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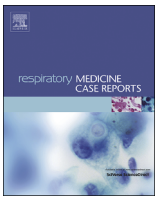

Case Report

Mixed invasive mucinous and non-mucinous adenocarcinoma of the lung with hematogenous metastases to multiple organs

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ABSTRACT

Mixed invasive mucinous and non-mucinous adenocarcinoma is a rare variant of lung adenocarcinoma. In pure invasive mucinous adenocarcinoma, multilobar and bilateral involvement are common, and extrathoracic metastasis is rare. Here, we report a case of mixed invasive mucinous and non-mucinous adenocarcinoma with distant metastasis to multiple organs without marked enlargement of the primary lung lesion. The pathological findings indicated high tumor invasiveness and the patient died 10 months after diagnosis despite chemoimmunotherapy. Further investigations are necessary to elucidate the clinical characteristics and appropriate management of mixed invasive mucinous and non-mucinous adenocarcinoma.

1. Introduction

Invasive mucinous adenocarcinoma (IMA) is a primary lung adenocarcinoma with tumor cells showing goblet cell or columnar cell morphology with abundant intracytoplasmic mucin [1]. When both mucinous and non-mucinous adenocarcinoma components comprise over 10 % of the tumor, it is diagnosed as a mixed invasive mucinous and non-mucinous adenocarcinoma. IMA is located peripherally in the lung and has a high frequency of multifocal, multilobar, and bilateral involvement. IMA spreads along the airways, and extrathoracic metastasis is rarely observed [2]. Here, we present a case of mixed invasive mucinous and non-mucinous adenocarcinoma of the lung with distant metastases to multiple organs without marked enlargement of the primary lesion.

2. Case presentation

A 68-year-old man presented at the hospital with lower back pain. Computed tomography (CT) depicted a 23-mm-sized nodule in the upper lobe of the left lung and swollen mediastinal lymph nodes (Fig. 1). Bone destruction was also indicated in the spinous processes of the L3 vertebra. Lung cancer with lymph node and bone metastases was suspected. A transbronchial biopsy was performed on the pulmonary nodule after palliative radiation to the spine. Tumor cells with abundant cytoplasmic mucin were evident, resulting in a diagnosis of IMA (Fig. 2). Immunohistochemistry revealed CK7 positivity and CK20 negativity; Thyroid transcription factor-1 expression was absent. Programmed death ligand 1 (PD-L1) expression was undetectable, and the tumor progression score was <1 %, and the tumor was positive for Kirsten rat sarcoma viral oncogene homolog (KRAS) G12R mutation but negative for epi-

Abbreviations: IMA, Invasive mucinous adenocarcinoma; CT, Computed tomography; PD-L1, Programmed death ligand 1; KRAS, Kirsten rat sarcoma viral oncogene homolog; EGFR, Epidermal growth factor receptor; ALK, Anaplastic lymphoma kinase.

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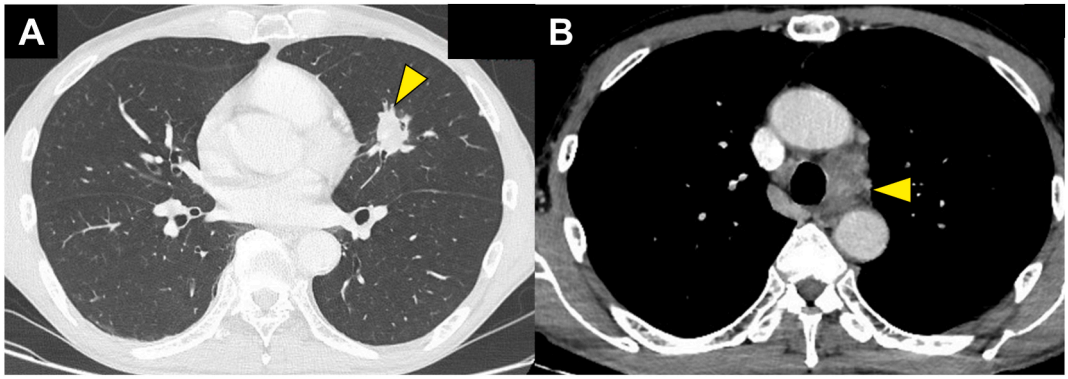

Fig. 1. Computed tomography findings at diagnosis. A) A 23-mm-sized nodule was detected in the left upper lobe (arrowhead). B) There were swollen lymph nodes in the upper mediastinum (arrowhead).

