

A Rare Case of Pulmonary Anaplastic Lymphoma Kinase Positive Signet Ring Cell Carcinoma in A Japanese Male

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Abstract

Here, we report an exceedingly rare case of pulmonary cancer, composed of more than 70% Signet Ring Cells (SRC) in a Japanese male in his early 70s. Computed tomography detected the tumor shadow in the right lower lobe of the lung revealing a size of 1.1 cm × 0.7 cm × 0.7 cm. The SRCs were positive for *Cytokeratin 7 (CK7)*, *Thyroid Transcription Factor-1 (TTF-1)*, and *Anaplastic Lymphoma Kinase (ALK)*.

The presence of SRC indicates one of the worst prognostic factors for patients with pulmonary cancer, based on the statistical analysis of *ALK*-positive cases. The possibility of the 5 year survival was reported to be only 11%. The anti-*ALK* inhibitor crizotinib has been applied in practical clinical therapy and obtained partial remission. However, drug resistance is exhibited in SRC cancer. This is a significant concern for future clinical application of the drug for this type of lung cancer that exhibits poor prognosis. However in our report, no recurrence or distant metastasis was detected in the patient 15 months after operation despite not using crizotinib.

Finally, the composition of SRC in lung cancer should be considered for the patient's prognosis, especially when *ALK* -positivity is detected.

Keywords: Pulmonary cancer; Signet ring cell carcinoma; Histopathology; Immunohistochemistry; *ALK*-positivity

Introduction

Signet Ring Cell (SRC) type cancer cells are extremely rare among primary pulmonary cancers. Since it was first reported in 1989 [1], only 5 out of 3,500 lung cancers cases (0.14%) containing SRC were reported [2-4]. However, only two reports collected data on SRC cancer cases [5,6], where the clinicopathological features of this type of cancer were clarified. Presently, there is no strict definition for the diagnosis of SRC lung cancer. Previous reports indicate that the prevalence of SRC in cancer ranges between 5 and 50% [1,7,8]. The proportion of SRC in the cancer is reported to be a prognostic factors [3,9,10]. Statistically, patients with SRC cancer are relatively younger,

and the prognosis is poorer than in other pulmonary cancers [1,4]. Another characteristic of SRC cancer is that it is often positive for *Anaplastic Lymphoma Kinase (ALK)* [11,12]. The positive percentages of *ALK* in Non-Small Cell Lung Cancer (NSCLC) were approximately 5%-6% in both Western and Asian countries [11]. The anti-*ALK* drug crizotinib is effective for *ALK*-positive cases, and it has already been applied in clinical practice [13,14]. This drug might be a valuable tool for the treatment of SRC cancer, although *ALK*-positive SRC cancer cases are rare [13,14].

We report a case of an *ALK*-positive pulmonary SRC cancer, composed predominantly of SRC.

Case Presentation

Clinical findings

The patient was a Japanese man in his early 70s. He had suffered from benign prostatic hyperplasia in his late 60s. The patient had a history of smoking from 20-45 years of age (20 cigarettes per day).

After screening, an abnormal shadow was detected in the lower lobe of the right lung. Because the shadow was suspected to be lung cancer, the patient returned to our hospital for a more precise examination.

Chest Computed Tomography (CT) findings demonstrated the tumor close to the sub pleural bulla at the right S8 area. The tumor was solid and 1.1 cm × 0.7 cm × 0.7 cm in size on CT (Figure 1). Under thoracoscopic operation, a portion of the tumor was removed. The tumor was diagnosed as SRC cancer based on the results of the frozen section examination. The tumor and right lower lobe were excised with the regional lymph nodes. Then excised pulmonary tissue was fixed in 10% buffered formalin to prepare the tumor for further examination. The patient was disease free with no recurrence or distant metastasis 15 months after the operation.

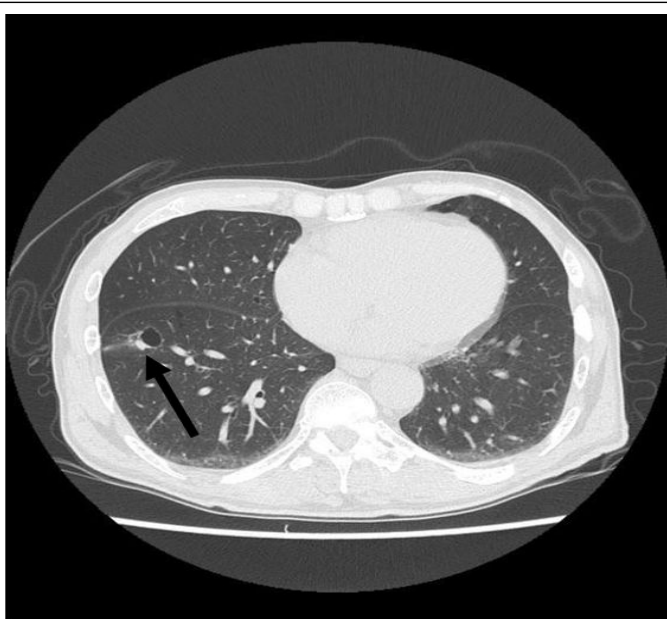


Figure 1: Finding of computed tomography of the tumor. An arrow indicates the tumor locating close to a cyst.

