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# A case of a rare non-invasive lung adenocarcinoma

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ABSTRACT

*BACKGROUND:* According to the WHO classification, adenocarcinoma in situ (AIS) is a localised small (≤3 cm) adenocarcinoma whose growth is restricted to neoplastic cells along pre-existing alveolar structures, lacking stromal, lymphovascular, or pleural invasion. There is no evidence to define AIS as having a tumour size of ≤3 cm. It is extremely rare for adenocarcinomas with pure lepidic growth lacking invasion to be >3.0 cm. The biological characteristics of these large AISs should be revealed.

*PRESENTATION OF CASE:* The patient was an 82-year-old asymptomatic woman. Chest computed tomography showed a 6-cm-diameter pure ground-glass opacity in the left lower lung. The patient underwent lobectomy. On histologic examination, the tumour was restricted to neoplastic cells along pre-existing alveolar structures, lacking stromal, vascular, alveolar space, and pleural invasion. Papillary patterns were absent. Initially, the histopathological diagnosis was AIS, but the total tumour diameter exceeded 3 cm. The final pathological diagnosis was lepidic adenocarcinoma lacking an invasive component and harbouring an EGFR exon 20 insertion V774_C775insHV mutation using next-generation sequencing (NGS).

*CONCLUSION:* We report a rare case of lepidic adenocarcinoma with a total tumour diameter of 6 cm and without an invasive component. Although EGFR mutations are oncogenic driver mutations, AISs have fewer EGFR mutations than invasive adenocarcinomas do. An adenocarcinoma that progresses to AIS, not stepwise progression, might have uncommon mutations and might be another type of adenocarcinoma. NGS could be useful for detecting uncommon genes that reveal the biological characteristics of AIS, and may contribute to the validation of next TNM classification.



## 1. Introduction

The 2015 World Health Organization (WHO) classification [1], which is based on the accumulated molecular features of cancer, has adopted the stepwise continuum of lung adenocarcinoma tumorigenesis and progression. Considering that the precursor of lung adenocarcinoma is atypical adenomatous hyperplasia (AAH), the 2015 WHO classification divides adenocarcinoma into adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and overt invasive adenocarcinoma, according to the extent of invasiveness [1]. According to the 2015 WHO classification, AIS is a localised small (≤3 cm) adenocarcinoma whose growth is restricted to neoplastic cells along pre-existing alveolar structures (lepidic growth), lacking stromal, lymphovascular, or pleural invasion. However, there are several controversial points regarding this classification. First, the progression of all lung adenocarcinomas does not follow a stepwise linear progression [2]. Second, there is no evidence to define AIS as having a tumour size of ≤3 cm. Certainly, it is extremely rare for adenocarcinomas with pure lepidic growth lacking invasion to be >3.0 cm. Travis et al. [3] described these tumours to be lepidic adenocarcinomas (LPAs) rather than AISs because of the lack of evidence for patients with such tumours having 100% disease-free survival. The biological characteristics of these large AISs need to be revealed. Here, we report a case of LPA with a total tumour diameter of 6 cm and which lacked an invasive tumour component. Furthermore, this tumour expressed a rare EGFR exon 20 insertion V774_C775insHV mutation.

This work has been reported in line with the SCARE 2018 criteria [4].

## 2. Case presentation

An 82-year-old woman was referred to our hospital because of an abnormal shadow on a chest roentgenogram during a medical

*Abbreviations:* WHO, World Health Organization; AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; MIA, minimally invasive adenocarcinoma; LPA, lepidic adenocarcinoma; TSCT, thin-slice computed tomography; GGN, ground-glass nodule; NGS, next-generation sequencing.

