referred to Babol Rohani Hospital with a one-month history of nonproductive cough. Biopsy with CT scan guidance from ground-glass opacities of the left lung revealed neoplastic cells with signet ring appearance infiltrating lung parenchyma. Immunohistochemistry (IHC) study revealed positivity of neoplastic cells for AE1/AE3, CK7, TTF-1 and negativity for CK20, CDX2, and CD68.

Conclusion: The signet ring feature of pulmonary adenocarcinoma has shorter survival, therefore, it is associated with poor prognosis. Immunohistochemistry (IHC) techniques provide the ability to originate tumor cells in these conditions.

Keywords: Signet ring, Adenocarcinoma, Lung cancer

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Introduction

Pulmonary carcinoma is a burdensome malignancy that has the third rank in prevalence among other cancers and is the leading cause of death in patients with cancer diagnosis (1, 2) but it is less prevalent in some areas of Iran (3). Signet ring morphology is encountered commonly in many sites like stomach, bladder, gallbladder and etc. but it is rather uncommon in lung, including around 5% of all surgically removed primary carcinomas (4). So it is important to search for other origins and rule out metastasis (5). In past, pulmonary adenocarcinoma with signet ring feature was considered as a distinct subtype of lung adenocarcinoma (6) but according to the WHO classification of lung tumors in 2015, it is a cytological change seen in several main histological types (7).

The signet ring feature most commonly occurs with solid subtype of adenocarcinoma, therefore, it results in poor outcome (4, 8, 9). In a study by Castro et al. (2001), 11 out of 15 patients with this diagnosis have a survival rate less than 36 months (10).

The lack of sufficient cases in this uncommon feature motivated us to report this case. It is important to diagnose this morphology correctly because today many studies focus on molecular testing and therapeutic options (11-13). Recently, it has been discovered that a high proportion of patients with this finding have ALK gene rearrangement (14, 15) and benefit from Crizotinib, an ALK and ROS1 inhibitor (8).

In addition, it is more commonly associated with poorly differentiated tumor and stage IV disease (16).

Case presentation

The patient was a 34-year-old nonsmoker man who referred to Babol Rohani Hospital with a one-month history of nonproductive cough. He had dyspnea and chest pain for two weeks and 10 kg weight loss during the last month. No history of fever, hemoptysis or any significant prior disease or medication were found. Physical examination revealed no abnormal finding. Vital signs were stable and chest auscultation was clear.

Materials and Methods

Lab tests were normal, and conventional sputum culture and smear and culture for tuberculosis were also negative. Paraclinical investigations showed bilateral pleural effusion, hilar prominence, diffuse ground-glass opacities, and septal thickening in chest spiral CT scan (Figure 1A and B). Pleurocentesis was performed. Additional tests were requested. Upper and lower GI endoscopy, echocardiography, and abdominopelvic ultrasonography were normal. Patient underwent fiberoptic bronchoscopy, and nodularity was identified in right main bronchus. Bronchoalveolar lavage was carried out but needle biopsy could not be obtained so Core needle biopsy with CT scan guidance was requested from ground-glass opacities of the left lung.



Figure 1. A. CT scan of chest presenting bilateral pleural effusion and (B) ground-glass opacities in parenchymal window.

Cytology of BAL showed the presence of malignant cells. The tissue obtained from biopsy processed and H&E sectioned slides revealed neoplastic cells with signet ring appearance infiltrating lung parenchyma (Figure 2-A and B).

For immunohistochemistry study for AE1/AE3, CK7, TTF-1, CK20, CDX2, and CD68 ((Dako, Glostrup, Denmark) was performed. Sections were dewaxed at 60°C in an oven for about one hour, and then they were put in xylol and rehydrated through a descending concentration of ethanol. For antigen retrieval, sections were microwaved for 15 minutes in ethylenediaminetetraacetic acid (EDTA) buffer (pH=9). Sections were left at room temperature for 15 minutes to cool down. They were washed in trisbuffered saline (TBS) for five minutes and incubated in 3% H₂O₂ in dark humid condition.

After that, they were washed in TBS for five minutes. Sections were incubated with primary antibody for 60 minutes at room temperature and with secondary antibody for 30 minutes. Sites of binding were detected by a 10-minute incubation with diaminobenzidine (DAB).

Results

Immunohistochemistry (IHC) study revealed positivity of neoplastic cells for AE1/AE3, CK7, TTF-1 and negativity for CK20, CDX2, and CD68 (Figure 2-C and D). Due to these findings, adenocarcinoma of lung, signet ring variant was reported for patient. Due to extensive nature of tumor, no further surgical procedure was performed on patient and despite administration of dense chemotherapy regimen, patient died of carcinomatosis 6 months later.

