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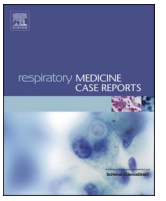

Case Report

A case report of high-grade fetal lung adenocarcinoma with KRAS mutation

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ABSTRACT

Fetal lung adenocarcinoma (FLAC) is a rare malignant tumor with a relatively good prognosis, and the probability of mutation with KRAS is very low. We report a middle-aged female patient with FLAC with KRAS mutation. The primary lesion was implanted with radioactive iodine 125 particles, and the lesion was smaller than before. However, the metastatic lesions progressed rapidly. After chemotherapy with pemetrexed disodium and cisplatin combined with bevacizumab to prevent angiogenesis, the primary lesions continued to shrink, and the metastatic lesions were significantly smaller than before. The patient has been followed up for 5 months and is generally in good condition. We report a case of H-FLAC with KRAS mutation, and its development and prognosis seem to be significantly abnormal from that of ordinary H-FLAC. It also provides a possible effective treatment for unresectable H-FLAC, but further research is needed.

1. Introduction

Fetal lung adenocarcinoma (FLAC) is an extremely rare malignant lung tumor originating from alveolar epithelium, so it is named because its histological morphology is similar to embryonic lung tissue of 8~16 weeks. According to different clinicopathological features, biological behaviors and clinical manifestations, FLAC can be divided into low-grade fetal adenocarcinoma (L-FLAC) and high-grade fetal adenocarcinoma (H-FLAC). Histologically, FLAC contains glandular components, and its tubules are lined with glycogen-rich non-ciliated cells. L-FLAC is characterized by complex gland structure, low nuclear atypia and significant mulberry formation, which is similar to fetal lung in pseudoglandular stage. However, H-FLAC showed the main nuclear heteromorphism, and the formation of mulberry was rarely observed. Clinically, H-FLAC is more common in elderly men, with a predilection age of 60–70 years, and a history of heavy smoking. Most of them are in stage III-IV at the time of seeing a doctor, and patients may have increased AFP. L-FLAC is more common in young women, aged 30–40, and most of them are in stage i-ii [1]. The adverse prognostic factors of FLAC include thoracic lymph node enlargement, metastasis at diagnosis and tumor recurrence [2]. The prognosis of FLAC is relatively good, and the 10-year survival rate is about 75 % [2]. According to reports, the incidence of FLAC in all lung tumors is estimated to be 0.1 %–0.5 %, while a recent study showed that the incidence of L-FLAC and H-FLAC in China patients were 0.32 % and 0.54 % respectively [3].

KRAS is the most common mutant oncogene in cancer, and its mutation is usually related to poor prognosis and treatment resistance. Studies have shown that KRAS mutation is more common in relatively common and life-threatening tumors, such as pancreatic cancer, colorectal cancer, small intestinal cancer, cholangiocarcinoma and lung adenocarcinoma; But it is rarely reported in

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FLAC; Therefore, the role of KRAS mutation in FLAC is still unknown.

2. Case report

Female, 53 years old, has no smoking history. In May 2020, under general anesthesia, she underwent radical resection of hilar cholangiocarcinoma + cholecystectomy + hilar cholangioplasty. During the operation, she was frozen, suggesting adenocarcinoma. After the operation, she was clinically diagnosed as "differentiated bile duct mucinous adenocarcinoma in hilar bile duct". I came to the hospital in February 2023 because of "cough for 1+ month"; Chest CT: "patch shadow of the outer basal segment of the lower lobe of the right lung", considering infection; Serum tumor marker carcinoembryonic antigen was significantly increased by 55.16ng/ml, cytokeratin 19 fragment was slightly increased by 7.89ng/ml, and neuron-specific enolase, squamous cell carcinoma antigen and alpha-fetoprotein were normal. CT-guided lung biopsy was performed, and the punctured tissue was sent for pathological examination. Microscopic examination showed that the tumor cells were partially columnar, the nucleus was moderately atypical, and there were glycogen vacuoles in the cytoplasm of the cells under and above the nucleus, and pathological mitosis and necrosis of the focus were seen (Fig. 1); Immunohistochemistry: PCK (+), CK7 (+), TTF-1 (−), Napsina (−), CK20 (−), CDX-2 (−), P40 (−), HMB-45 (−), S-100 (−), β. Pathological diagnosis of "high-grade fetal adenocarcinoma" (Fig. 1) showed that KRAS(p.G12D) was positive, with an abundance of 14.83 %, and there were no gene mutations in EGFR, ALK, ROS1, MET, RET and BRAF. The stage of thoracic surgery consultation was late, and there was no surgical indication. On February 23, 2023, CT-guided radioactive iodine 125 seed implantation was performed. After reexamination, the patients' primary lesions were smaller and CEA was lower than before (Table 1), but the metastatic lesions in the lung were significantly increased (Figure 2). Therefore, on April 15th, 2023, May 13th, 2023 and June 15th, 2023, chemotherapy with pemetrexed disodium and cisplatin combined with bevacizumab was given to prevent angiogenesis. The primary lesion continues to shrink, the metastatic lesion also significantly shrinks, and CEA continues to decline. The patient has been followed up for 5 months, and the patient is generally in good condition.