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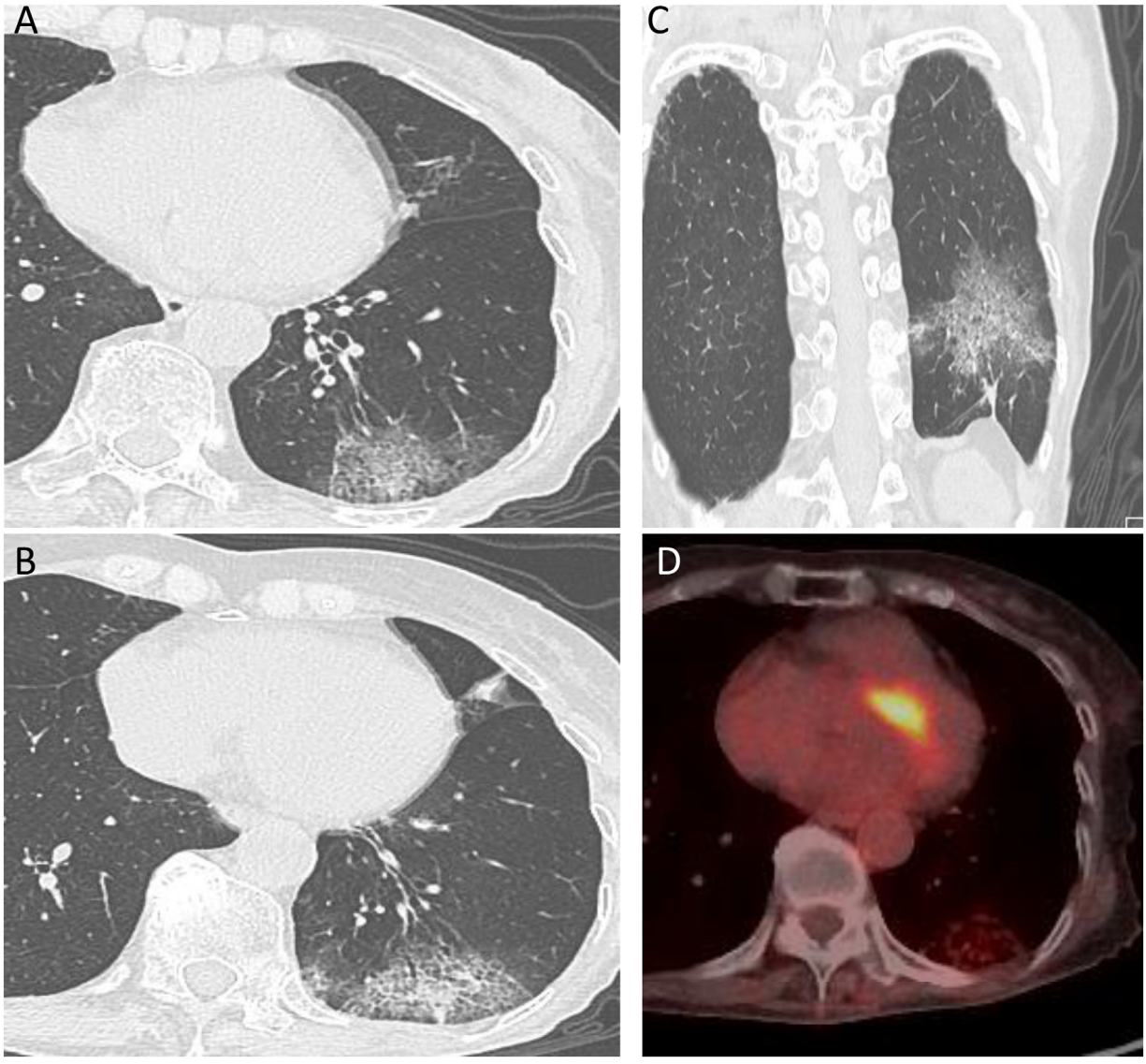


**Fig. 1.** (A, B, C) Chest computed tomography. Left lower lung shows a 6-cm-diameter pure ground-glass opacity. (D) Positron emission tomography/computed tomography. The left lower lung mass shows an unremarkable uptake of 18F-fluorodeoxyglucose; the early maximum standardised uptake value of the mass was 1.9.

check-up. She had no symptoms and past history of lung disease and was a never-smoker. Physical and laboratory test findings were normal. Chest thin-slice computed tomography (TSCT) showed a 6-cm-diameter pure ground-glass nodule (GGN) in the left lower lung (Fig. 1A–C). Positron emission tomography/computed tomography showed that the mass had an unremarkable uptake of 18F-fluorodeoxyglucose, with an early maximum standardised uptake value of 1.9 (Fig. 1D). The patient underwent left lower lobe lobectomy via video-assisted thoracotomy. Lymph node dissection was performed. The operation time was 62 min, and the estimated blood loss was scanty.