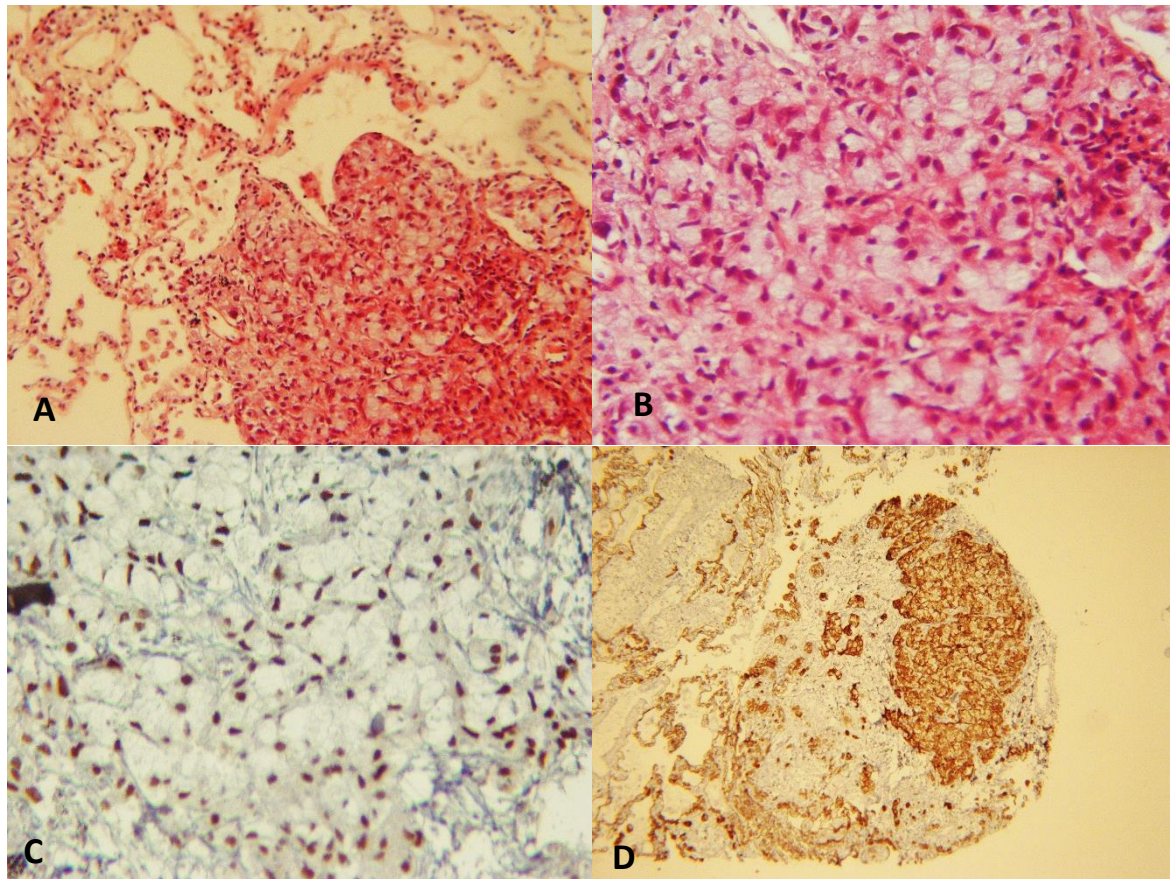


Figure 1. A. Tumor cells infiltrated lung parenchyma (HE stain, $\times 100$); B. Tumor cells had signet ring appearance (HE stain, $\times 400$); C. Tumor cells showed nuclear reactivity with TTF-1 (TTF-1 IHC $\times 400$); D. Tumor cells showed reactivity with cytokeratin 7 (CK7 IHC $\times 100$).

Discussion

Signet ring variant of primary pulmonary adenocarcinoma is a rare finding (17). In the process of diagnosis, it is important to rule out metastasis from other organs, among which signet ring carcinoma is more prevalent,

especially gastrointestinal tract. Nowadays, this issue could be conquered with utilization of IHC technique. Many studies focused on this method and a wide range of markers are now available. It is important to choose the most appropriate markers.

Report of 17 cases with signet ring carcinoma of the lung, demonstrated 82.4% positivity for TTF-1 and 94% for CK7+/CK20- pattern (18).

Another study on 15 cases with the same diagnosis showed 100% TTF-1 and CEA positivity and 50% CK7 positivity. In this study, CK20, ER, PR, and GCDFP15 were all negative (10).

In present case, CK7 and CK20 were requested for originating tumor. The pattern of staining (CK7+/CK20-) raise the possibility of pulmonary, gastrointestinal tract (specially stomach), breast, salivary, and thyroid carcinoma. TTF-1 and CDX2 were requested and TTF-1 positivity suggested primary pulmonary adenocarcinoma.

The same findings were observed by Vallonthaiel et al. (2016) who studied 11 cases of pulmonary adenocarcinoma with signet ring feature. All cases were positive for TTF-1. They also assessed ALK rearrangement by IHC, which was positive in 7 cases (1).

In the study of Ou et al. (2010), patients with signet ring adenocarcinoma of the lung were more likely to be nonsmokers and younger with worse prognosis compared to other types of adenocarcinoma (8). Our case was a young nonsmoker man who died after 6 months of diagnosis despite all struggles.

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Further studies focusing on target therapies for this kind of tumor to improve survival rate are recommended.

Conclusion

In this report, we presented a case with a rare subtype of pulmonary adenocarcinoma and its IHC profile. The signet ring feature of pulmonary adenocarcinoma has shorter survival, therefore, it is associated with poor prognosis. Lung is a common site for metastasis, and Immunohistochemistry (IHC) techniques provide the ability to originate tumor cells in these conditions.

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Conflict of interests

The authors declare that there is no conflict of interests.

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