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CASE REPORT

Late-Onset Lung Metastasis in Rectum Cancer Can Be Confused with Primary Lung Cancer; a Case Report and Literature Review

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Introduction

About 20 to 50% of patients who undergo curative resection for colorectal cancer and receive adjuvant treatment will eventually develop metastases. Early studies reported that the liver, lungs, peritoneum, and bones are the main metastatic sites of rectal cancer [1, 2]. Recently published studies have reported that lungs are the leading site for metastases from rectal cancer [3–6]. Although most recurrences occur within the first 5 years after the initial treatment in patients with rectal cancer, occasional recurrences may occur after 5 years from the time of initial treatment [7, 8]. Most studies have researched recurrences within 5 years after surgery; however, there are few studies that have researched recurrences within 10 years [9, 10]. Therefore, there is no consensus on optimum follow-up duration.

Herein, we report a patient who presented with a primary mass lesion in the lung 10 years after the surgery for rectal cancer.

Case Report

A 52-year-old female patient was underwent colonoscopy due to the presence of rectal bleeding and changes in bowel habits. The procedure was revealed an ulcerated, infiltrative rectal mass of 6 cm in diameter. Histopathological examination of the biopsy specimen obtained during colonoscopy was reported as adenocarcinoma. The serum level of carcinoembryonic antigen (CEA) was within the normal range (2.3 ng/ml), and imaging studies did not reveal any distant metastases; consequently, a low anterior resection procedure was performed. The histopathology report described a rectal tumor 6 cm in diameter which spread beyond the muscularis propria with negative lymphovascular invasion and negative perineural invasion, and no tumor had been found on proximal, distal, and radial surgical resection margins; however, three lymph nodes were positive for tumoral infiltration and the tumor was reported as well-differentiated adenocarcinoma (T3N1). Therefore, our patient received 6 cycles of chemotherapy regimen including fluorouracil + folinic acid (FUFA) days 1–5 which was followed by long-term radiation therapy with a total irradiation dose of 50 cGy given concurrently with fluorouracil. Follow-up visits were scheduled every 3 months for the first 2 years and every 6 months for the next 3 years and then annually. The patient presented with fatigue and cough during the interval between two follow-up visits. Fatigue and cough were present for the last 2 months and cough did not respond to antitussives. His physical examination did not reveal pathological findings other than rhoncus in the medial and basal parts of the left lung. Complete blood count, blood chemistry, and CEA results (1.6 ng/ml) were within normal limits. Colonoscopy did not reveal any pathological findings at the anastomotic site and in the other colonic segments visualized during colonoscopy. Computed tomography (CT) scans of the chest and abdomen showed a 6-cm spiculated mass in the perihilar region, in the superior aspect of the left lower lobe, and in mediastinal lymphadenopathies 2 cm in diameter. He had no history of tobacco use, and F-18 fluoro-2-deoxy-glucose (FDG) positron-emission tomography (PET) CT showed an increased uptake in the soft tissue (6 cm in diameter extending to the lateral and posterobasal aspects of the left lower lobe) (SUVmax 12.9); increased uptake was also observed in both lungs, in multiple nodules 1.6 cm in diameter (SUVmax 1.8–12.0), and in mediastinal lymph nodes with a short axis varying between 1 and 2 cm

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(SUVmax 3.8–7.9) (Fig. 1). The result of the histopathological examination of the biopsy specimen obtained during bronchoscopy was reported as adenocarcinoma negative for cytokeratin (CK) 7, TTF, P63, chromogranin, synaptophysin, napsin, and ER and positive for CK 20 and CDX2 (Fig. 2). The pulmonary mass lesion was considered a metastasis from rectal adenocarcinoma and found to be KRAS C.35G>T p.G12V mutant, in the mutation analysis. A permanent central venous port catheter was implanted, and a chemotherapy regimen including FOLFOX (5-fluorouracil, folinic acid, oxaliplatin) + bevacizumab was started. The assessment conducted during the cycle 6 revealed that cough had resolved, and a repeat FDG PET-CT showed that the uptake in the 2.5-cm mass in the left lower lobe was relatively decreased (SUVmax 7.4) compared to that in the baseline and mediastinal lymph nodes as well as certain lung nodules disappeared. Currently, active chemotherapy is still ongoing.

Discussion

The standard of care in patients with locally advanced rectal adenocarcinoma (clinically T3–T4 and/or node positive) includes fluoropyrimidine-based chemotherapy combined with neoadjuvant radiation therapy which is followed by a total mesorectal excision. Although the administration of adjuvant chemotherapy is a common practice, there is no consensus on its use [11]. Twenty-five to 50% of patients with resected rectal cancer who have received adjuvant therapy will develop metastases. When compared to patients with colon cancer, the rate of lung metastases has been reported to be higher in patients with rectal cancer [12, 13]. The most likely cause of this difference may be the difference in the venous drainage of the colon and rectum.

