MET exon 14 skipping gene-positive lung adenocarcinoma associated with atypical adenomatous hyperplasia in lungs and metachronous lung adenocarcinoma

Adenokarcinom plic se skipping mutací MET exonu 14 spojený s atypickou adenomatózní hyperplazií v plicích a metachronním adenokarcinomem plic

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Summary

Background: Recently, there has been interest in the CT imaging characteristics of lung cancer positive for mesenchymal-epithelial transition (MET) exon14 skipping mutation. Herein, we present a patient with MET exon 14 skipping gene-positive lung adenocarcinoma associated with multiple ground-glass opacities (GGOs) in both lungs and metachronous contralateral lung adenocarcinoma. ***Case:*** A 67-year-old man was referred to our hospital due to abnormal finding on chest radiograph. A chest CT on admission revealed a mass in the right lung. A chest CT scan showed a mass in the middle lobe of the right lung, and numerous GGO nodules of various sizes in both lungs. The mass was resected and it was diagnosed as a MET exon 14 skipping gene-positive invasive adenocarcinoma. A GGO nodule resected at the same time was pathologically diagnosed as atypical adenomatous hyperplasia (AAH). A GGO nodule in the left lung that was present at the initial consultation grew in size on a CT scan performed 1 year and 4 months after the right lung resection, and was therefore resected. The nodule was pathologically diagnosed as a MET exon 14 skipping gene-negative invasive adenocarcinoma. Genetic testing for an AAH adjacent to the second adenocarcinoma was negative for the MET exon 14 skipping gene. ***Conclusion:*** The clinical course of this patient was interesting clinical information in terms of providing insight into the morphology, imaging findings, and origin of MET exon 14 skipping gene-positive adenocarcinoma.

Key words

MET exon 14 skipping gene – lung adenocarcinoma – atypical adenomatous hyperplasia – double cancers

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Souhrn

Východiska: V poslední době jsou předmětem zájmu charakteristiky CT zobrazení karcinomu plic se skipping mutací exonu 14 genu pro mezenchymální epiteliální tranzici (MET). V tomto článku představujeme pacienta s adenokarcinomem plic se skipping mutací MET exonu 14 spojeným s vícečetnými opacitami mléčného skla (ground-glass opacities – GGOs) v obou plicích a metachronním kontralaterálním adenokarcinomem plic. ***Případ:*** Muž ve věku 67 let byl do naší nemocnice odeslán kvůli abnormálním nálezům na rentgenovém snímku hrudníku. Vstupní CT hrudníku odhalilo masu v pravé plíci. CT hrudníku ukázalo masu ve středním laloku pravé plíce a v obou plicích četné GGO noduly různé velikosti. Masa byla resekována a byla diagnostikována jako invazivní adenokarcinom se skipping mutací MET exonu 14 . Současně resekovaný GGO nodulus byl patologickým vyšetřením diagnostikován jako atypická adenomatózní hyperplazie (AAH). GGO nodulus v levé plíci, jehož výskyt byl zaznamenán při prvním vyšetření, byl na CT provedeném 1 rok a 4 měsíce po resekci pravé plíce zvětšený, a proto byl resekován. Nodulus byl patologickým vyšetřením diagnostikován jako invazivní adenokarcinom bez výskytu skipping mutace MET exonu 14. Výsledek genetického testování AAH sousedící s druhým adenokarcinomem na skipping mutaci MET exonu 14 byl negativní. ***Závěr:*** Klinický průběh onemocnění tohoto pacienta představoval zajímavou klinickou informaci z hlediska vhledu do morfologie, nálezů ze zobrazovacích technik a původu adenokarcinomu s výskytom skipping mutace MET exonu 14

Klíčová slova

gen se skipping mutací MET exonu 14 – adenokarcinom plic – atypická adenomatózní hyperplazie – duplicitní nádory

Introduction

The mesenchymal-epithelial transition (MET) gene is an oncogene discovered in the 1980s [1,2]. MET gene is a proto-oncogene located at 7q21-q31 that encodes a receptor tyrosine kinase that acts on hepatocyte growth factor as a ligand [1,2]. This gene is involved in tumor proliferation, anti-apoptosis, and metastasis [1,2]. In 2006, it was discovered that mutations in the intron region of the MET gene prevent translation of exon 14, and this was reported as MET exon 14 skipping mutation [3]. This mutation is a driver gene abnormality in cancer and has recently attracted attention with the development of MET inhibitors [4,5]. MET exon 14 skipping mutations are found in 1.8–4.0% of lung adenocarcinoma [6–8]. This mutation is common in the elderly, regardless of gender or smoking status [8]. Recently, there has been interest in the CT imaging characteristics of lung cancer positive for MET exon14 skipping mutation [9–12]. Although ground-glass opacities (GGOs) have been reported to be rare [9], cases of lung cancer positive for this driver gene with GGO have been reported [10–12].