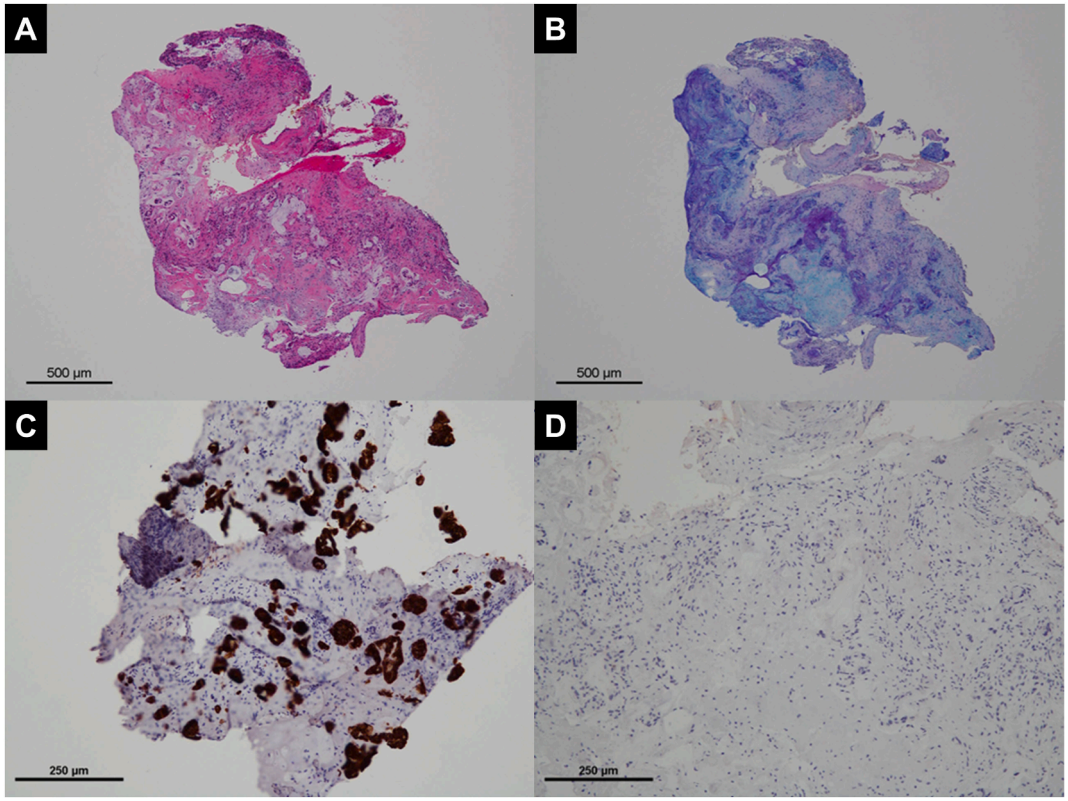

Fig. 2. Pathological findings of the biopsy specimen. A) Tumor cells containing abundant cytoplasmic mucins with unevenly distributed nuclei were proliferating. (Hematoxylin and eosin stain. Bar: 500 μm) B) Mucin-containing cells showed alcian blue and periodic acid-Schiff (PAS) positivity. (Alcian blue – PAS stain. Bar: 500 μm) C) Tumor cells were positive for CK7. (CK7 stain. Bar: 250 μm) D) CK20 negativity was demonstrated. (CK20 stain. Bar: 250 μm). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

dermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) mutation. Treatment with carboplatin, pemetrexed, and pembrolizumab was initiated 4 weeks after confirmation of the diagnosis. Common Terminology Criteria for Adverse Events grade 3 anemia was noted however, dose reduction and blood transfusions were required. Although the left lung nodule and mediastinal lymph nodes had shrunk slightly, growing masses in the left adrenal gland and right retroperitoneum were observed after four courses of chemoimmunotherapy. Progression of the lung lesion and liver and bone metastases were indicated after three cycles of treatment with pemetrexed and pembrolizumab. Seven months after diagnosis, albumin-bound paclitaxel was initiated as second-line treatment. However, bone metastases had spread to the scapula, clavicles, ribs, and pelvis (Fig. 3). Since the patient had severe abdominal and back pain, he underwent palliative radiation to Th10–12, and the right ribs, but the symptoms did not improve significantly. The patient died 10 months after diagnosis, and an autopsy was performed. Although the primary pulmonary tumor was 25 mm in size (Fig. 4), which was almost the same size indicated by CT at the diagnosis, marked tumor invasion into the pulmonary

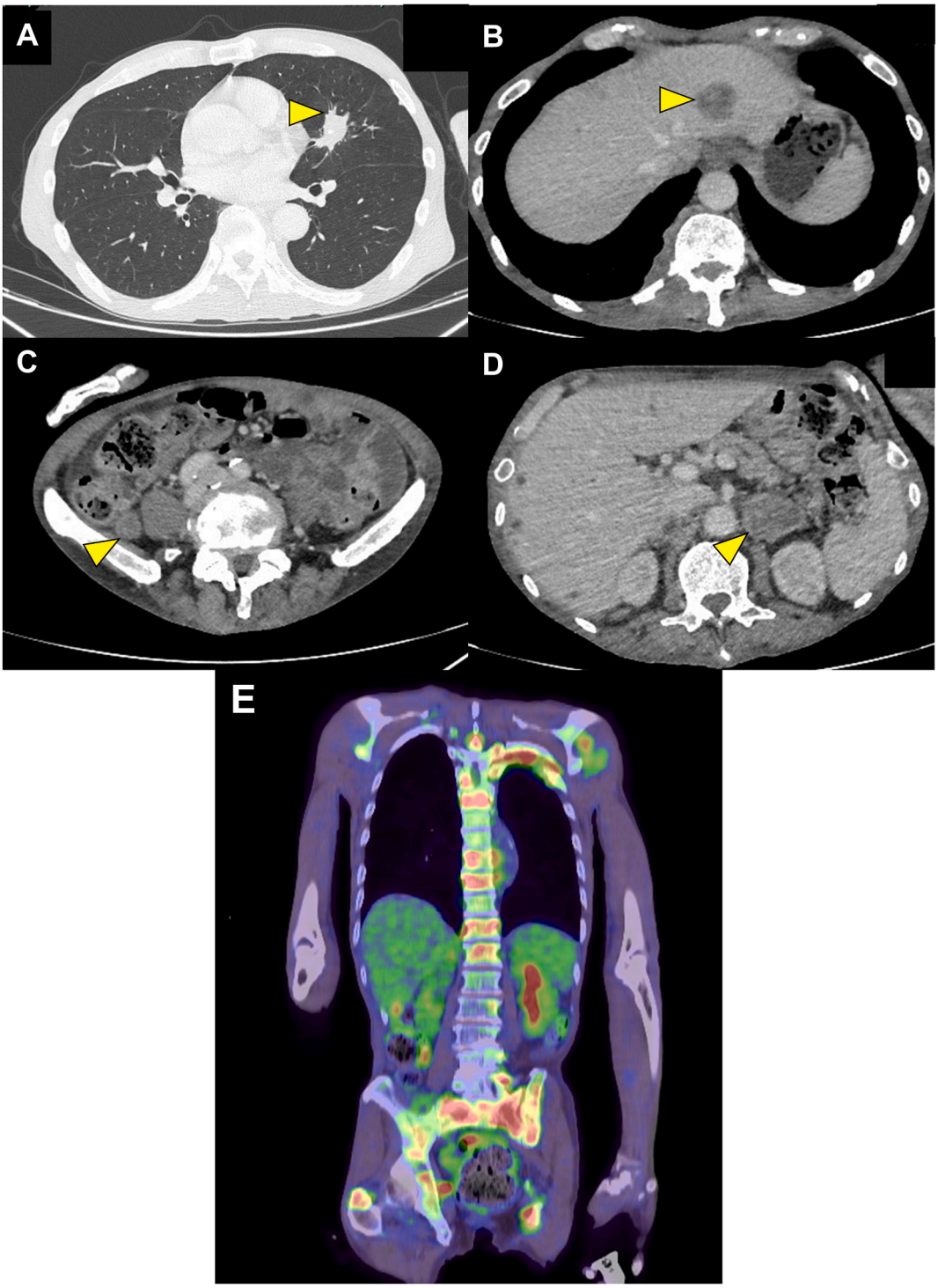

Fig. 3. Computed tomography (CT) and positron emission tomography (PET)-CT findings 9 months after diagnosis. A) The lung nodule size was 25 mm, and no significant enlargement was observed compared to that before the treatment (arrowhead). B) Hypoattenuating hepatic lesions were evident in segment 2 (arrowhead). C) A 21-mm-sized mass was detected in the right retroperitoneum (arrowhead). D) There was a 39-mm-sized mass in the left adrenal gland (arrowhead). E) PET-CT (coronal view) depicted multiple bone metastases in the scapula, ribs, clavicles, pelvis, and vertebrae.

