



Gene profiling of metastatic small intestinal squamous cell carcinoma after lung squamous cell carcinoma surgery: a case report

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Background: Isolated metachronous metastatic small intestinal squamous cell carcinoma is rare, and it is sometimes difficult to determine whether small intestinal squamous cell carcinoma is metastatic by immunohistochemistry alone. At present, there is no literature analyzing the gene profile of metastatic small intestinal squamous cell carcinoma.

Case Description: We met a 62-year-old male patient who had a history of lung squamous cell carcinoma surgery. He was admitted for simultaneous jejunal squamous cell carcinoma, gastric adenocarcinoma, rectal adenocarcinoma. Endoscopic resection was performed for gastric cancer and rectal cancer, surgical resection was performed for jejunal squamous cell carcinoma, and docetaxel adjuvant chemotherapy were performed after surgery. No tumor recurrence was found in the reexamination in August 2021, and the patient was still alive during telephone follow-up before submission. This case presented two key challenges: (I) we could not determine whether the small intestinal squamous cell carcinoma was primary or metastatic; and (II) whether the patient, who had four different cancers, carried a genetic mutation that causes disease. We performed next generation sequencing (NGS) on four kinds of tissues and white blood cells, and found that the *EGFR* gene exhibited the same pathogenic mutation in both the lung and small intestine (c.2155G>Tp.G719C and c.2303G>Tp.S768I), and that the *PPM1D* gene had the same unidentified mutation (c.1787A>G:p.H596R) in two organs, therefore jejunal squamous cell carcinoma is considered as metastasis of lung squamous cell carcinoma. We found the *FGFR4* mutation (c.1162g>A:p.g388r) in the blood and four kinds of tissues, which may be pathogenic and significantly increase the risk of cancer in patients.

Conclusions: Genetic testing helped us identify the source of metastases, helped us find two rare mutations in the squamous cell carcinoma *EGFR* gene, and helped us find that *FGFR4* (c.1162G>A:p.G388R) mutation may play an important role in tumor development.

Keywords: Squamous cell carcinoma of lung; squamous cell carcinoma of small intestine; gene mutation; next-generation sequencing technology (NGS); case report

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Introduction

At present, about half of all lung cancer patients have distant metastasis at diagnosis, with the common metastatic sites being the lung, liver, bone, brain, and adrenal gland. Surprisingly, approximately 4.6–14% of lung cancer patients have gastrointestinal metastasis at autopsy, only 0.3–1.7%

of lung cancer patients were found with gastrointestinal metastasis due to abdominal symptoms such as obstruction, perforation, and bleeding (1–3). Sometimes persistent fecal occult blood suggests gastrointestinal metastasis of lung cancer (4). Small intestine and large intestine account for 60% and 25% of gastrointestinal metastases of lung

