

## Case Report

# Primary signet-ring cell carcinoma of the lung: a case report with an immunohistochemical study

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**Abstract:** Primary signet-ring cell adenocarcinoma (SRCA) of the lung is very rare. A 78-year-old man consulted to our hospital because of loss of appetite. Physical examination showed lymphadenopathy of the cervical lymph nodes. Chest X-ray showed a tumor of the right upper lobe. Blood laboratory test showed an increase of LDH and CRP. Tumor markers (CYFRA, SCC, CEA, ProGRP) were within normal range. Clinical diagnosis was suspected malignant lymphoma of the lung. Transbronchial lung biopsies showed SRCA (70%) mixed with poorly differentiated adenocarcinoma (30%). The SRCA cells were positive for mucins. Immunohistochemically, the SRCA cells were positive for cytokeratin (CK) AE1/3, CK CAM5.2, CK7, CK18, EMA, p53, Ki-67 (labeling=60%), CEA, CA19-9, TTF-1, and MUC1. They were negative for CK34BE12, CK5/6, CK8, CK14, CK19, CK20, vimentin, chromogranin, synaptophysin, CD45, CD20, CD3, surfactant Apoprotein-A, CDX-2, MUC2, MUC5AC and MUC6. A pathological diagnosis of SRCA of the lung was made. The patient showed downhill course, and died of carcinomatosis 3 months after the first manifestation. In conclusion, a vary rare case of primary pulmonary SRCA was reported with an immunohistochemical study.

**Keywords:** Lung, signet ring cell adenocarcinoma, histopathology, immunohistochemistry

## Introduction

Extragastric signet-ring cell adenocarcinoma (SRCA) is very rare. In the lung, only several case reports and series of primary SRCA of the lung have been reported [1-4]. However, only a few studies have been performed on immunohistochemical studies of primary pulmonary SRCA [1-3], and extensive immunohistochemical study has not been performed in pulmonary SRCA. Herein reported is a very rare case of primary SRCA of the lung clinically diagnosed as malignant lymphoma.

## Case report

A 78-year-old man consulted to our hospital because of loss of appetite. Physical examination showed lymphadenopathy of the cervical lymph nodes. Chest X-ray showed a tumor of the right upper lobe. Blood laboratory test showed an increase of LDH (406 IU/L) and CRP (6.0 mg/ml). Tumor markers (CYFRA, SCC, CEA, ProGRP) were within normal range. Imaging techniques including CT demonstrated a 3.5 cm

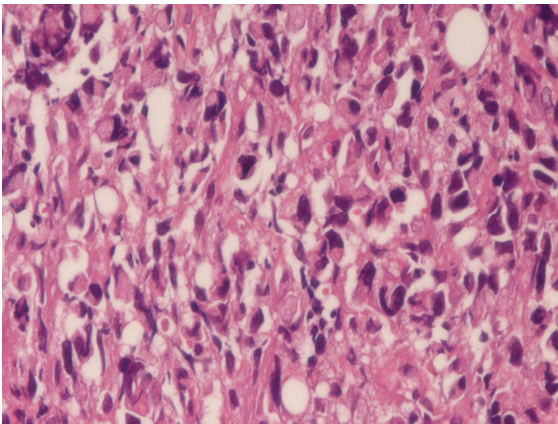


**Figure 1.** Chest CT. It demonstrates a 3.5 cm tumor (arrow) in the right upper lobe of the lung. Pleural effusion is also seen.

tumor in the right upper lobe of the lung (**Figure 1**). Upper and lower gastrointestinal endoscopy revealed no tumors. Imaging modalities did not demonstrate other tumors. Therefore the lung tumor or cervical lymph nodes appeared primary. Because of lymphadenopathy and in-

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creased LDH, the clinical diagnosis was suspected malignant lymphoma of the lung.

