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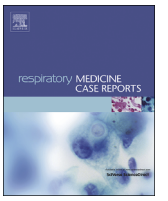

Case Report

Pulmonary adenocarcinoma in situ with morule - like components: A surgical case report

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ABSTRACT

Unusual lung adenocarcinoma with morule-like components is characterized by uniform, tightly packed spindle-shaped cells filling the lumens of neoplastic glandular structures. We present a case of a 78-year-old woman who presented with a part-solid ground-glass nodule in the upper lobe of the right lung. Following right upper lobectomy, histological examination revealed adenocarcinoma in-situ with multiple morule-like intra-alveolar proliferative nests of epithelial cells. Immunostaining was positive for thyroid-transcription factor 1 in the tumor cells and morule-like components. The tumor was also positive for an epidermal growth factor receptor mutation. This case provides valuable insights about lung adenocarcinoma in-situ with morule-like components.

1. Introduction

Thoracic surgery achieves the best outcomes when performed on early-stage lung cancer; hence, early diagnosis and analysis are important. Lung adenocarcinomas (ADCs) have several histological growth patterns, namely, lepidic, acinar, papillary, micropapillary, and solid. Recent analyses associate growth patterns with survival and specific gene mutations. Papillary-predominant ADC, for example, is an invasive carcinoma with a slightly unfavorable prognosis [1] and an epidermal growth factor receptor (EGFR) mutation [2].

Morules are small spindle-cell proliferation buds lacking nuclear atypia and mitotic activity. They are present in uterine endometrioid carcinomas and, in rare instances, thyroid carcinomas [3] and colonic adenomas [4]. Lung ADC with morule-like components is a rare variant, accounting for 1.9% of all ADCs [5]. It is characterized by uniform, tightly packed spindle-shaped cells in the lumens of glandular structures. At present, no known clinicopathological features or genetic alterations exist that might serve as drug targets, likely because of the small number of reported cases and the performance of studies before the emergence of molecular target therapy.

2. Case presentation

In accordance with the Japanese ethical guidelines, the [XXX] ethics committee waived study approval and the requirement for patient consent for this case report.

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A 78-year-old woman had a chronic subdural hematoma resulting in right hemiplegia 7 years ago. During a routine follow-up with her previous doctor, chest computed tomography (CT) showed a part-solid ground-glass nodule (GGN) in the upper lobe of the right lung. She was subsequently referred to our hospital for treatment. She had no history of smoking or drinking.

Chest radiography revealed an abnormal shadow in the lung and mediastinal areas, but the tumor location could not be identified. Chest CT confirmed the presence of a part-solid GGN in the upper lobe of the right lung (S1 area) (Fig. 1A). The tumor was 22 mm in size with a 2-mm solid component. No mediastinal or hilar lymph node swelling was observed. Positron emission tomography-CT revealed weak accumulation in the tumor (maximum standardized uptake value, 1.8) but none in the lymph nodes or other organs.

The preoperative diagnosis was lung cancer, and minimally invasive ADC was suspected. We performed a right upper lobectomy and ND2a-1 lymph node dissection. In the resected specimen, the tumor had a morule-like component (8 × 9 mm, the green-colored area in Fig. 1B) and an area with a lepidic pattern (18 × 16 mm, the yellow-colored area).

Histologically, the tumor was classified as an ADC in situ (AIS) with lepidic growth of atypical columnar cells without stromal desmoplasia. Multiple intra-alveolar proliferative nests of epithelial cells morphologically resembling morules were observed (Fig. 2A and B).

Immunostaining revealed that the proliferative nests and surrounding atypical cells were positive for thyroid transcription factor-1 and negative for p40, synaptophysin, chromogranin A, and insulinoma-associated protein 1 (Fig. 2C and data not shown). The MIB-

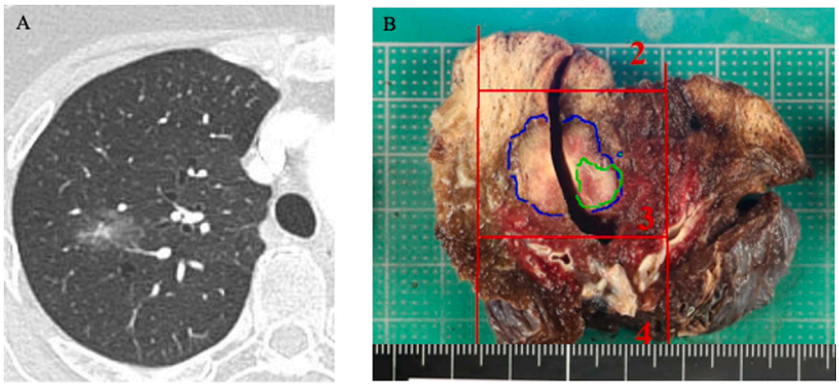

Fig. 1. A. Chest computed tomography. A part-solid ground-glass nodule was detected in the upper lobe of the right lung (S1 area). The tumor was 22 mm in size with a 2-mm solid component. No mediastinal or hilar lymph node enlargement was observed.
B. Resected specimen. The morule-like component (green-colored area) was 8 × 9 mm, and the lepidic component (yellow-colored area) was 18 × 16 mm. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