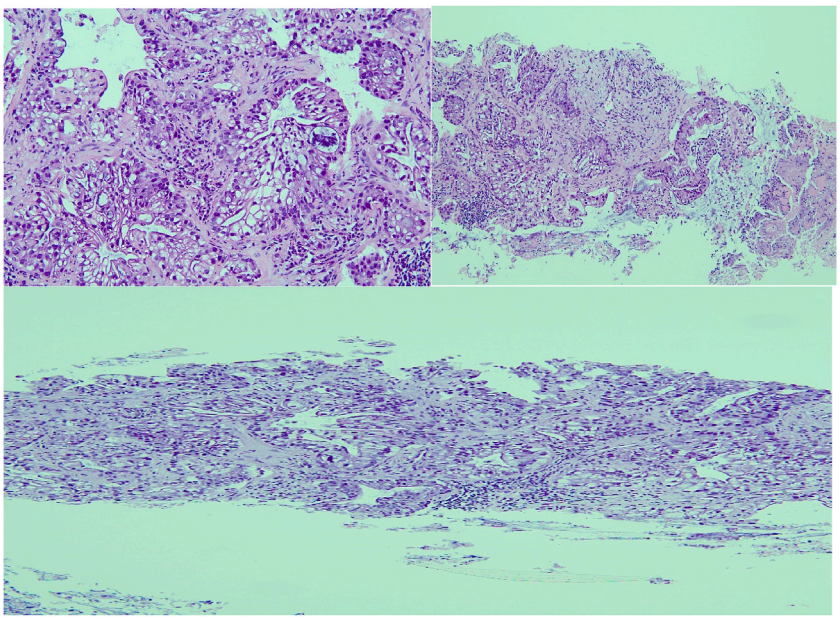
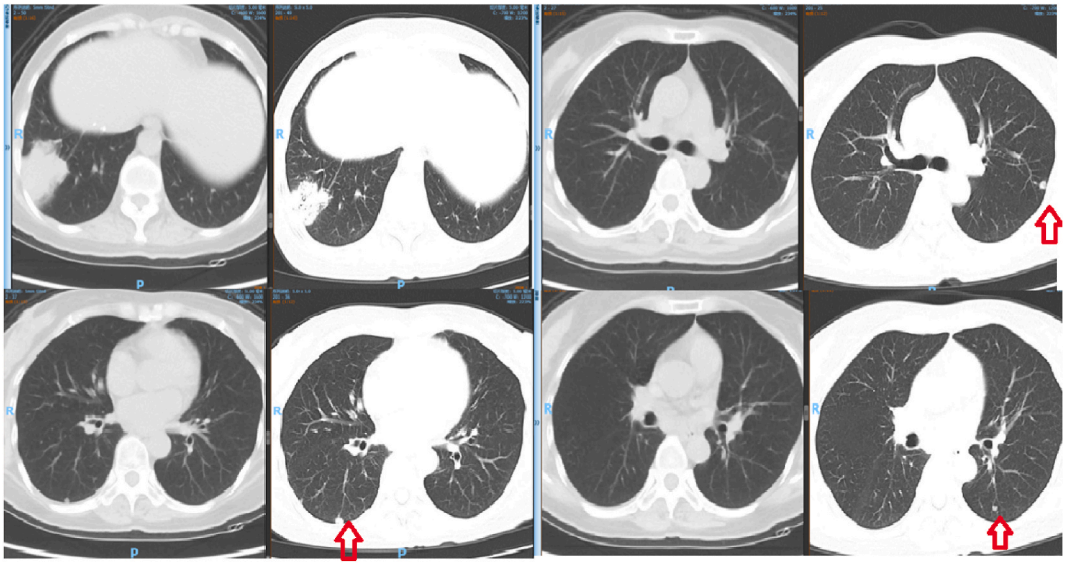
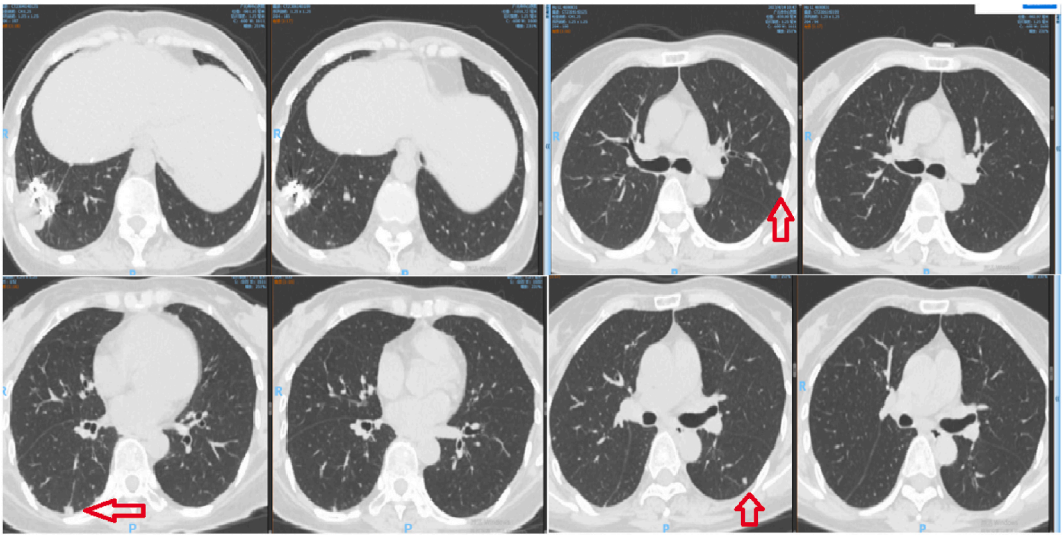