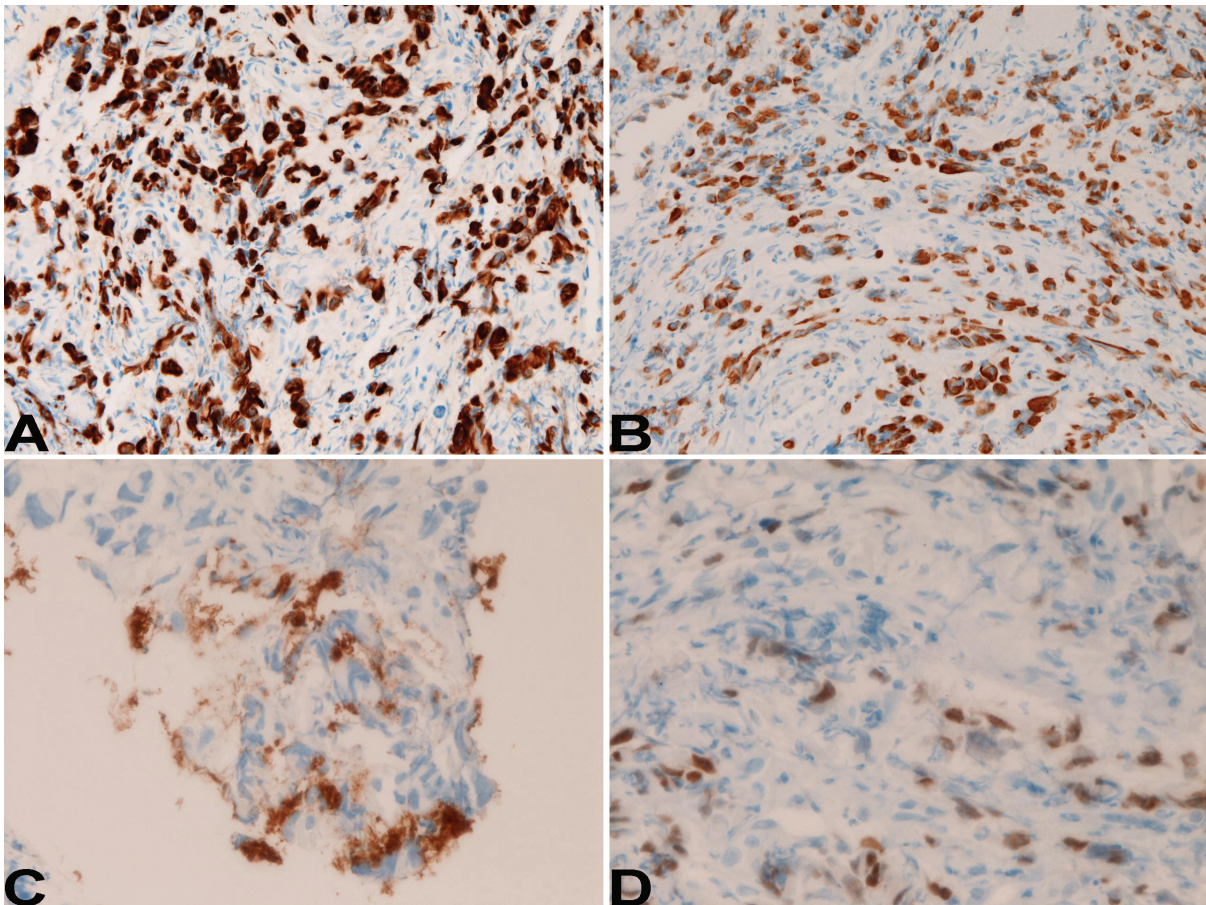


**Figure 2.** Biopsy features. The biopsy shows typical signet ring cell adenocarcinoma. HE,  $\times 200$ .

Transbronchial lung biopsies were performed and they showed SRCA mixed with poorly differentiated adenocarcinoma cells (**Figure 2**). The former accounted for 70% and the latter 30%. The SRCA cells were positive for mucins.

An immunohistochemical study was performed with the use of Dako Envision method, as previously described [5, 6]. Immunohistochemically, The SRCA cells were positive for cytokeratin (CK) AE1/3 (**Figure 3A**), CK CAM5.2, CK7, CK18 (**Figure 3B**), EMA, p53, Ki-67 (labeling=60%), CEA (**Figure 3C**), CA19-9, TTF-1 (**Figure 3D**), and MUC1. They were negative for CK34BE12, CK5/6, CK8, CK14, CK 19, CK20, vimentin, chromogranin, synaptophysin, CD45, CD20, CD3, surfactant Apoprotein-A, CDX-2, MUC2, MUC5AC and MUC6. A pathological diagnosis of SRCA of the lung was made.

The patient showed downhill course. Massive



**Figure 3.** Immunohistochemistry. The tumor cells are positive for cytokeratin AE1/3 (A), cytokeratin 18 (B), CEA (C), and TTF-1 (D). Immunostaining,  $\times 200$ .

pleural effusion emerged, and clinical cytology revealed malignant cells in the pleural effusion. The lung tumor became infiltrative, and superior vena cava syndrome appeared. The patient died of carcinomatosis 3 months after the first manifestation.

### Discussion

Extragastric SRCA is very rare. In the lung, several case reports and case series of primary SRCA have been reported [1-4]. Most of the cases of gastric and lung SRCA, signet-ring carcinoma cells are present in addition to other histological subtypes such as mucinous carcinoma and tubular carcinoma [4]. Therefore, in general, adenocarcinoma with more than 50% signet-ring cell carcinoma cells is called SRCA [4]. In the present case, the percentage of signet-ring cell carcinoma cells was 70%, thus fulfilling the diagnosis of primary SRCA of the lung.

