RECTAL METASTASIS IN LUNG CANCER: A CASE REPORT AND REVIEW OF THE LITERATURE

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Gastrointestinal metastasis in lung cancer is not commonly encountered clinically, of which rectal involvement is a sporadic event. There were few reports about rectal metastasis in lung cancer. All of them had a dismal prognosis. We report a case of synchronous rectal metastasis in a lung cancer patient with a different clinical scenario, treatment, and prognosis. The patient presented with infrequent hematochezia due to a rectal mass confirmed as adenocarcinoma on core biopsy. Computer tomography showed many nodules in both lungs, which raised the initial diagnosis of pulmonary metastasis in rectal cancer. However, we decided to perform immunohistochemistry on the rectal biopsy specimen, which, surprisingly, revealed the site of origin was from the lung. Subsequently, next gene sequencing was performed and detected an exon 19 deletion on the EGFR gene. Though he had infrequent hematochezia, we decided to treat him with Erlotinib (a first-generation TKI) and closely monitored the rectal symptoms. Six months later, he achieved a complete response of both lung and rectal lesions. At present, he has been progression-free for 14 months. Thus, physicians should always be aware of this differential diagnosis in synchronous tumors and carefully consider the optimal treatment to start.

Keywords: rectal metastases, lung cancer, TKI.

I. INTRODUCTION

Gastrointestinal metastasis in lung cancer is not commonly encountered clinically, of which rectal involvement is a sporadic event. This rare disease could be diagnosed by carefully reviewing the biopsy regimen of gastrointestinal lesions and performing immunohistochemistry (IHC) to confirm the site of origin. To the best of our knowledge, there were only three case reports about rectal metastasis in lung cancer.[1-3] All of them had metachronous rectal metastasis progressing after treatment of the primary lung cancer. The patients had undergone hemicolectomy or palliative chemotherapy in those cases, but all had a dismal prognosis. Besides, none of them harboured the sensitizing EGFR mutations (exon19 del or exon21 L858R), thus could not opt for Tyrosine kinase inhibitors. Here we report a case of synchronous rectal metastasis in a non-small cell lung cancer patient with a different clinical scenario, treatment of choice, and prognosis.

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II. CASE PRESENTATION

In June 2020, a 63-year-old former smoker male (20 pack-years) came to his primary physician at Hoang Long Clinic with a complaint of infrequent hematochezia. Colonoscopy was performed, revealing a 1.5 cm mass with centered ulceration located at the middle rectum. The core biopsy result was adenocarcinoma, and patient was transferred to Hanoi Medical University Hospital for further evaluation. On clinical examination, he did not show any other abnormal symptoms and had a good performance status. We performed the CT-scanner of the chest and abdomen, and

detected many nodules in both lungs, with the largest spiculated nodule in the left upper lobe. (**Figure 1A**). Transthoracic biopsy of this mass was performed, which also revealed an adenocarcinoma lesion. (**Figure 2**)

This finding raised the suspicion of stage IV rectal cancer metastatic to both lungs. However, given the spiculated border of the upper left lung tumor, which might be more compatible with a primary lesion than a secondary lesion, we decided to perform immunohistochemistry (IHC) of the rectum biopsy specimen. Surprisingly, the IHC feature was positive for TTF-1, EGFR and negative for CDX2, SATB2, and Her-2. (**Figure 3**). These markers were consistent with a metastatic lesion from lung cancer. The biopsy and IHC were also performed on the largest lung lesion, concordance with primary adenocarcinoma lung cancer (positive for CK7, TTF1, NapsinA, and negative for CK20, CDX2, P40, CK34BE12) (**Figure 4**). Subsequently, next gene sequencing was performed on lung tumor specimens and detected an exon 19 deletion on the EGFR gene.