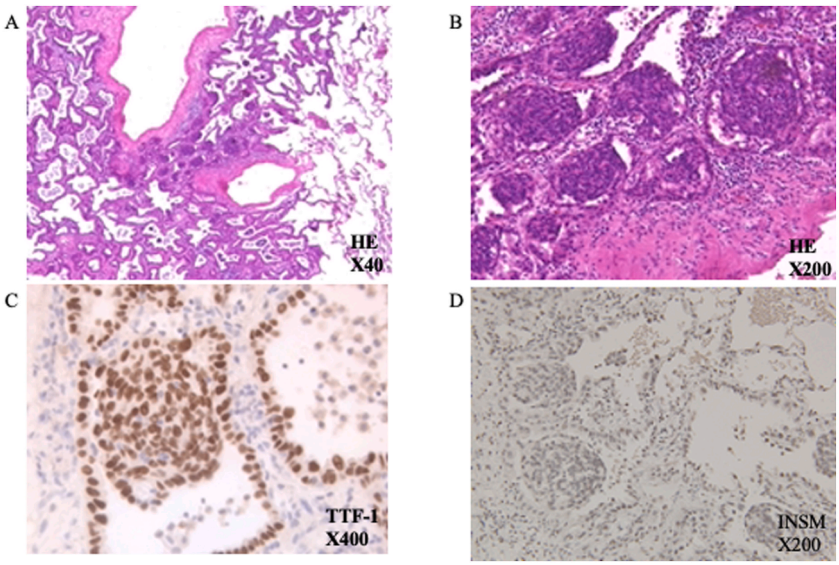

Fig. 2. A, B. Hematoxylin and eosin staining. The tumor was adenocarcinoma in situ (AIS) with lepidic growth of atypical columnar cells without stromal desmoplasia. Multiple intra-alveolar proliferative nests of epithelial cells morphologically resembling morules were observed.
C. Immunostaining. The immunostaining pattern was the same in the proliferation nests and the surrounding atypical cells. The cells were positive for thyroid transcription factor 1 (TTF-1) and negative for p40.
D. The MIB-1 index of the proliferation nests and the lepidic components was 3.6% and 6.8%, respectively.

1 index of the proliferative nests was 3.6%, whereas that of the lepidic components was 6.8% (Fig. 2D). We assessed that this area was equivalent to the morule-like component. The tumor was positive for the L861Q EGFR mutation but negative for BRAF, anaplastic lymphoma kinase, receptor tyrosine kinase, and anti-programmed cell death-1 ligand 1 antibody.

The patient's condition after surgery was favorable. Presently (7 months after surgery), she is being monitored through outpatient observation.

3. Discussion

Only a few cases of pulmonary ADC with morule-like components have been reported. Hence, little is known about its clinical features and survival outcomes [1].

Tsuta et al. reported that patient age and incidence of lymphovascular invasion were slightly (although not significantly) higher in ADCs with morule-like components than in those without [5]. Clinical factors, including sex, history of smoking, lymph node status, and pathologic stage, did not differ significantly between these variants.

ADCs with morule-like components have a lower 5-year overall survival (OS) rate (37.8%) than papillary-predominant (74%), micropapillary-predominant (62%), and solid-predominant (58%) ADCs [6]. As reported by Tsuta et al., they frequently harbor EGFR mutations (70.6%), particularly the DEL mutation [5]. In the multivariate analysis by these investigators, the presence of morule-like components independently predicted EGFR mutation positivity.

Lee et al. reported 26 cases of lung ADC with morule-like features, which included papillary (15 cases), micropapillary (three cases), acinar (three cases), and solid-predominant (three cases) ADC, ADC with a lepidic pattern (one case), and a bronchoalveolar carcinoma (one case) [7]. Tsuta et al. reported that lung ADCs with morule-like features have lower 5-year OS rates, suggesting that morule-like features are an invasive component analogous to an aggressive histologic micropapillary pattern [5]. Morule-like components are often observed in the backgrounds of acinar, lepidic, and papillary ADCs. Lung ADCs with morule-like components tend to appear as a solid mass on CT. The micropapillary and cribriform components of these tumors may lead to a poor prognosis [8].

4. Conclusion

- This case was a rare type of AIS with morule-like components.
- Further investigation of the histological changes is required.
- We believe that our findings will aid the prognostic assessment of patients with lung cancer with morule-like features.

Funding

This study did not receive any funding.

Contributions

MT and HU performed the histological examination of the morule-like components and were major
contributors to the writing of this manuscript. TS contributed to the management of this patient's care. NK contributed to the surgery for this patient. RY, KM, and HT contributed to the structure of the manuscript.

Ethics declarations

Ethics approval and consent to participate

Study approval and the requirement for patient consent were waived by the Tokushima University ethics committee in accordance with Japanese ethical guidelines.

6.2. Consent for publication

Study approval and the requirement for patient consent were waived by the Tokushima University ethics committee in accordance with Japanese ethical guidelines.

Availability of data and materials

The materials described in the manuscript, including all relevant raw data, will be freely available to any scientist wishing to use them for non-commercial purposes without breaching participant confidentiality.

Declaration of competing interest

The authors declare no conflicts of interest associated with this manuscript.

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