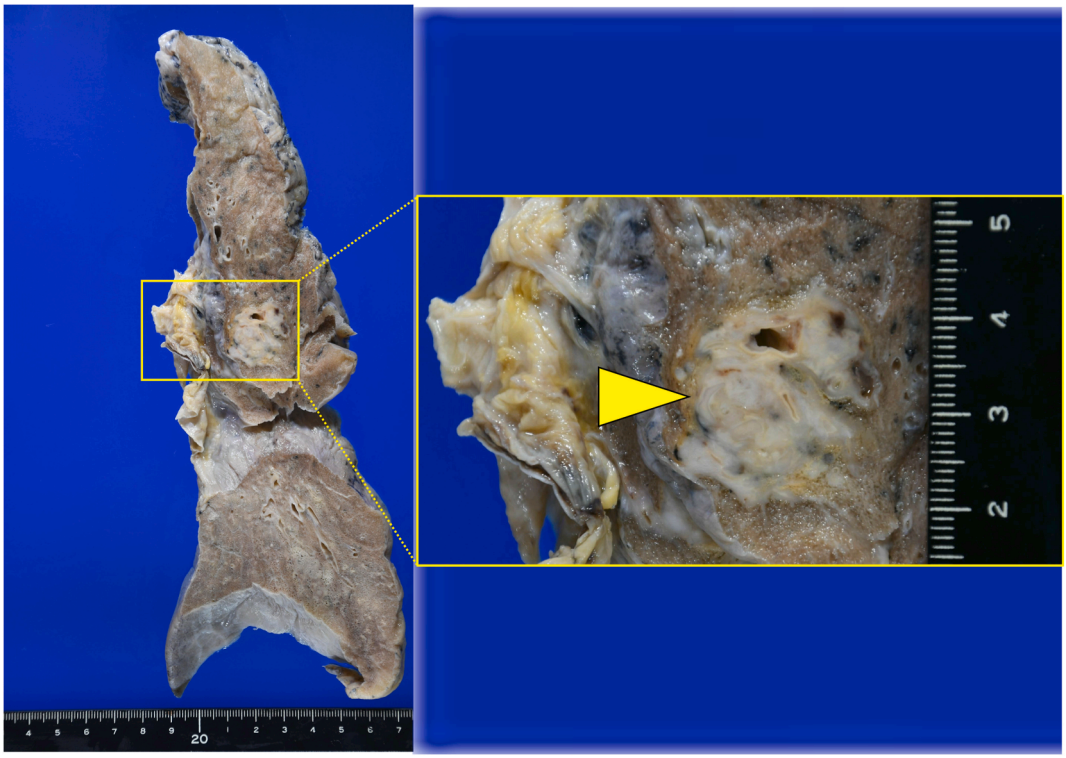

Fig. 4. Macroscopic examination of the whole left lung and the tumor in the lingular segment in the autopsy. The solitary nodule was 25 mm in size (arrowhead), and no other lung involvement was identified.

artery was microscopically noted. Both mucinous and non-mucinous components were shown in the primary lung lesion, and therefore, the diagnosis was updated to mixed invasive mucinous and non-mucinous adenocarcinoma. Multiple tumor metastases were observed in the liver, adrenal glands, bones, pulmonary hilar lymph nodes, and peritoneum (Fig. 5). In addition, severe bronchopneumonia with numerous colonies of gram-positive bacteria was presumed to be the direct cause of death.

3. Discussion

IMA is a rare subtype accounting for 2%–10 % of lung adenocarcinomas, characterized by tumor cells showing goblet cell or columnar cell morphology with abundant intracytoplasmic mucin [3]. Multiple growth patterns have been observed, including a lepidic growth pattern with microscopic skip lesions, which is also a subtype of IMA. Multilobar and bilateral involvement are the most common spread patterns of IMA, but extrapulmonary metastasis is rare. Some reports indicate that the prognosis of IMA is favorable compared to other subtypes of adenocarcinoma, while others do not [3–5]. CT often indicates multiple pneumonia-like consolidations or ground-glass opacities, but a solitary nodule pattern can also be observed [6,7]. A solitary nodule pattern in resected IMA cases has been associated with a reduced likelihood of postoperative recurrence [8].