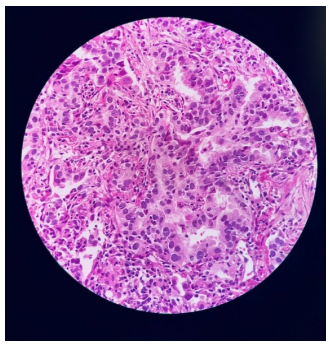


Figure 2. Adenocarcinoma characteristic of the largest lung lesion

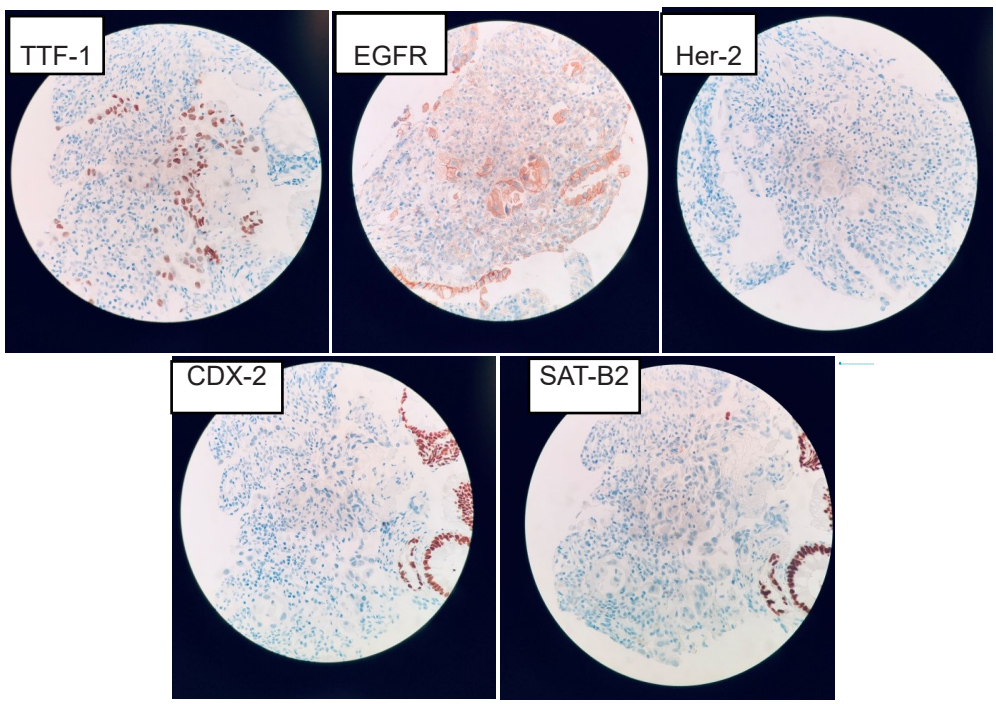


Figure 3. Immunohistochemical staining of histological biopsy from rectal mass: an adenocarcinoma positive for TTF-1, EGFR and negative for CDX2, SATB2, and Her-2

