Ground-glass nodule in a patient with echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK)-positive lung cancer: a case report

Yuki Owada¹,², Atsushi Yonechi¹,², Mitsunori Higuchi² and Hiroyuki Suzuki²*

Abstract

Background: Grand-glass nodule for CT image has thought to be less aggressive tumor in lung cancer. Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK)-positive lung cancer presenting with Ground-glass nodules (GGNs) is relatively rare, and few such cases have been reported.

Case presentation: An asymptomatic 56-year-old woman exhibited a 1.1-cm GGN in the lower lobe of the left lung on computed tomography during a medical checkup. Positron emission tomography showed no difference in uptake by the nodule compared with other organs. We elected to perform surgery because the nodule included a solid component and had grown only slightly during the last 2 years according to thin-section computed tomography. Partial resection of the lower left lung was performed by video-assisted thoracic surgery. Pathological examination revealed mucus-producing high columnar epithelium forming an irregular tubular-acinar-like structure partly replacing the alveolar epithelium on hematoxylin and eosin staining. More than 50 % of the tumor demonstrated a lepidic growth pattern. The tumor was negative for epidermal growth factor receptor mutation but positive for the EML4-ALK fusion oncogene according to fluorescence in situ hybridization.

Conclusions: We herein report a case of EML4-ALK-positive lung cancer presenting with a GGN along with a review of the relevant literature, including histopathological findings and imaging features. We consider that EML4-ALK-positive lung cancer is often highly progressive and that careful follow-up is therefore essential in these patients.

Keywords: Lung cancer, EML4-ALK-positive, Ground-glass nodule, Surgery

Background

Almost all ground-glass nodules for computed tomography (CT) image have thought to be less aggressive tumor in lung cancer. However, we find that there are a few GGN that would potentially be a progressive type. Here, we show a case of lung cancer with EML4-ALK positive that shows GGN for CT with potentially aggressive.

Case presentation

An asymptomatic 56-year-old woman with no smoking history exhibited a 1.1-cm ground-glass nodule (GGN) in the lower lobe of the left lung on CT during a medical checkup (Fig. 1a). Positron emission tomography showed no difference in uptake by the nodule compared with other organs (Fig. 2). All tumor markers were within the normal range. Over 2 years, the size of the nodule had grown from 0.9 to 1.1 cm according to thin-section CT (Fig. 1b); thus, the patient was clinically suspected of having lung cancer. Transbronchial lung biopsy was not performed before surgery because the nodule was small and peripherally located. We elected to perform surgery

* Correspondence: hiro@fmu.ac.jp
¹Department of Regenerative Surgery, School of Medicine, Fukushima Medical University, 1 Hikarioka, Fukushima 960-1295, Japan
Full list of author information is available at the end of the article

© 2016 Owada et al. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
for both diagnosis and treatment. Partial resection of the lower left lung was performed by video-assisted thoracic surgery. The tumor with a slight change in the visceral pleura was confirmed macroscopically. We got a judgement of a not invasive tumor by intraoperative pathological diagnosis; thus, lymph node excision has not been done. Finally, pathologically, the tumor was diagnosed as an adenocarcinoma, and mucus-producing high columnar epithelium formed an irregular tubular-acinar-like structure partly replacing the alveolar epithelium on hematoxylin and eosin staining (Fig. 3a). More than 50% of the tumor demonstrated a lepidic growth pattern, while the remainder showed an invasive adenocarcinoma structure. Accordingly, the tumor was diagnosed as type C according to the Noguchi classification. The tumor was negative for epidermal growth factor receptor mutation but positive for the echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion oncogene according to fluorescence in situ hybridization (Fig. 3b). Finally, the pathological stage of lung cancer was determined to be T1aN0M0 stage 1A. The patient was discharged on postoperative day 5 and showed no signs of postoperative complications or recurrence 13 months after surgery.

**Discussion**

The EML4-ALK fusion oncogene is present in 3.7 to 6.8% of patients with lung adenocarcinomas [1, 2]. Few reports have discussed the imaging features of EML4-ALK-positive lung cancer, although many such tumors present as solid masses. The CT findings in patients with EML4-ALK-positive lung cancer are shown in Table 1. EML4-ALK-positive lung cancer presenting with GGN is relatively rare. To the best of our knowledge, only one previous case report of a patient with EML4-ALK-positive
lung cancer presenting with GGN has been published [3]. In another study that examined lesions in 104 patients with a ≥50 % GGN component on thin-section CT, EML4-ALK positivity was only observed in 3 % of cases, whereas epidermal growth factor receptor (EGFR) mutation was observed in 64 % [4]. Park et al. [5] found only one case with a GGN component among 47 EML4-ALK-positive lung cancer cases. Fukui et al. [1] also reported only one case with a GGN component among 28 EML4-ALK-positive lung cancer cases, whereas 69 of 140 cases (49.3 %) of EML4-ALK-negative lung cancer included GGN components. Few reports have focused on the imaging findings of EML4-ALK-positive lung cancer. Three of the five reports in Table 1 are proceedings only, and reports include considered both in thin-section CT and in not thin-section CT. Therefore, it is necessary to consider the detailed imaging features of EML4-ALK-positive lung cancer.