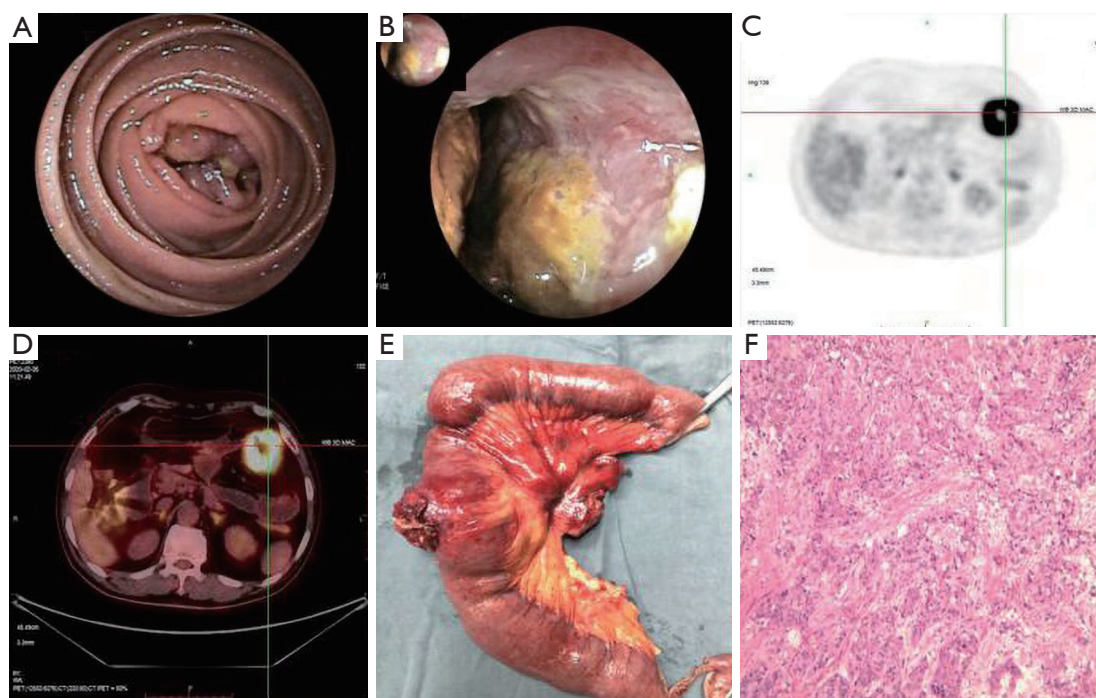


Figure 1 The small intestine squamous cell carcinomas (A,B) endoscopic pictures; (C,D) PET-CT pictures; (E,F) surgical specimens and immunohistochemical image. (200×, HE stain). PET-CT, positron emission tomography-computed tomography.

cancer. However, most previous reports mainly discussed the diagnosis and treatment of the disease, but none of the studies looked at the gene profiles of small intestinal cancer and lung cancer to gain insight into the characteristics of the disease. We encountered a case of jejunal squamous cell carcinoma who had lung squamous cell carcinoma surgery, we performed next generation sequencing (NGS) testing and found some interesting genetic mutations. We present the following case in accordance with the CARE reporting checklist (available at <https://tcra.amegroups.com/article/view/10.21037/tcr-22-481/rc>).

Case presentation

Our patient is a 65-year-old male with a history of smoking 15 cigarettes a day, his father died of colon cancer. On July 25, 2019, positron emission tomography-CT (PET-CT) showed left lung malignant tumor with left hilar lymph node metastasis, and no abnormal metabolic lesions were found in other organs.

On August 5, 2019, radical treatment was performed on the left lobe of lung in the Shanghai Pulmonary Hospital, and postoperative pathology showed squamous cell

carcinoma. Immunohistochemistry showed CK (+), VIM (+), TTF-1 (–), P40 (+), and PD-L1 (22c3) (30%). Postoperative adjuvant chemotherapy (gemcitabine + carboplatin) was administered over eight courses, and the last chemotherapy was conducted on February 10, 2020.

On February 20, 2020, the patient experienced abdominal pain. Endoscopic biopsy showed high-grade intraepithelial neoplasia of the gastric horn mucosa. Enteroscopy found protuberant lesions of rectal mucosa, and endoscopic mucosal resection (EMR) was conducted. Postoperative pathology showed rectal adenocarcinoma infiltrating half of the submucosa, with negative basal and lateral margins. All blood tumor markers were normal. Enteroscopy showed a jejunal mass (*Figure 1A,1B*), and biopsy pathology showed squamous cell carcinoma. PET-CT showed an irregular ring thickening of the jejunal wall, abnormal increase of glucose metabolism, and enlargement of the lymph nodes adjacent to mesenteric space (*Figure 1C,1D*).

On March 10, 2020, endoscopic mucosal dissection (ESD) + laparoscopic jejunal tumor resection were performed simultaneously. Postoperative pathology of the gastric mucosal lesions showed moderately differentiated adenocarcinoma in the muscularis mucosa, negative cutting