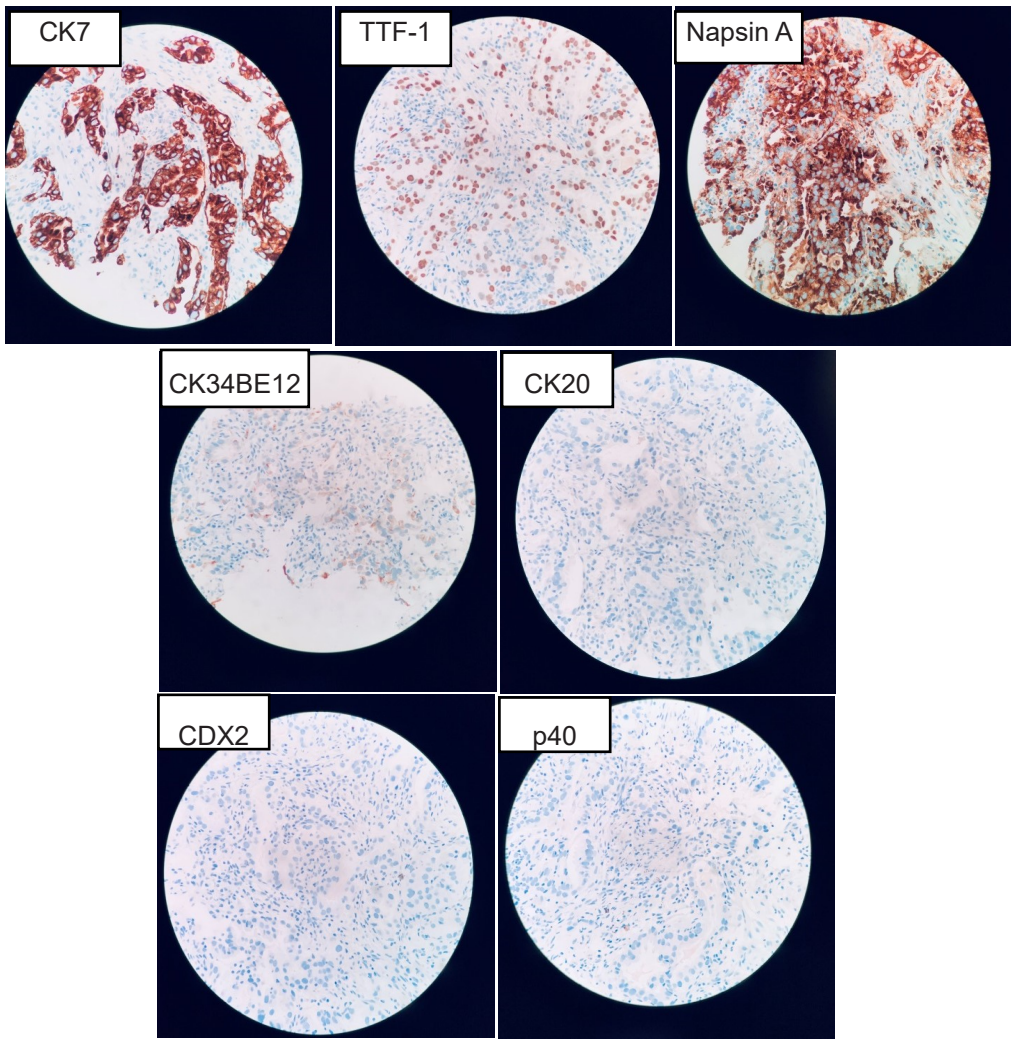
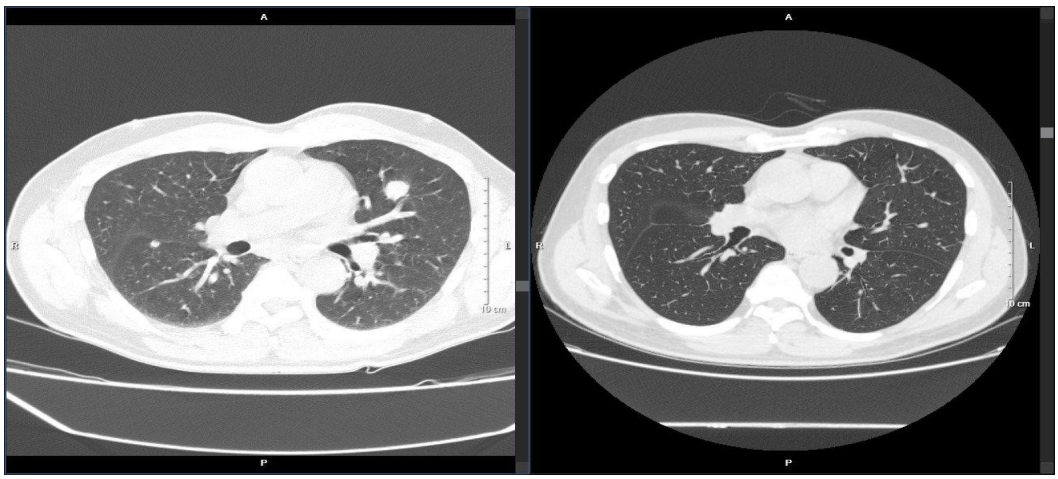


Figure 4. Immunohistochemical staining of histological biopsy from the largest lung lesion: an adenocarcinoma positive for positive for CK7, TTF1, NapsinA, and negative for CK20, CDX2, P40, CK34BE12

PET/CT revealed multiple PET-positive sites, including a mass in the left lung 20x15 mm in size (SUV max 3.18) (correlation with the primary malignant site), numerous small nodules in both lungs (SUV max 1.37), a subcarinal lymph node (SUV max 4.64), a right adrenal gland mass 20x13 mm (SUV max 8.7), left adrenal gland mass (SUV max 6.04). His final diagnosis was of a T4N2M1 (stage IV, metastasis to contralateral lung, adrenal glands, and rectum) non-small-cell lung cancer (NSCLC). The pretreatment CEA level was 26.7 ng/mL.