Tumour sections had a delicate lace-like appearance with no central scar or pleural depression (Fig. 2). Histologic examination revealed that the tumour was restricted to neoplastic cells along pre-existing alveolar structures (lepidic growth), lacking stromal, vascular, and pleural invasion. Intra-alveolar papillary or micropapillary growth was absent. Tumour cells were cuboidal with round nuclei, but some were taller with long oval nuclei. Cellular atypia was inconspicuous throughout the tumour. Immunohistochemical staining was positive for thyroid transcription factor 1. Mitotic figures were rare, and the MIB-1 index was 2%.

We performed genetic examination of formalin-fixed and paraffin-embedded materials. Although EGFR mutations were not detected with the Cobas® 4800 System (Cobas EGFR Mutation Test v2.0; Roche Molecular Diagnostics), the tumour harboured an EGFR exon 20 insertion V774_C775insHV mutation, detected on next-generation sequencing (NGS) (Illumina Cancer Hotspot Panel® v2). Initially, the histopathological diagnosis was AIS, but the total tumour diameter exceeded 3 cm. The final pathological diagnosis was LPA lacking an invasive component (Fig. 2). No lymph node metastasis was observed, and the postsurgical course was uneventful. Postoperative adjuvant chemotherapy was not performed.

## 3. Discussion

With the wide application of TSCT, the detection rate of pure GGNs has been increasing. Most of these nodules were small and were AAH or AIS. About one-third of all AAH cases progress to AIS and then to MIA and finally to invasive adenocarcinoma [5].

Adenocarcinomas with a predominant lepidic component of >3 cm in total diameter or an invasive component of >0.5 cm are classified as LPAs [1]. It is rare for adenocarcinomas with pure lepidic