Pathological findings

The tumor cells were arranged in solid, trabecular, papillary patterns. Approximately more than 70% of tumor cells were occupied by SRC located in the center of the tumor and had an irregular growth pattern at the periphery with no capsule. The cytoplasm of SRC appeared light eosinophilia granules with crescent-shaped nuclei. The SRC were relatively uniform. There was no mitosis. Interestingly the transitions from non-SRC cells to SRC clusters were noted. No vascular and pleural invasions were detected. No cancer metastasis was found in the resected lymph node. The margins of the resected lung were negative.

The cystic cavities near the tumor were considered as emphysematous bulla due to the effect of smoking.

Upon examination, no lesions were found in the gastrointestinal tract.

According to the classification rule, this case is as follows,

RLL, S8, 1.1 cm × 0.7 cm × 0.7 cm in CT, and 0.8 cm × 0.5 cm in maximum cut section of Hematoxylin and Eosin (H&E) stain, adenocarcinoma (sig, more than 70%>solid), pT1a, ly0, v0, pbr-, pa-, pv-, pm0, pl0, pN0(0/8; #7:0/4, #11i:0/2, #12i:0/2), p Stage IA1. In Mucin stains, the cytoplasm of SRC was positive with Periodic Acid Schiff (PAS) reaction, disclosing resistance to diastase-digestion. In Alcian Blue (AB) stain, the cytoplasm of SRC was also positive with hyaluronidase resistance.

In immunohistochemistry, antibodies used were prediluted AE1/AE3, CK20, CDX-2, ALK (p80NAM), each from DAKO, and prediluted CAM5.2, CK7, Napsin A from Roche.

Immunohistochemical results of SRC cancer disclosed positive for cytokeratins, such as AE1/AE3, CK7, CAM5.2, but not CK20 and CDX-2. All of cancer cells including SRC cells were positive with anaplastic lymphoma kinase (ALK, p80NAM) and Napsin A, also showing nuclear positivity with TTF-1.

From the results of the H&E and Mucin stains, and the immunohistochemistry, although fusion gene products of *Echinoderm Microtubule-associated Protein-Like 4 (EML4)-ALK* could not be tested yet at molecular level, the pulmonary tumor was diagnosed as a case of ALK-positive SRC cancer located in the right lower lobe of the lung (Figures 2 and 3).