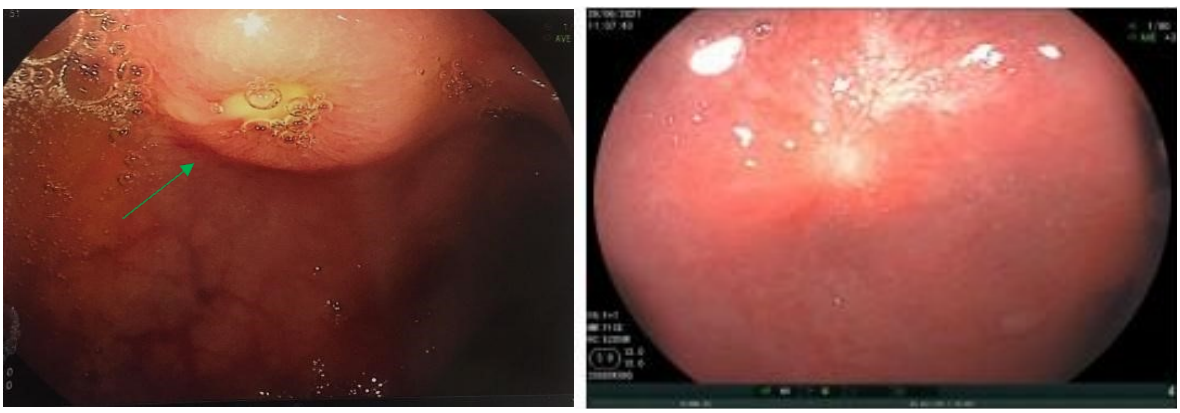
After discussion with the multidisciplinary team, treatment was commenced with Erlotinib (Tarceva 150 mg) once a day - a first-generation tyrosine kinase inhibitor (TKI). The drug was taken continuously until progression. The patient responded well to the regimen and had no serious adverse events. CT scans showed a complete response of all lung lesions and adrenal lesions after six months (**Figure 1B**). Colorectal endoscopy also showed a complete response of the rectal mass (**Figure 5)**. CEA

level was also reduced to 5.7 ng/mL. At present, he has been progression-free for 14 months after erlotinib administration.



A B

Figure 1A-1B. Complete response in lung lesions (arrow) on CT scan: (A) before treatment, (B) after six months of erlotinib administration



A B

Figure 5. Complete response in rectal metastasis (arrow) on colonoscopy: (A) before treatment, (B) after six months of erlotinib administration

III. DISCUSSION

The scenario of patients presenting with both synchronous rectal and lung tumors is commonly encountered clinically, which is usually attributed to lung metastases from rectal cancer. This diagnosis is supported by the fact that the lung is one of the most frequent sites of metastatic dissemination in colorectal carcinoma, affecting 10 – 25% of all patients throughout the disease.[4] However, in this particular case, we did not satisfy the initial diagnosis of a stage IV colorectal cancer due to the spiculated lung lesion, which was not compatible with rounded nodules frequently observed in pulmonary metastases.[5] Thus, we performed the IHC on the rectal mass specimen, intending to figure out the site of origin. This

step is crucial before making a final diagnosis since treatment is different between these two differential diagnoses.

Gastrointestinal (GI) metastases are not common in lung cancer, accounting for only 0.3% to 1.7% in clinical studies.[6,7] In a series of 2,066 lung cancer patients, only seven patients (0.33%) had GI metastases. None of them had rectal involvement.[6] Other study has also shown that colorectal metastases were exceptionally encountered, particularly the rectum.[5] The underlying spreading of cancer cells from the lung to the gastrointestinal tract remains uncertain, though some observational studies showed that malignant cells of lung cancer tend to deposit in the subserosal layer of the bowel and subsequently proliferate into new foci.[7] This could be attributed to several following mechanisms. Small bowel and stomach are frequent localization as part of hematogenous dissemination through the spinal vein.[8,9] Colorectum metastases, on the other hand, are less usual and may involve retroperitoneal and mesenteric lymphatic routes.[7] Besides, in terms of histology, squamous cell carcinoma is one of the most frequent causes of GI metastases.[7] Similarly, large-cell and small-cell carcinomas contribute to a high percentage of GI metastases.[7] This may be because the adenocarcinoma histology is less aggressive than other subtypes, thus having a lower metastatic rate.