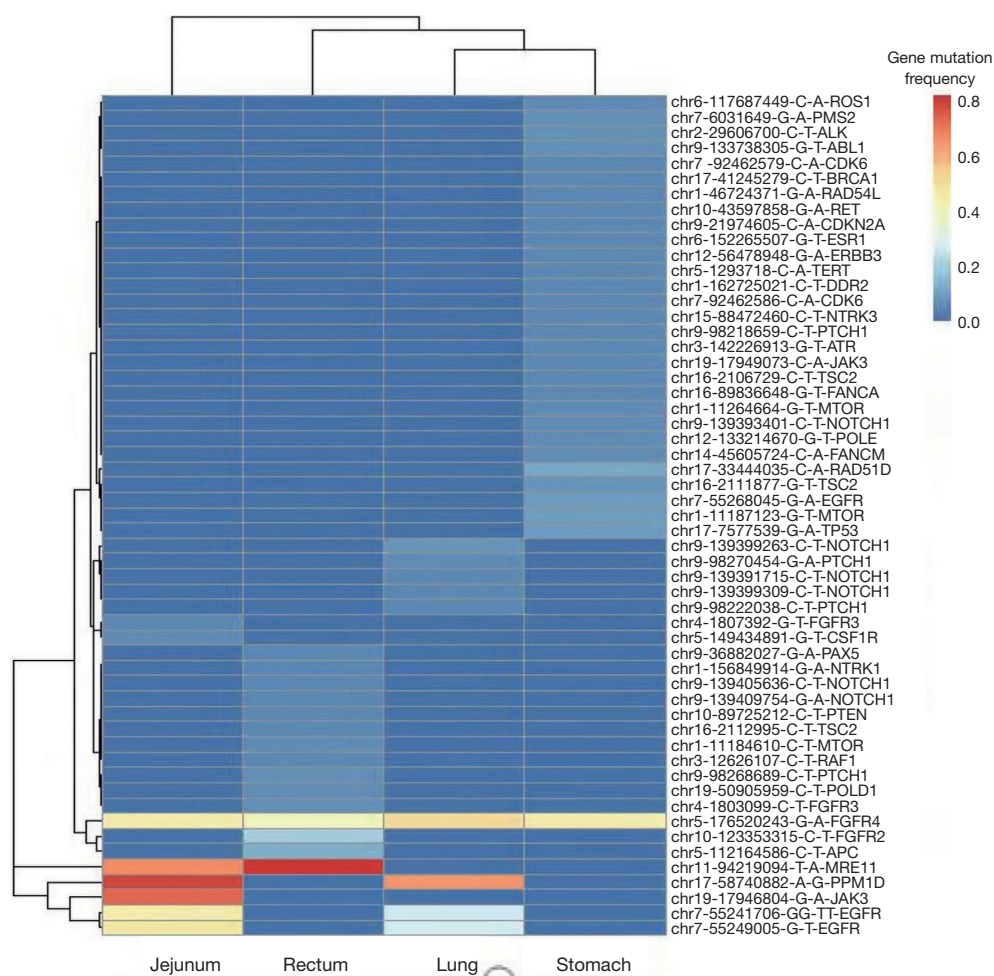


Figure 2 Gene mutation spectrum of four tissues (jejunum, rectum, lung, stomach).

edge, and negative vessels. Postoperative pathology of the jejunal tumors showed poorly differentiated squamous cell carcinoma of the jejunum, infiltrating into the serous layer, cancer invasion of vessels and nerves, one cancer nodule in the mesentery, and no lymph node metastasis. Immunohistochemistry showed that P40 (+), CK5/6 (+), CK7 (+), CK20 (-), TTF-1 (-), PD-L1 (22c3) (60%), CDX2 (-), Ki-67 80% (+), Villin (-) (*Figure 1E, 1F*). The postoperative diagnosis was as follows: (I) poorly differentiated squamous cell carcinoma of the jejunum; (II) early gastric cancer; (III) early rectal cancer; and (IV) postoperative squamous cell carcinoma of the left lung.

We detected a 642-gene panel NGS in four kinds of cancer tissues and blood leukocytes, and found the following: (I) the *EGFR* gene exhibited the same pathogenic mutation in both lung and small intestine tissues (c.2155G>Tp.G719C and c.2303G>Tp.S768I), and the

mutation frequencies in the lung and small intestine were 27.5% and 26.4%, and 46.4% and 45%, respectively; (II) the mutation frequencies of the *PPM1D* gene (c.1787A>G:p. H596R) in the lung and small intestine were 64.6% and 78.2%, respectively; (III) *FGFR4* mutation (c.1162G>A:p. G388R) was found in the blood and four tissues (jejunum, lung, stomach, rectum); and (IV) the mutation spectrum of gastric and rectal tissues was almost different from that of squamous cell carcinoma (*Figure 2*).

The lung and small intestine had identical *EGFR* gene mutation sites. The patient was diagnosed with metastatic jejunal squamous cell carcinoma and was given 8 courses of docetaxel at 120 mg each. On August 7, 2021, chest and abdominal CT was conducted and blood tumor markers were re-examined, and no tumor recurrence was observed. The patient was still alive during telephone follow-up before submission. (*Figure 3*).

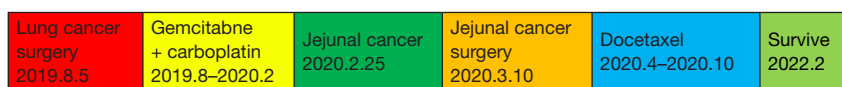


Figure 3 Treatment and follow-up timeline.

All procedures performed in this study were in accordance with the ethical standards of the institutional review board of Wenzhou central Hospital and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

Discussion

The patient was diagnosed with jejunal squamous cell carcinoma 9 months after lung cancer surgery, but we don't know if jejunal squamous cell carcinoma is primary or metastatic. On the one hand, primary tumor was considered because there was no intestinal metastasis on PET-CT (which is more sensitive to squamous cell carcinoma) before lung cancer surgery. On the other hand, metastatic tumor was considered because lung and jejunum are squamous cell carcinomas, the interval between onset is not long, and small intestinal metastasis of lung cancer is more common than primary small intestinal squamous cell carcinoma.

