Double-mutant invasive mucinous adenocarcinoma of the lung in a 32-year-old male patient: A case report

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Abstract

BACKGROUND
Invasive mucinous adenocarcinoma of the lung, formerly known as mucinous bronchioloalveolar carcinoma, is a rare category of lung tumors and radiologically characterized by dense pneumonic consolidation, ground-glass opacity, crazy paving, and nodules. However, early pleural effusion is uncommon in this malignancy.

CASE SUMMARY
The case of a 32-year-old male patient who visited our facility with symptoms of cough and gradually aggravated shortness of breath was reported. X-ray examination revealed a massive left hydrothorax. The patient underwent thoracentesis, and pleural fluid tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, neuron-specific enolase, and cytokeratin 21-1 fragment, were significantly elevated. A similar tendency was observed among the serum tumor markers. After draining the pleural effusion, the patient underwent chest computed tomography, and no obvious mass was found in the lung. Thoracoscopy revealed that the left visceral pleura was covered with nodular, cauliflower-like protrusions of various sizes. These histopathological results suggested cancerous cells, and the immunohistochemical findings were consistent with mucinous adenocarcinoma of pulmonary origin. It tested positive for cytokeratin, cytokeratin 5/6, carcinoembryonic antigen, and thyroid transcription factor-1.

CONCLUSION
The patient was diagnosed with a rare case of lung mucinous adenocarcinoma. Subsequent genetic testing was positive for epidermal growth factor receptor-21 mutations and echinoderm microtubule-associated protein-like 4-lymphoma anaplastic kinase fusion. This prompted treatment with alfatinib and crizotinib.

Key Words: Lung mucinous adenocarcinoma; Hydrothorax; Double mutant; Case report
Invasive mucinous adenocarcinoma of the lung is a rare category of lung tumors, radiologically characterized by dense pneumonic consolidation, ground-glass opacity, crazy paving, and nodules. Early pleural effusion is uncommon in this malignancy. Molecularly, invasive mucinous adenocarcinoma has frequent Kirsten rat sarcoma viral oncogene mutations and a lower prevalence of epidermal growth factor receptor and anaplastic lymphoma kinase rearrangements. Here, a rare case of double-mutant invasive mucinous lung adenocarcinoma presenting as a massive malignant pleural effusion in a 32-year-old male patient was reported.

**Case Presentation**

**Chief complaints**
A 32-year-old male chronic smoker (ten cigarettes a day for more than 10 years) was referred to our hospital’s respiratory department on June 25, 2020. He complained of shortness of breath and a cough.

**History of present illness**
The patient had a history of progressive shortness of breath and a cough for 20 d before consult.

**History of past illness**
He had no prior chronic diseases but recently lost 4 kg of his body weight.

**Personal and family history**
The patient denied having a family history of lung cancer, hypertension, and coronary heart disease.
**Physical examination**

Physical examination showed that respiratory sounds were absent in the patient’s left lung field.

**Laboratory examinations**

He was admitted to our department where he underwent thoracocentesis that resulted in the extraction of 700 mL of pleural effusion. Related laboratory results of the yellow turbid pleural fluid revealed an exudate with dramatically high tumor biomarkers and normal adenosine deaminase, which was unexpected. Detailed data are as follows: total cell count = 8015 × 10^6/L, leukocyte count = 440 × 10^6/L, positive Rivalta test, lactate dehydrogenase = 676 U/L, total protein 51 g/L, adenosine deaminase = 13 U/L, carcinoembryonic antigen = 34.6 ng/mL (normal range: 0-5), carbohydrate antigen 19-9 > 1000 U/mL (normal range: 0-37), neuron-specific enolase = 22.65 ng/mL (normal range: 0-18), and cytokeratin 21-1 fragment > 500 ng/mL (normal range: 0-3.3). The patient’s serum tumor biomarkers exhibited a less obvious upward trend than their counterparts in the pleural effusion, with carcinoembryonic antigen 7.96 ng/mL, carbohydrate antigen 19-9 204.2 U/mL, and cytokeratin 21-1 fragment 6.33 ng/mL. Cytological tests revealed allotype tumor cells in the hydrothorax. We then performed closed thoracic drainage because of the massive pleural effusion and apparent symptoms of this patient.

**Imaging examinations**

Chest X-ray showed a severe left hydrothorax ([Figure 1](#)), and the patient was hospitalized with a suspected diagnosis of tuberculous exudative pleurisy. After pleural effusion drainage, the patient underwent chest CT, demonstrating no evident pulmonary masses or nodules; however, multiple nodules were found in the left visceral pleura ([Figure 2](#)). Subsequent thoracoscopy revealed that the visceral pleura was filled with nodular, cauliflower-like protrusions of various sizes ([Figure 3](#)).