In making the diagnosis of extragastric SCRA, it is very important to exclude metastatic SRCA from the stomach, breast and other organs. In the present case, the other organs including stomach and breast were radiologically free from tumors. In addition, TTF-1 was positive immunohistochemically. Thus, the present case is primary pulmonary SRCA. In the lung SRCA, the clinicopathology was unclear, because of the rarity of lung SCRA. According to the largest series (n=39) [4], lung carcinoma with signet-ring cell components accounted for 1.5% (39/2640) of all lung malignancies. The mean age was 54.6 years (range 32-76 years). The male to female ratio was 1.16:1.00, and 5-year survival was 28% [4]. The present case is a 78-year-old man, and the survival was only 3 months.

Three immunohistochemical studies are available in lung SRCA [1-3]. Hayashi et al [1], who reported 5 cases of lung SRCA, showed that 80% (4/5) was immunoreactive for lactoferrin, 100% (4/4) showed k-RAS mutations, 100% (5/5) was positive for MUC1, and 100% (5/5) was negative for MUC2. Merchant et al [2], who investigated 17 cases of lung SRCA, showed that 82.4% (14/17) showed TTF-1 positivity, CK7+ / CK20 - pattern was seen in 94% (16/17). Villin expression was seen in 29.4% [2]. Castro et al [3], who examined 15 cases of lung SCRA, showed immunoreactivity of TTF-1 (100%, 6/6), CEA (100%, 9/9), and CK7 (50%, 3/6). CK20, estrogen receptor, progesterone

receptor, and GCDFFP-15 were negative [3].

In the present bronchial SRCA, the cytokeratin profile was as follows: CK AE1/3 +, CK CAM5.2 +, CK7 +, CK18 +, CK34BE12 -, CK5/6-, CK8-, CK14-, CK19-, and CK20-. Thus, it is thought that the SRCA cells of the lung shows low-molecular weight cytokeratin. The CK7+/CK20-pattern is consistent with pulmonary SRCA cases of Merchant et al [2]. In the current case, immunoreactive CEA was positive, being compatible with lung SRCA cases of Castro et al [3]. CA19-9 and EMA were positive in the present study, indicating that these molecules are present in the pulmonary SRCA. In the present case, Ki-67 labeling is high (60%), indicating active proliferation. In the present case, p53 was positive, suggesting p53 mutations. TTF-1 was positive in the current case, suggesting the lung primary. In the present study, MUC1 was positive, while MUC2, MUC5AC and MUC6 were negative. MUC1 positivity and MUC2 negativity were reported in lung SRCA [1], being compatible with pulmonary SRCA in the present case. In addition, the current case was negative for MUC5AC and MUC6, suggesting that MUC1 gene is operative while genes of MUC2, MUC5AC and MUC6 were not expressed. In the present study, there were no immunoreactivity of p63, CD3, CD20, CD45, vimentin, chromogranin, synaptophysin, surfactant apoprotein A, and CDX-2. p63 negativity may show the present case was not related to squamous cells or myoepithelial cells. The negative immunoreactivities of CD3, CD20 and CD45 indicate that the tumor cells are not malignant lymphoma cells. Vimentin, a mesenchymal marker, was negative, as expected. The negative reaction of chromogranin and synaptophysin indicate that the present tumor has not neuroendocrine features and is not a large cell neuroendocrine carcinoma. Surfactant apoprotein A was negative. This protein is well known to have low sensitivity. The negativity of this protein may be due to the low sensitivity. In the present case, CDX2 was negative, suggesting that the present case was not associated intestinal phenotypes.

In conclusion, a very rare case of SCRA of the lung was described with an immunohistochemical study.

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### References

- [1] Hayashi H, Kitamura H, Nakatani Y, Inayama Y, Ito K, Kitamura H. Primary signet-ring cell carcinoma of the lung: histochemical and immunohistochemical characterization. *Hum Pathol* 1999; 30: 378-383.
- [2] Merchant SH, Amin MB, Tamboli P, Ro J, Ordonez NG, Ayala AG, Czemiak BA, Ro JY. Primary signet-ring cell carcinoma of lung: immunohistochemical study and comparison with non-pulmonary signet-ring cell carcinoma. *Am J Surg Pathol* 2001; 25: 1515-1519.
- [3] Castro CY, Moran CA, Flieder DG, Suster S. Primary signet ring cell adenocarcinoma of the lung: a clinicopathological study of 15 cases. *Histopathology* 2001; 39: 397-401.
- [4] Tsuta K, Ishii G, Yoh K, Nitadori J, Hasebe T, Nishiwaki Y, Endoh Y, Kodama T, Nagai K, Ochiai A. Primary lung carcinoma with signet-ring cell carcinoma components: clinicopathological analysis of 39 cases. *Am J Surg Pathol* 2004; 28: 868-874.
- [5] Terada T, Kawaguchi M, Furukawa K, Sekido Y, Osamura Y. Minute mixed ductal-endocrine carcinoma of the pancreas with predominant intraductal growth. *Pathol Int* 2002; 52: 740-746.
- [6] Terada T, Kawaguchi M. Primary clear cell adenocarcinoma of the peritoneum. *Tohoku J Exp Med* 2005; 206: 271-275.