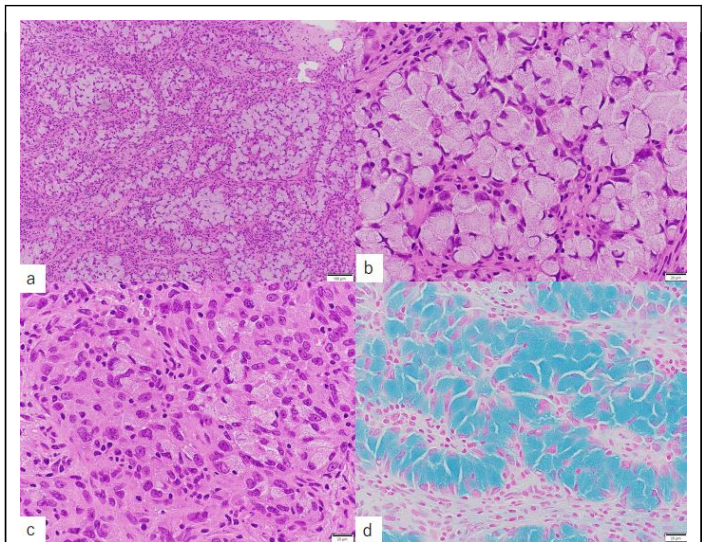
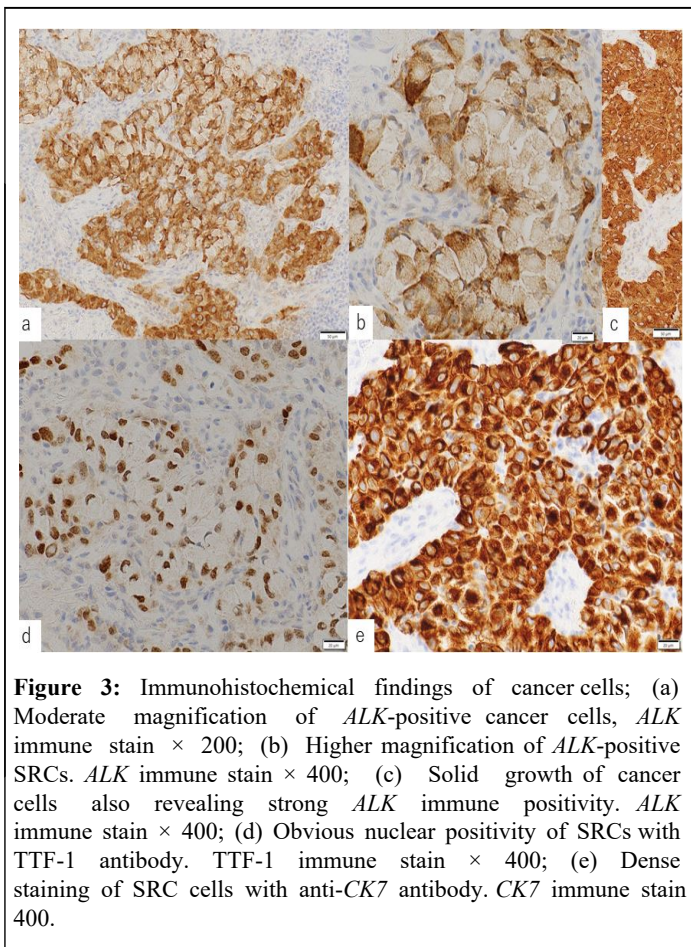


Figure 2: Histopathology of the tumor. (a) Lower magnification of the dense aggregation of Signet Ring Cancer Cells (SRCs). HE stains × 100; (b) Moderate magnification of the part of pure growth of SRCs. HE stains × 200; (c) Higher magnification of the solid proliferation of cancer cells, intermingling a small number of SRCs. HE stains × 400; (d) Strongly positive Alcian Blue (AB) stain of the cytoplasm of SRCs. AB stain, × 400.



Discussion

Among lung cancer, SRC cancer accounted for only 0.14 to 1.9% as reported [1,2]. And most of the cases were positive with Thyroid Transcription Factor-1 (TTF-1), although negative cases have also been reported [15]. From cases (262 cases 5 or 738 cases 6) collected and analyzed, the patients with SRC cancer were younger, and more often distant metastases were detected, resulting in worse prognosis. The five-year survival rate was reported to be 11% [6]. On the other hand, non-smokers are reported to account for 66.7% of patients, 9 including ex-smoker similar to the present case.

In SRC cancer, *ALK*-positive cases were often reported as in the present case. Among NSCLC, it was reported that in Asian countries, *EML4-ALK* fusion genes were detected 6.7% (5/75 cases) [16], and that in Western countries, *ALK*-positive NSCLC was 5.6 % (20/358 cases) [11].

According to the reports collected, nine cases of *ALK*-positive SRC cancer, 4 cases were positive with *EML4-ALK* fusion gene [16]. Recently, if *EML4-ALK* molecular product is not detected, the diagnosis would be based on *ALK*-immunopositivity as well as histopathological characteristics and usual immune reaction, such as TTF-1, Epithelial Membrane Antigen (EMA), *Cytokeratin 7 (CK7)*, and CAM5.2.

CDX-2 positive cases were detected in 12% [17], although negative in the present case. As reported, the population of SRCs adversely affects the patients prognosis [9], and can subsequently affect one of the prognostic markers [9,10].

ALK-positive cases generally carry the *EML4-ALK*-fusion gene product, as reported [16]. *ALK* inhibitor, crizotinib was applied 13 Partial remission was attained after one month; however, drug resistance was exhibited in SRC cancer [13].

In the present case targeted therapy was not clinically applied, fortunately 15 months after operation, the patient was disease free with no sign for recurrence or distant metastasis. Drug resistance is an important and serious issue for future treatment of this type of lung cancer. Future studies should focus on this point to improve the treatment efficacy of *ALK*-positive SRC cancers. In addition, the SRC component, if present in lung adenocarcinoma should be noted for proper prognosis.