**FINAL DIAGNOSIS**

The initial pathological diagnosis was allotypic epithelioid cells, and immunohistochemical analysis showed tumor cell positivity for cytokeratin, cytokeratin 5/6, carcinoembryonic antigen, thyroid transcription factor-1, and Ki-67 (20%). The tumor tested negative for calretinin, cytokeratin 20, and p53, which were compatible with lung IMA ([Figure 4](#)). Genetic testing revealed positive EGFR-21 mutations and echinoderm microtubule-associated protein-like 4-ALK fusion. This prompted treatment with alfatinib and crizotinib.

**TREATMENT**

Considering the side effects of the two targeted drugs, we initially prescribed alfatinib alone with a daily dose of 40 mg. After 1 mo, re-examination showed decreased pleural nodules, no pleural effusion recurrence, and significantly reduced serum lung cancer biomarkers. Meanwhile, the patient had a long-standing unresolved left lateral chest pain. After 2 mo, the second follow-up showed no changes in serum lung cancer biomarkers. However, the number of pleural nodules increased, and small metastases were observed in the contralateral lung. We adjusted the therapeutic plan based on these findings. Both alfatinib and crizotinib were administered.

**OUTCOME AND FOLLOW-UP**

The patient’s left lateral chest pain resolved within 1 wk. Thus far, the patient has taken alfatinib 40 mg per day and crizotinib 250 mg twice per day for more than 10 mo, and side effects, such as mild diarrhea and skin rashes, have occurred. After 12 mo, chest CT scan re-examination showed apparent reductions in the pleural nodules and no recurrence of pleural effusion.
Figure 1 A chest radiograph showed severe left hydrothorax.

Figure 2 Chest computed tomography demonstrated multiple nodules on left visceral pleura (indicated by orange arrows) and part of atelectasis in the left lower lung (showed by the blue arrow).

**DISCUSSION**

Lung cancer, which is associated with high morbidity and mortality among all types of tumors, frequently occurs in the sixth to eighth decades of life. It is uncommon among people around 30 years of age[8]. A new and rare type of adenocarcinoma, IMA, was reclassified as a variant of invasive adenocarcinoma by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society lung adenocarcinoma classification system because of its unique clinical, pathological, and radiological features as well as its unique genetic characteristics (lower prevalence of EGFR mutations)[9,10].
IMA has a tall columnar morphology with abundant mucus inside or outside the tumor cells. It exhibits adenocarcinoma patterns, including acinar, papillary, micropapillary, and solid predominant patterns. Specifically, IMA is divided into two groups based on the mucinous percentage: pure mucinous (invasive mucinous component > 90%) and mixed mucinous/non-mucinous (non-mucinous invasive pattern > 10%)[11]. IMA, a classification with poor survival outcomes compared with other adenocarcinoma subtypes, frequently spreads aerogenously, forming satellite tumors. Lymph node involvement and distant metastasis are less common[3,12].

On CT, IMA presents as consolidation, nodules, or ground-glass opacity. In a study by Nie et al.[13], 54 of 68 patients with IMA had solitary-type tumors on their chest CT scan. Nearly 80% of the imaging signs of IMA are solitary nodules or masses. The other 20% of CT findings are the pneumonic type, which is defined as consolidation without a defined shape, distributed along the lung lobe or lung segment, and sometimes with air bronchogram. In contrast, pleural effusion, as an early sign of IMA, is rare. In our case, immunohistochemical analysis showed that the tumor cells were of pulmonary origin. No clear pulmonary signs were observed on chest imaging after pleural effusion drainage. Instead, multiple nodules were observed in the left visceral pleura, which was more suggestive of pleural mesothelioma. Atelectasis was also observed in the left lower lung, which may have negatively influenced assessment and diagnosis.

Concerning the molecular features of IMA, several studies have linked IMA with frequent Kirsten rat sarcoma viral oncogene mutations and a lower prevalence of EGFR and ALK rearrangements, indicating a poor prognosis for target-specific drug treatment[14,15]. In our case, the EGFR-21 mutations and echinoderm microtubule-associated protein-like 4-ALK fusion were both positive, which is rare for IMA. This case emphasizes the significance of applying medicine to different targets in lung cancer. We will conduct a continuous follow-up of this young patient in the future.
Immunohistochemical analysis showed that the tumor cells were positive for cytokeratin, cytokeratin 5/6, carcinoembryonic antigen, thyroid transcription factor-1 and Ki-67. A: Cytokeratin; B: Cytokeratin 5/6; C: Carcinoembryonic antigen; D: Thyroid transcription factor-1; E: Ki-67.

CONCLUSION

In conclusion, atypical IMA is challenging to diagnose, especially in young patients. It is necessary to consider IMA in patients with unusual laboratory test results and radiological presentations.

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