The imaging features of EML4-ALK-positive lung cancer are often discussed in relation to their histopathological findings. EML4-ALK-positive lung cancer is common among adenocarcinomas and is associated with an acinar-type histology and sieve-like structure and/or signet ring cells with abundant mucin growing in solid sheets [6]. Therefore, tumors tend to present as solid masses on CT. In the current case, however, mucus-producing cells eventually substituted the alveolar epithelium to produce an irregular tubular-acinar-like structure, resulting in the GGN appearance.

Clinical features of EML4-ALK-positive lung cancer include onset at a younger age and a history of no to light smoking [6, 7]. Additionally, the EML4-ALK fusion gene is mutually exclusive of the EGFR mutation gene [8–10]. One report showed no statistically significant difference in tumor size or lymph node metastasis at the time of diagnosis between EML4-ALK-positive and EML4-ALK-negative cancers [11]. Another study showed no statistically significant difference in overall or progression-free survival between EML4-ALK-positive and EML4-ALK-negative cancers [7]. The same study found that EML4-ALK-positive lung cancer tended to be diagnosed in more advanced stages [7]; however, the present patient showed no difference in her clinical stage for 2 years. Further consideration of the growth speed of EML4-ALK-positive lung cancer is needed; for example, the tumor doubling time may be measured. However, EML4-ALK-positive lung cancer is often highly progressive [9], and careful follow-up is therefore essential in these patients.

**Conclusions**
Almost pure GGN had been considered to be less aggressive tumor in lung cancer. In this report, we have shown relatively rare case with potentially aggressive EML4-ALK-positive lung adenocarcinoma showing almost pure GGN. We have to follow this case more carefully than usual.
Consent
Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editor-in-chief of this journal.

Abbreviations
CT: computed tomography; EGFR: epidermal growth factor receptor; EML4-ALK: echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; GGN: ground-glass nodule.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
YO collected and assembled data and drafted the article. AY was the attending physician of the patient and helped to collect data. MH constructed conception and design of the article. HS helped to draft the article and finally approved the article. All authors read and approved the final manuscript.

Author details
1 Department of Thoracic Surgery, Takeda General Hospital, Fukushima, Japan.
2 Department of Regenerative Surgery, School of Medicine, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan.

Received: 14 August 2015 Accepted: 5 March 2016
Published online: 10 March 2016

References
1. Fukui T, Yatabe Y, Kobayashi Y, Tomizawa K, Ito S, Hatooka S, et al. Clinicoradiologic characteristics of patients with lung adenocarcinoma harboring EML4-ALK fusion oncogene. Lung Cancer. 2012;77:319–25.
2. Zhao F, Xu M, Lei H, Zhou Z, Wang L, Li P, et al. Clinicopathological characteristics of patients with non-small-cell lung cancer who harbor EML4-ALK fusion gene: a meta-analysis. PLoS One. 2015;10, e0117333.
3. Nakata T, Okumura S, Kuroda H, Nagasaka T, Maeda J, Uehara H, et al. A case of a small ALK lung cancer mainly presented ground-glass-shade on the image. Haiyakkan. 2011;51:152.
4. Kobayashi Y, Mitsudomi T, Sakao Y, Yatabe Y. Genetic features of pulmonary adenocarcinoma presenting with ground-glass nodules: the differences between nodules with and without growth. Ann Oncol. 2015;26:156–61.
5. Park J, Yamaura H, Yatabe Y, Hosoda W, Kondo C, Shimizu J, et al. Anaplastic lymphoma kinase gene rearrangements in patients with advanced-stage non-small-cell lung cancer: CT characteristics and response to chemotherapy. Cancer Med. 2014;3:118–23.
6. Rodig SJ, Mino-Kenudson M, Dacic S, Yeap BY, Shaw A, Berletta JA, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res. 2009;15:5216–23.
7. Shaw AT, Yeap BY, Mino-Kenudson M, Dignanthy SR, Costa DB, Heist RS, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009;27:4247–53.
8. Mano H. Non-solid oncogenes in solid tumors: EML4-ALK fusion genes in lung cancer. Cancer Sci. 2008;99:2349–55.
9. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363:1693–703.
10. Yoshida A, Tsuta K, Nakamura H, Kohno T, Takahashi F, Asamura H, et al. Comprehensive histologic analysis of ALK-rearranged lung carcinomas. Ann J Surg Pathol. 2011;35:1226–34.
11. Fallet V, Cadot C, Dobre H, Toper C, Monnet L, Chinet T, et al. Prospective screening for ALK: clinical features and outcome according to ALK status. Eur J Cancer. 2014;50:1239–46.

Submit your next manuscript to BioMed Central and we will help you at every step:
- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at www.biomedcentral.com/submit