Conclusion

We report a very rare case of primary pulmonary SRC cancer in the right lower lobe of the lung of a Japanese male in his early 70s. The SRCs were arranged in trabecular, solid or papillary pattern disclosing strong PAS, D-PAS, AB and D-AB Mucin stains. In addition, SRC cancer could be immunopositivity related with *ALK*, in addition to AE1/3, CAM5.2, *CK7*, EMA, TTF-1 and Napsin A. Although anti-*ALK* targeted drug, crizotinib, was not administered, the present case is alive, 15 months after the operation exhibiting no cancer metastasis and recurrence. We report an exceedingly rare case of SRC cancer of the lung in a Japanese male, *ALK*-immunopositivity. Finally, if SRC component is present, it should be noted for proper prognosis.

Author's Contributions

SF, TO, WK contributed the management of this patient. YO and SF were the leaders of the clinicopathological team, and YO and YH conducted the literature review and wrote the manuscript. YO revised the article. All the authors read and approved the final manuscript.

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Conflict of Interest

The authors have no conflicts of interest to declare.

Consent for Publication

Written informed consent was obtained from the patient.

References

1. Kish JK, Ro JY, Ayala AG, McMurtry MJ (1989) Primary mucinous adenocarcinoma of the lung with signet-ring cells: A Histochemical comparison with signet-ring cell carcinoma of other sites. *Hum Pathol* 20: 1097-1102.
2. Castro CY, Moran CA, Flieder DG, Suster S (2001) Primary signet ring cell adenocarcinoma of the lung: A Clinicopathological study of 15 cases. *Histopathology* 39: 397-401.

3. Terada T (2012) Primary signet ring cell carcinoma of the lung: A Case report with an immunohistochemical study. *Int J Clin Exp Pathol* 5: 171-174.
4. Wang Y, Wang Y, Li J, Che G (2020) Primary signet-ring cell carcinoma of the lung: A Report of seven cases. *Thoracic Cancer* 11: 3015-3019.
5. Ou SH, Ziogas A, Zell JA (2010) Primary Signet-Ring Carcinoma (SRC) of the lung: A Population-based epidemiologic study of 262 cases with comparison to adenocarcinoma of the lung. *J Thorac Oncol* 5: 420-427.
6. Wu SG, Chen XT, Zhang WW, Sun JY, Li FY, et al. (2018) Survival in signet-ring cell carcinoma varies based on primary tumor location: A surveillance, epidemiology, and end results database analysis. *Expert Rev Gastroenterol Hepatol* 12: 209-214.
7. Rajkumar A, Li J, D'cruz C, Patel K, Elreda L (2014) Pure signet-ring cell carcinoma of lung by fine needle aspiration in a smoking Asian American: Case report and literature review. *J Clin Exp Pathol* 4: 155.
8. Yang M, Yang Y, Chen J, Stella GM, UM S-W, et al. (2021) A Case report of primary signet ring cell carcinoma of the lung: Imaging study and literature review. *Transl Lung Cancer Res* 10: 3840-3849.
9. Tsuta K, Ishii G, Yoh K, Nitadori J, Hasebe T, et al. (2004) Primary lung carcinoma with signet-ring cell carcinoma component; Clinicopathologic analysis of 39 cases. *Am J Surg Pathol* 28: 868-874.
10. Iwasaki T, Ohta M, Lefor AT, Kawahara K (2008) Signet-ring cell carcinoma component of in primary lung adenocarcinoma: Potential prognostic factor. *Histopathology* 52: 639-640.
11. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, et al. (2009) Unique clinicopathologic features characterize *ALK*-rearranged lung adenocarcinoma in western population. *Clin Cancer Res* 15: 5216-5223.
12. Yoshida A, Tsuta K, Watanabe S, Sekine I, Fukayama M, et al. (2011) Frequent *ALK* rearrangement and TTF-1/p63 co-expression in lung adenocarcinoma with signet- ring cell component. *Lung Cancer* 72: 309-315.
13. Hao YQ, Tang HP, Liu HY (2015) Primary signet-ring cell carcinoma of the lung treated with crizotinib: A case report. *Oncol Lett* 9: 2205-2207.
14. Muscarella LA, Trembetta D, Fabrizio FP, Scarpa A, Fazio VM, et al. (2017) *ALK* and *NRG 1* fusions coexist in a patient with signet ring cell lung adenocarcinoma. *J Thorac Oncol* 12: E161-E163.
15. Narita D, Miyauchi E, Saito R, Eba S, Okada Y, et al. (2020) A case of lung adenocarcinoma with signet ring cell carcinoma features diagnosed by thoracoscopic lung resection. *AJRS* 9: 345-349.
16. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, et al. (2007) Identification of the transforming *EML4-ALK* fusion gene in non-small-cell-lung cancer. *Nature* 448: 561-566.
17. Cowan ML, Li QK, Illei PB (2016) *CDX-2* expression in primary lung adenocarcinoma. *Appl Immunohistochem Mol Morphol* 24: 16-19.