To the best of our knowledge, this was the fourth case of rectal metastasis in lung cancer, and our case had different presentations and outcomes from previous cases. We found three published case reports on rectal metastases from lung cancer. The first patient had metachronous rectal metastases after two years of treating small-cell lung cancer.[1] He underwent an abdominoperineal resection and then received six courses of etoposide, cyclophosphamide, methotrexate, and vincristine. Unfortunately, the disease recurred six months later, and he died after one year of detecting pulmonary metastases.[1] The second patient had a hemicolectomy due to severe rectal haemorrhage. The pathological diagnosis was non-small-cell lung cancer (large cell carcinoma). Four months later, she passed away because of disease progression.[2] The third patient had T2N2M1 (metastasis to the contralateral lung) squamous cell lung cancer and received gemcitabine monotherapy due to poor performance status. After four cycles of gemcitabine, he developed abdominal pain, and the pelvic MRI showed the thickening of the rectum wall with enlarged regional lymph nodes. IHC pattern of rectal lesioned was then performed, which later confirmed squamous cell carcinoma from lung cancer. Rectal radiotherapy was started for symptomatic control, but only five weeks after, he died due to respiratory insufficiency.[3] Our case, therefore, would be the first case report of rectal metastasis in adenocarcinoma lung cancer using TKI for first-line treatment.

In terms of diagnosis, immunohistochemical staining is essential for the clarification between pulmonary and GI malignancies. A positive TTF-1 stain is essential in lung adenocarcinomas, in which TTF-1 differentiates between adenocarcinoma of lung from colorectal origin. The test result occurs with 57.5–76% sensitivity and a specificity of 99 – 100%.[11] Additionally, positive staining for CK5/6 or p63 with negative staining for CK20 and CDX-2 typically represents adenocarcinoma of the lung; a positive stain for CDX-2 rules out adenocarcinoma from the lung.[12] CDX2 expression has been reported to be organ-specific and usually is expressed throughout embryonic and postnatal life within

the nuclei of epithelial cells of the alimentary tract from the proximal duodenum to the distal rectum. Thus, a negative result tends to rule out adenocarcinoma from the GI tract.[12] The patient, in this case, had a positive stain for TTF-1 and a negative stain for CDX2, which was highly suggestive of pulmonary origin.

Concerning whether treatment should be used first, we initially intended to perform the segmentectomy of the rectum to solve the haemorrhage of the tumor or give him palliative rectal radiation. However, given the detrimental effect on the quality of life after surgery or radiotherapy and the high response rate of EGFR-TKI in lung cancer with a mutation on exon 19, we decided to begin with Erlotinib (a first-generation EGFR-TKI) first to control both the primary and metastatic lesions. Previous studies showed that the median time to response ranged from 4 to 8 weeks, which was short enough for us to go with TKI and wait for an early response.[13,14] Indeed, the haemorrhage stopped entirely just after the first month, and the patient achieved a complete response of all lung lesions after six months. Colorectal endoscopy also showed a complete response of the rectal mass. At present, he has been progression-free for 14 months after erlotinib administration. This treatment procedure showed a very different prognosis from the three cases mentioned above.

IV. CONCLUSION

Rectal metastasis from lung cancer is a rare event, but it does happen. Thus, physicians should always be aware of this differential diagnosis in synchronous tumors and carefully consider the optimal treatment to start. In similar cases, patients with sensitizing EGFR mutations should opt for Tyrosine kinase inhibitors in first-line treatment to achieve the best response and clinical benefit.

V. ETHICS IN SCIENTIFIC RESEARCH

This report was approved by the Head of Oncology and Palliative Care Department, Hanoi Medical University Hospital. The patient agreed to public his case without his detailed personal information and gave written informed consent.

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