We show herein a case with MET exon 14 skipping gene-positive lung adenocarcinoma associated with multiple GGOs in both lungs and metachronous contralateral lung adenocarcinoma. We do believe it might provide somewhat suggestions into the treatment of patients who might have a similar course in the future.

Case report

A 67-year-old man was referred to our hospital due to abnormal finding on chest radiograph detected in mass-screening. He had no medical history. He was a former smoker with a smoking index of 25 pack-years. There was no history of occupational exposure to asbestos or dust. Physical examination on admission was unremarkable. There were no abnormalities in blood and respiratory function tests. A chest radiograph on admission revealed a mass in the right middle lung. A chest CT scan showed 35 × 24 mm mass in the middle lobe of the right lung (Fig. 1), and numerous GGO nodules of various sizes in both lungs (Fig. 2). The mass in the middle lobe was evaluated to be lung can-

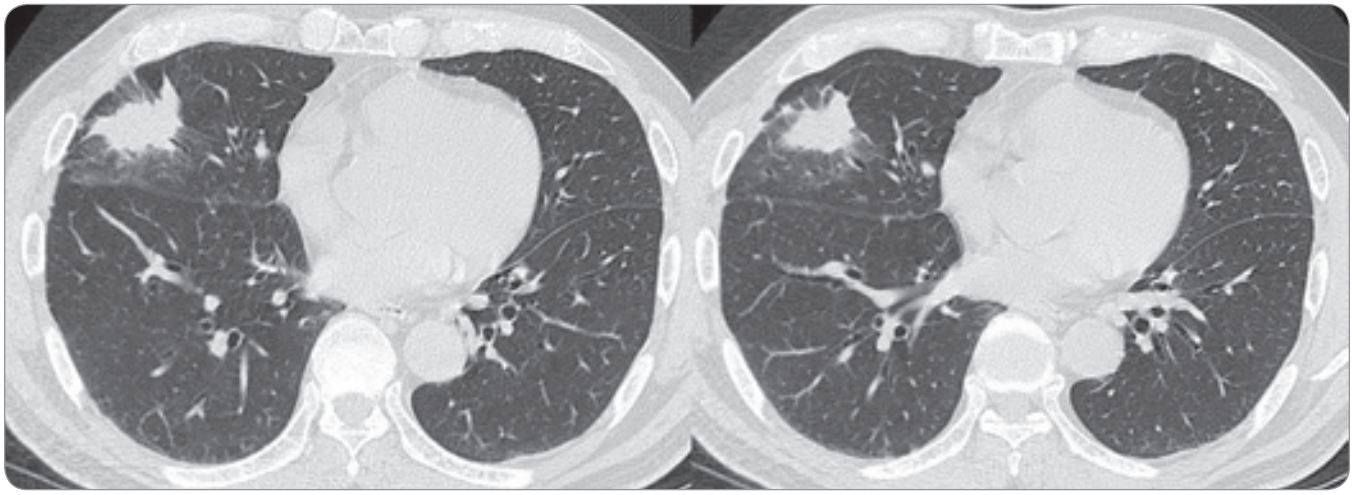

Fig. 1. A chest CT on admission revealed a 35 × 24 mm mass in the middle lobe of the right lung.