In the current case, the primary pulmonary lesion did not grow significantly, and there was no evidence of skip metastasis in either lung. However, marked tumor invasion into the pulmonary arteries caused multiple tumor metastases to the liver, adrenal glands, and peritoneum. The hematogenous metastasis to multiple organs observed in this case was inconsistent with the reported characteristics of IMA, and it seems very rare. This case was diagnosed as a mixed invasive mucinous and non-mucinous adenocarcinoma. This rare subtype has similar demographic and genetic profiles to pure IMA but may have a worse prognosis [9]. Loss of cytoplasmic mucin production in mixed cases is possibly associated with the transformation of preexisting mucinous components and tumor progression [3,9]. These pathological features may have contributed to the high tumor invasiveness observed in the present case.

Although 63%–90 % of patients with IMA have KRAS mutations, EGFR mutations are only detected in 0%–5% of patients [5]. In contrast, some studies have reported that patients with mixed invasive mucinous and non-mucinous adenocarcinoma have significantly fewer KRAS mutations and ALK rearrangements than patients with pure IMA [9,10]. Additionally, IMAs rarely express PD-L1. In the current case, the tumor harbored a KRAS G12R mutation that was not amenable to targeted therapy. The patient underwent chemoimmunotherapy, but the tumor progressed within 5 months. Despite second-line treatment with albumin-bound paclitaxel, he died 9 months after the initiation of first-line chemoimmunotherapy. Cha et al. [3] reported that conventional platinum-based chemotherapy does not improve the prognosis of patients with IMAs. Therefore, in cases without PD-L1 expression and the availability of targeted therapy, treatment could be challenging.