It has been reported that CK7, CK20, TTF-1, and CDX2 have high sensitivity and specificity in distinguishing primary from metastatic tumors. CK7 and TTF-1 are expressed in lung tissue, while CK20 and CDX2 are mainly expressed in intestinal tissue (5); however, the above indicators can be used to judge adenocarcinoma tissue. Only CK7 positive in the patient's small intestinal squamous cell carcinoma could not confirm that the small intestinal squamous cell carcinoma is a metastatic tumor. Therefore, we analyzed whether the gene mutation spectrum and mutation frequency of the tumors were consistent. NGS detection showed that there were high frequency *EGFR* gene mutations (c.2303G>T, c.2155G>T) in the lung and small intestinal squamous cell carcinomas. These two mutations were included in the ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>); considering the pathogenic mutation combined with the pathogenesis sequence, they were diagnosed as metastatic jejunal squamous cell carcinoma.

This is the first reported gene mutation profile of

metastatic small intestinal cancer. A rare pathogenic double site *EGFR* gene mutation was observed in squamous cell carcinoma. Previous reports have indicated that compared with other rare mutations in non-small cell lung cancer (NSCLC), the frequency of these two mutations may be higher (6,7), and compared with single site mutation, double site mutation has shorter a progression free survival (PFS) and a lower object response rate (ORR) (8). *EGFR* mutation are present in 4.5% of lung squamous cell carcinomas, and treatment with tyrosine kinase inhibitor (TKI) provide a survival benefit, but this benefit may still be lower than that of lung adenocarcinomas with *EGFR* mutations (8). We also found a high frequency mutation of *PPM1D* (c.1787A>G) in lung and small intestinal squamous cell carcinoma tissues for the first time, which were included in the exome aggregation consortium (EXAC) (<http://exac.broadinstitute.org>) and the Chinese 1,000 genome databases (<http://www.internationalgenome.org/data>). The minor allele frequency (MAF) values were g =0.000059/7 and g =0.0002/1, respectively. *PPM1D* is a negative regulatory gene of deoxyribonucleic acid (DNA) damage repair and a negative regulatory of the tumor suppressor gene, *p53* (9). It is involved in the occurrence and progression of numerous tumors, including pancreatic, colorectal, NSCLCs (10), etc. It is worth noting that *PPM1D* may be a potential therapeutic and prognostic target for multiple tumors. A study has shown that PD-L1 is highly expressed in the gastrointestinal metastasis of lung cancer (11). In our case, PD-L1 expression in lung cancer and small intestinal squamous cell cancer tissues was 30% and 60%, respectively.

Considering that the patient's father had a history of colon cancer, and the patient had both gastric and rectal adenocarcinoma, we suspected whether there was a pathogenic germline gene mutation. We found *FGFR4* (c.1162G>A:p.G388R) in patients' blood leukocytes and four tumor tissue samples, which was included in the ClinVar database as variant of undetermined significance (VUS), MAF =0.3 in the 1,000 human genome database, and was common to nearly half of cancer patients. Ulaganathan *et al.* reported that in a mouse model of breast cancer and lung cancer carrying the mutation, this mutation changed

the transmembrane structure of *FGFR*, exposed the signal transducer and activator of transcription 3 (STAT3) binding site in the membrane, and made STAT3 protein aggregate and phosphorylate, thereby activating the STAT3 signaling pathway and accelerating tumor progression, resulting in a worse prognosis (12).

Since the patient's history and immunohistochemistry results could not determine the origin of the rare small intestinal squamous cell carcinoma, we examined the lung and small intestinal squamous cell carcinoma tissues by NGS, and confirmed that the small intestinal squamous cell carcinoma is a metastatic malignant tumor. We revealed the gene mutation spectrum of metastatic small intestinal squamous cell carcinoma for the first time, and identified a rare double site mutation of the *EGFR* gene, which has considerable diagnostic and treatment value. We also discovered, for the first time, a high frequency mutation of *PPM1D* gene (c.1787A>G) in lung and small intestine squamous cell carcinoma tissues, which may be involved in tumor occurrence and progression. In addition, we found that the patient carried a potentially pathogenic germline mutation in the *FGFR4* gene, which may increase the patient's risk of various cancers.

This is the first paper to analyze the gene profile of metastatic small intestinal squamous cell carcinoma. Genetic testing helped us identify the source of metastases, helped us find two rare mutations in the squamous cell carcinoma *EGFR* gene, and helped us find that *FGFR4* (c.1162G>A:p.G388R) mutation may play an important role in tumor development. The limitations with our study including the nature of work, only one case report, and the significance of *PPM1D* gene and *FGFR4* gene mutations is uncertain. So the significance of these mutations need to be explored in the future, and the patient need follow-up to see if other malignancies recur.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-481/rc>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-481/coif>).

YW is from Zhejiang Shengting Medical Laboratory Co., Ltd. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional review board of Wenzhou central Hospital and with the Helsinki Declaration (as revised in 2013). 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 editorial office of this journal.

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