Fig. 1. Pathologically, some tumor cells are columnar, the nucleus is moderately heteromorphic, and there are glycogen vacuoles in the cytoplasm under and above the nucleus of the cells, showing pathological mitosis and necrosis in the focal area.

Table 1
CEA continues to decline.

Changes of CEA				
time	02–12	04–14	05–12	06–14
CEA(ng/ml)	55.16	32.34	12.41	6.91





3. Discussion

Fetal lung adenocarcinoma is a rare tumor, so the literature about FLAC mostly comes from case series or reports. It is found that the mutation rate of KRAS in FLAC is very low. KRAS mutation was not found in a study of 45 cases of FLAC in China [3], and in another study of 3 L-FLAC and 5 H-FLAC in China [4]. KRAS mutation was found in only one of 17 H-FLAC patients in Japan [5]. Since the mutation rate of KRAS in conventional lung adenocarcinoma is about 13 % [2],FLAC may have a unique molecular mechanism. Considering that the prognosis of FLAC is relatively good, our patient has made rapid and significant progress, and the age and sex of this patient are not in line with the common clinical manifestations of H-FLAC. It is not excluded that it is because of KRAS mutation.

At present, there are still many controversies about the treatment scheme of FLAC. Complete surgical resection is very important for its long-term survival, but the therapeutic effect of chemotherapy and radiotherapy is relatively limited. Therefore, the treatment of

unresectable FLAC is still being explored. Our patient was treated with radioactive iodine 125 seed implantation + pemetrexed + cisplatin + bevacizumab. The imaging and tumor markers showed that the treatment effect was remarkable and the patient was in good condition. For inoperable FLAC, it is a therapeutic scheme worth trying.

Compared with the rarity of KRAS mutation in FLAC, KRAS mutation is very common in cholangiocarcinoma and is a common carcinogen in cholangiocarcinoma. A study on surgical resection of 54 cases of hilar cholangiocarcinoma in Italy found that the mutation rate of KRAS was 22 %, and it was an independent predictor of prognosis [6]; In another study of 69 patients with cholangiocarcinoma, KRAS mutation was found in 17 patients, with a mutation rate of 24.6 %, and the mutation rate of KRAS in hilar cholangiocarcinoma was 53.3 %(8/15) [7]. KRAS in cholangiocarcinoma can inhibit autophagy pathway through ERK signal transduction, thus stabilizing the expression of PD-L1. Therefore, for this patient, it is worth studying whether KRAS mutation is a common pathogenic factor of cholangiocarcinoma and H-FLAC.

4. Conclusion

We report a case of H-FLAC with KRAS mutation, and its development and prognosis seem to be significantly abnormal from that of ordinary H-FLAC. It also provides a possible effective treatment for unresectable H-FLAC, but further research is needed.

Author's contribution

writing-manuscript preparation, Wang Jiaqi; Writing-criticism and editing, Yang Wenyong; Review-Zhao Shicai and Yu Bin. All authors have read and agreed to the published version of the manuscript.

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Informed consent statement

the patient's written informed consent has been obtained for publishing this article.

Data availability statement

No new data was created or analyzed in this study. Data sharing does not apply to this article.

Declaration of competing interest

No conflict.

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