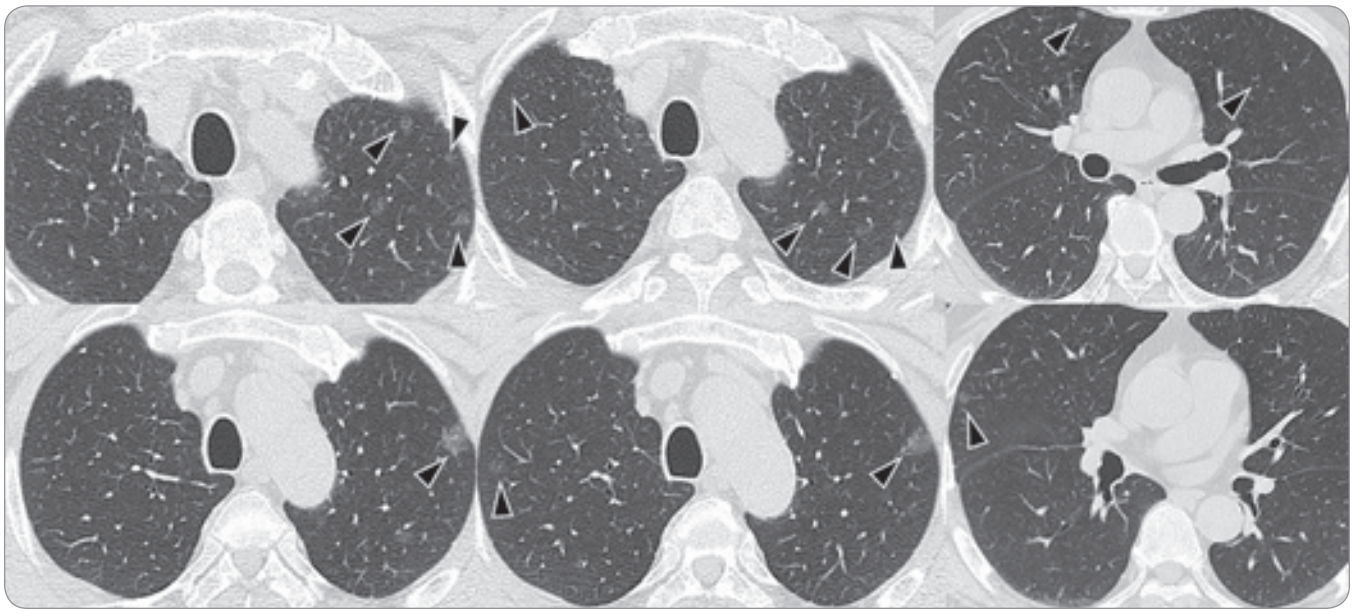

Fig. 2. A chest CT scan showed numerous ground-glass opacity (GGO) nodules of various sizes in both lungs (arrows).

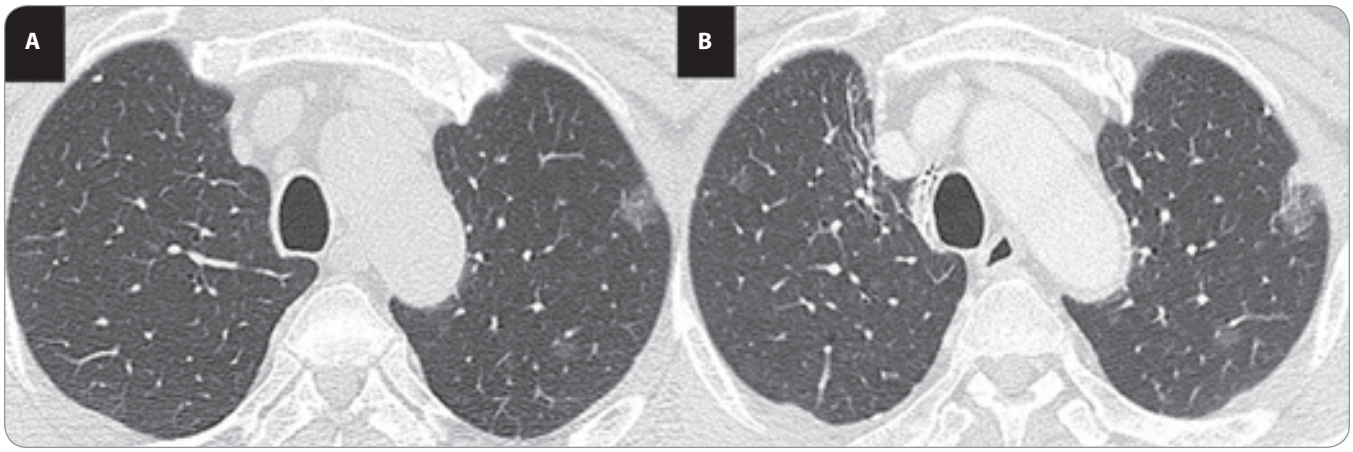

Fig. 3. A ground-glass opacity (GGO) nodule in the left upper lobe that was present at the initial consultation (A) had grown in size on a CT scan performed 1 year and 4 months after the right lung resection (B).

cer, and the multiple GGO nodules were also deemed to require pathological evaluation, so the middle lobe was resected and the GGO nodule located in the right upper lobe was resected by video-assisted thoracic surgery.