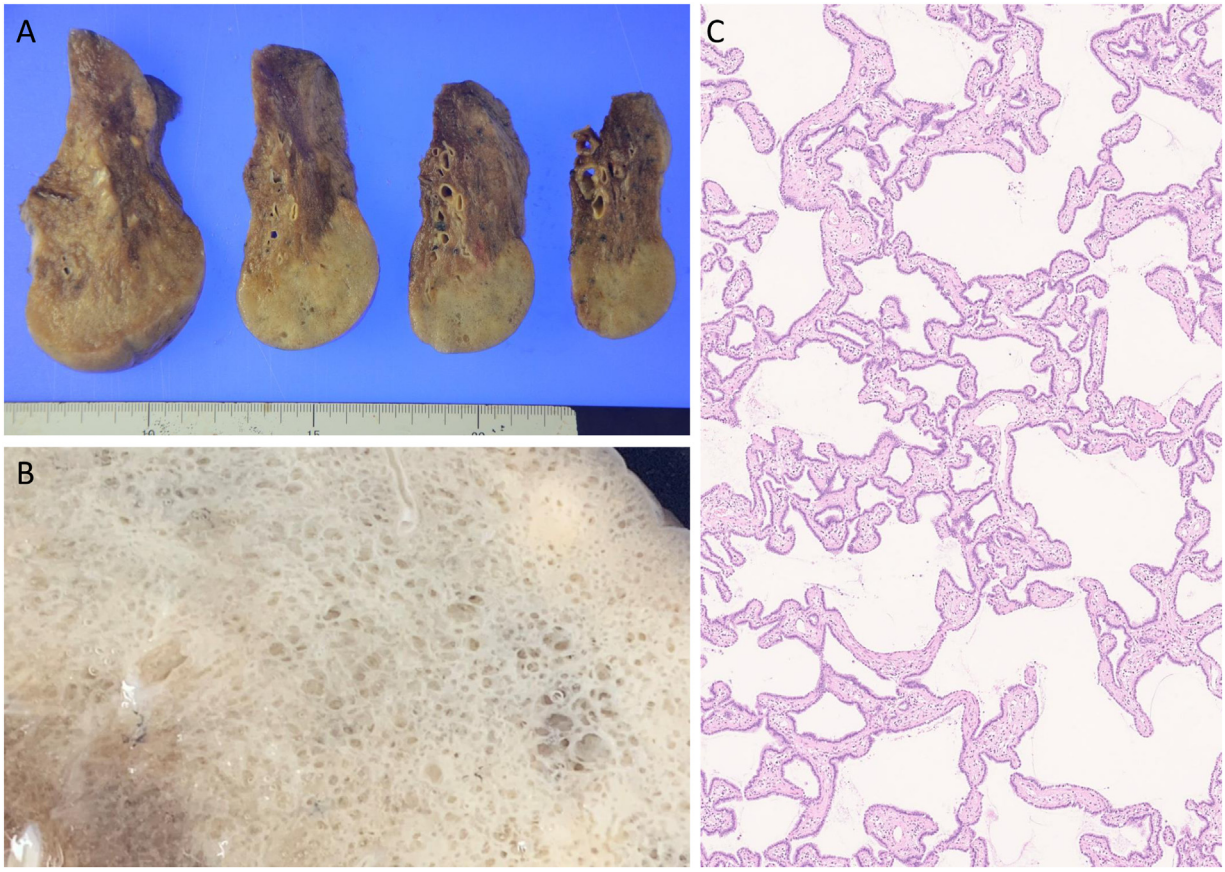


**Fig. 2.** Histological findings. (A, B) Grossly, the tumour is widely distributed to the dorsal region of the inferior lobe and measures 6 cm in diameter without central scarring or pleural indentation. The delicate lace-like cut-surface suggests well-preserved alveolar structures. (C) Microscopically, the neoplastic cells proliferate in a single layer along pre-existing alveolar structures (lepidic growth), lacking stromal invasion or papillary growth in the low-power view. Tumour cells are columnar with uniform-sized round to ovoid nuclei. Nuclear atypia is inconspicuous. (Haematoxylin and eosin: ×10).

growth lacking invasion to be >3.0 cm. Because of the lack of evidence regarding patients with AIS, the tumour is detected as having a pure lepidic pattern without any invasive component and is therefore classified as LPA rather than a very large AIS [1,3].

Numerous studies have demonstrated that a GGN is a good prognostic indicator for lung cancer [6]. The extent of ground-glass opacity within a lung nodule on TSCT can be correlated with the extent of lepidic tumour growth on histopathology, and a consolidation tumour ratio of ≤0.5 can indicate less invasiveness [6]. However, approximately 40% of pure GGNs are reported to be invasive lung adenocarcinomas [7].

In our case, the tumour was a 6-cm pure GGN without a pathologically invasive component. This tumour is classified as pT3 by the 7th TNM classification, but it is pT1a based on the current TNM classification. However, we believe the current TNM classifications are more suitable for GGNs when considering tumour behaviours because tumour invasive size is actually reflected in tumour malignancy. Meanwhile, pure GGNs of ≥3 cm are rare, and the characteristics and prognosis of lung cancer showing a GGN exceeding 3 cm on TSCT remain unclear. Inafuku et al. [8] reported that the prognosis of patients with non-invasive adenocarcinoma exceeding 3 cm was comparable to that of patients with AIS.

EGFR exon 20 insertions account for 4%–10% of all EGFR mutations in lung cancer, and among EGFR exon 20 insertions mutations, 4.3% are V774_C775insHV mutations [9,10]. In our case, the V774_C775insHV mutation was not detected in the first genetic examination, as this mutation was not included in the target genetic mutation in the Cobas EGFR Mutation Test. Finally, it was detected by NGS. Although EGFR mutations are oncogenic driver mutations, AISs have fewer EGFR mutations than invasive adenocarcinomas do [11]. We might need to inspect EGFR mutations using NGS. An adenocarcinoma that progresses to AIS, not stepwise progression, might have uncommon mutations, and might be another type of adenocarcinoma. Thus, NGS could show good performance in multiple testing, especially for uncommon genes that reveal the biological characteristics of AIS, and may contribute to the validation of the next TNM classification. More research is needed to accumulate enough cases with pure GGNs exceeding 3 cm in diameter and to obtain more accurate evidence of these cases.

## 4. Conclusions

We report an extremely rare case of LPA measuring 6 cm in total tumour diameter, lacking an invasive component, and harbouring an EGFR exon 20 insertion V774_C775insHV mutation. An adenocarcinoma that progresses to large AIS might have uncommon mutations and might be another type of adenocarcinoma. NGS could be useful for detecting uncommon genes that reveal the biological characteristics of AIS.

## Declaration of Competing Interest

The authors report no declarations of interest.

## Funding

None.

## Ethical approval

This case report is not research study, therefore approval was not given. The ethical approval has been exempted by our institution.

## Consent

Written informed consent was obtained from the patient for 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 on request.

## Author's contribution

MY performed the operation.
MY prepared and wrote the manuscript.
HI, TF, and CO made the pathological diagnosis.
ST reviewed the manuscript.
All authors have read and approved the final manuscript.

## Registration of research studies

N/A.

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