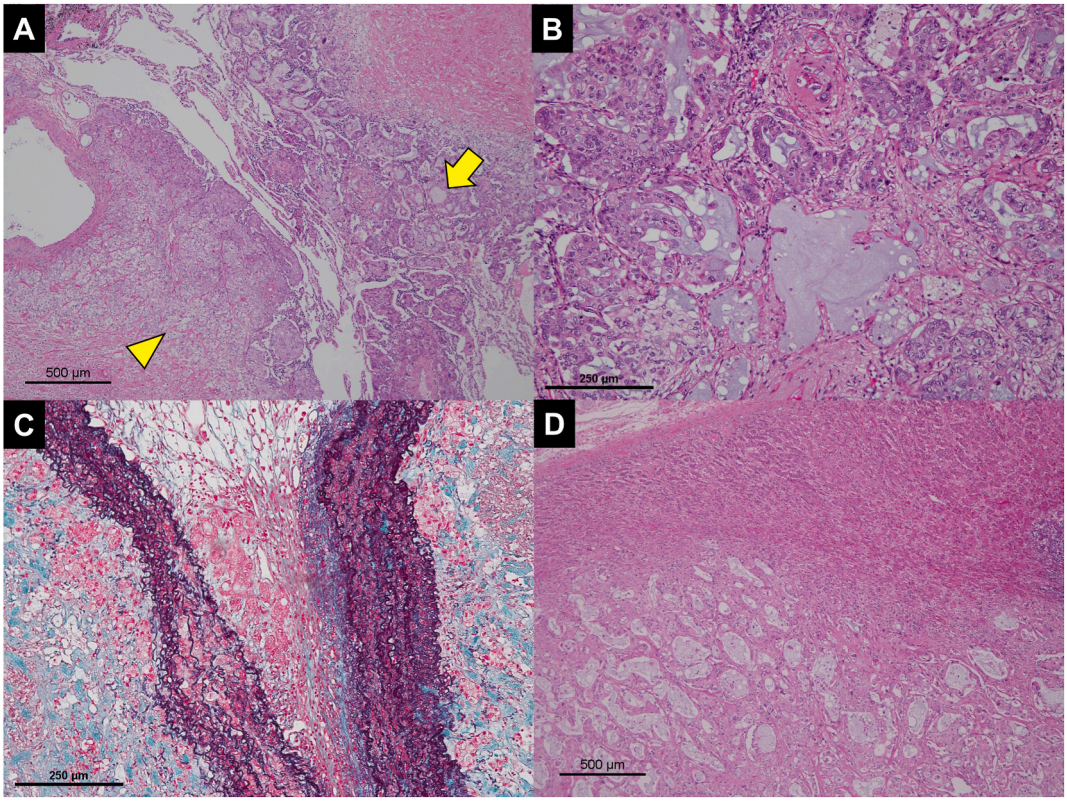

Fig. 5. Histopathological findings of the left lung and adrenal grand at the autopsy. A, B) Columnar tumor cells had mucinous (arrow) and non-mucinous (arrowhead) components, diagnosed as mixed invasive mucinous and non-mucinous adenocarcinoma. The majority of non-mucinous components were classified as solid type. (Hematoxylin and eosin stain. A Bar: 500 μm, B Bar: 250 μm) C) Tumor cells infiltrated into the pulmonary artery. (Elastica Masson stain. Bar: 250 μm) D) A mucinous component was detected in the adrenal metastasis. (Hematoxylin and eosin stain. Bar: 500 μm).

4. Conclusion

Here, we report a rare case of IMA with hematogenous metastases to multiple organs. As with other subtypes of lung adenocarcinoma, the prognosis can be poor when the tumor is highly aggressive and vascular invasion is present. It is unclear whether the tumor invasiveness in this case represented a feature of mixed invasive mucinous and non-mucinous adenocarcinoma, and further investigation is necessary.

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Authorship statement

All authors meet the ICMJE authorship criteria.

CRediT authorship contribution statement

Shinya Otsuka: Writing – review & editing, Writing – original draft, Visualization, Data curation, Conceptualization. **Kei Hiraoka:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Nozomu Iwashiro:** Visualization, Validation, Supervision. **Noriko Kimura:** Writing – review & editing, Visualization, Validation, Supervision. **Masanori Ohara:** Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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