The resected mass was an invasive adenocarcinoma (lepidic 80%, papillary 10%, solid 10%) with an overall size of 52 × 20 × 37 mm, including an invasive size of 20 × 10 × 15 mm. There was no spread to the lymph nodes, and the tumor was diagnosed as an invasive adenocarcinoma (lepidic 80%, papillary 10%, solid 10%) pT4N0M0 stage IIIA. Regarding driver genes, the MET exon 14 skipping gene using Oncomine DxTT (Life Technologies Japan Ltd., Tokyo, Japan) was positive. On the other hand, the GGO nodule located in the upper lobe was pathologically diagnosed as atypical adenomatous hyperplasia (AAH). There were multiple small GGO nodules in the resected upper lobe that were not evident on CT, and these were also evaluated to be adenomatous hyperplasia. Driver genes were negative for all of these AAHs. As the patient did not wish to receive adjuvant chemotherapy, it was not administered, and imaging follow-up was performed. Although there were no symptoms, chest CT scans were performed approximately every three months. A GGO nodule in the left upper lobe that was present at the initial consultation had grown in size on a CT scan performed 1 year and 4 months after the right lung resection (Fig. 3), and was therefore resected. The nodule was pathologically diagnosed as invasive adenocarcinoma (70% lepidic, 20% papillary, 10% solid, 20 × 10 × 15mm). Genetic testing of this nodule was negative for the MET exon 14 skipping gene. The GGOs surrounding this tumor were diagnosed as AAH. Genetic testing for this AAH was negative for the MET exon 14 skipping gene. Two years and ten months have passed since the resection of the second

cancer that developed in the left lung, and there has been no recurrence or new cancer development. The patient is doing well.

Discussion

Two studies investigating the characteristics of MET exon 14 skipping-positive NSCLCs have pointed out that they occurred in the upper or middle lobes [9,13]. In one of the two reports, Watari et al., a study of 15 patients, CT features of MET exon 14 skipping-positive non-small cell lung cancer (NSCLC) were the presence of internal low-density areas and invasion into surrounding tissues. However, they reported that GGO was rare, occurring in only 1 of 15 patients (6.7%) [9]. Regarding GGOs in MET exon 14 skipping-positive NSCLC, as far as we could search, there were the following few case reports [10–12]. The patient presented by Washioka et al. had MET exon 14 skipping-positive NSCLC with a mass accompanied by extensive GGO, and cancer cells were pathologically confirmed in the GGO area [10]. Ikeo et al. reported transient GGO in a patient with MET exon 14 skipping-positive NSCLC [11]. Wang et al. reported two MET exon 14 skipping-positive NSCLCs in a single lobe. One of these NSCLCs was a part-solid nodule with GGO [12]. Careful examination of the CT images presented for this patient revealed that both nodules were part of the GGO. More interestingly, their detailed analysis of the MET exon 14 skipping gene in these two nodules revealed that they were not the same genetic abnormality.

Two notable points in clinical course of our patient were as follows. First, areas of GGO were found around the primary cancer that developed in this patient's right lung.

This was completely different histologically and genetically from the surrounding GGO that was diagnosed as AAH. In other words, lung adenocarcinoma, which is the primary cancer positive for the MET exon 14 skipping gene, did not arise from AAH as the origin. Second, the second cancer in the left lung showed similar morphological and immunohistochemical features to the first cancer, but was negative for the MET exon 14 skipping gene. Based on these results, genetic testing confirmed that the second cancer that developed metachronous in the left lung was not a pulmonary metastasis from the first cancer. The AHHs in the left lung were also negative for the MET exon 14 skipping gene. These results suggest that AAH was not involved in the development of primary or secondary cancers.

Double lung cancers, whether synchronous or metachronous, might be misdiagnosed as metastases. Distinguishing between metastases and double cancers is essential for accurate staging and prognosis. Biopsies of each lesion should be performed, if possible, and appropriate staging and treatment should be performed accordingly. Integrating molecular analysis in addition to standard clinical, imaging, and pathological criteria in a multidisciplinary approach allows for more accurate diagnosis and personalized treatment plans for selected patients. Considering economic efficiency, it might not be appropriate to implement this approach in all lung cancer patients. However, in complicated and rare cases such as this patient, we had better to perform these integrated approaches. We reported this case as we do believe it might provide somewhat suggestion into the management of future patients who might have a similar course.

Conclusion

We presented clinical course in a patient with MET exon 14 skipping gene-positive lung adenocarcinoma associated with multiple AAH in both lungs and metachronous contralateral lung adenocarcinoma. The clinical course provided interesting information in terms of providing insight into the morphology, imaging findings, and origin of MET exon 14 skipping gene-positive adenocarcinoma.

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Statement of ethics

This study was approved by the institutional ethics committee of our institute (NO-1639). Written comprehensive informed consent at the time of admission for obtaining pathological specimens was obtained from the patient.

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No funding was received.

Authors' contributions

Hiroya Sunabe, Yosuke Maezawa and Hiroaki Satoh designed the study. Hiroya Sunabe, Yosuke Maezawa, Toshihiro Shiozawa, Gen Ohara and Hiroaki Satoh collected the data. Norio Takayashiki was responsible for the pathological diagnosis. Hiroya Sunabe, Yosuke Maezawa and Hiroaki Satoh prepared the manuscript. Toshihiro Shiozawa and Hiroaki Satoh supervised this manuscript. All the authors approved the final version for submission.

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