In patients with colorectal cancer, 90% of recurrences following curative surgery occur within the first 5 years (mostly within 3 years after surgery) [14]. Although postoperative follow-up policies vary widely between healthcare facilities, most follow-up programs end 5 years after the curative surgery. Therefore, there are a limited number of studies on the characteristics of late recurrences and the majority of these studies have been conducted in patients with colon cancer. Studies on recurrence rates in patients with rectum cancer after the first 5 years reported that recurrences occurred in 1.2 to 9% of these patients > 5 years after the surgery and the majority of these studies had a follow-up period of 5 to 10 years [15–17]. In a study conducted by Cho et al. in 352 patients with colorectal cancer, the rate of late recurrence (> 5 years) was found to be 1.2% ($n = 18$) and the lung was the most common site of

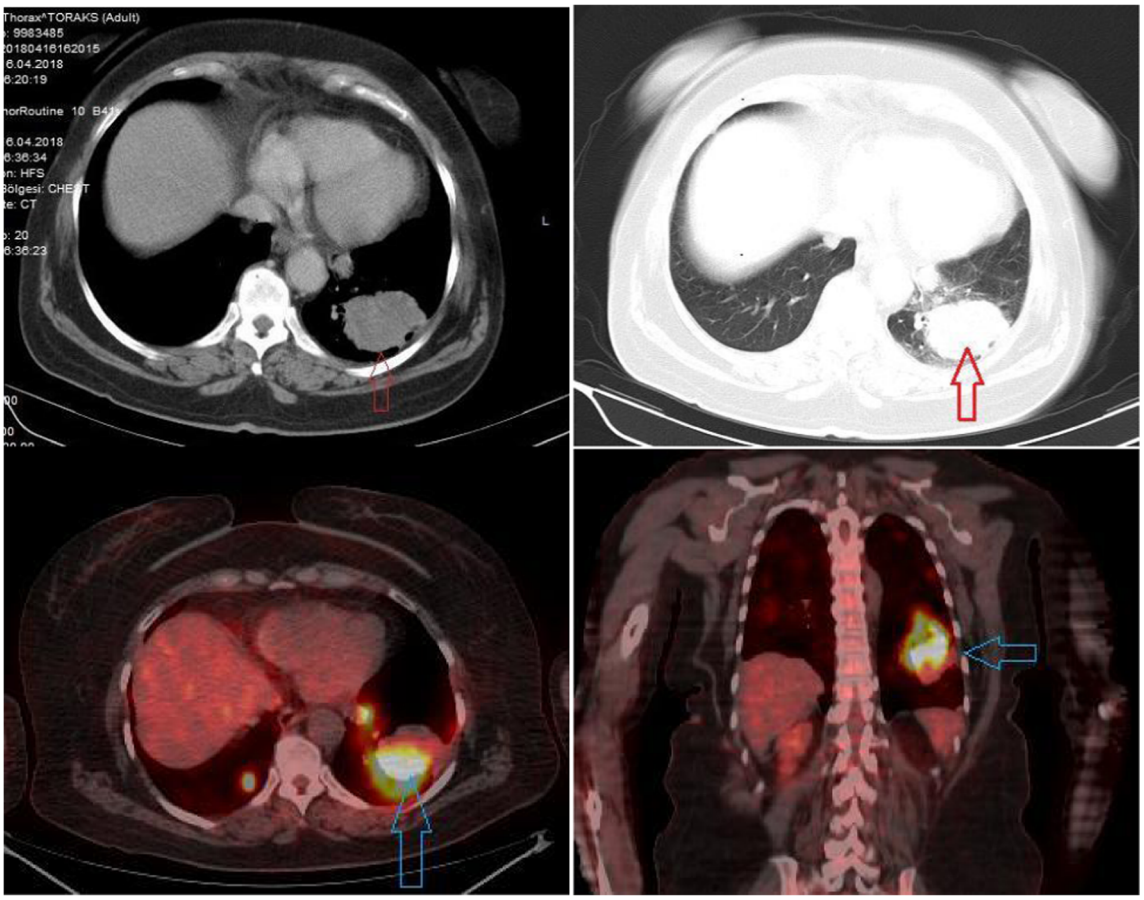

Fig. 1 Computed tomography (CT) and positron-emission tomography/CT scan of the mass, showing left lung metastasis (indicated with arrows)

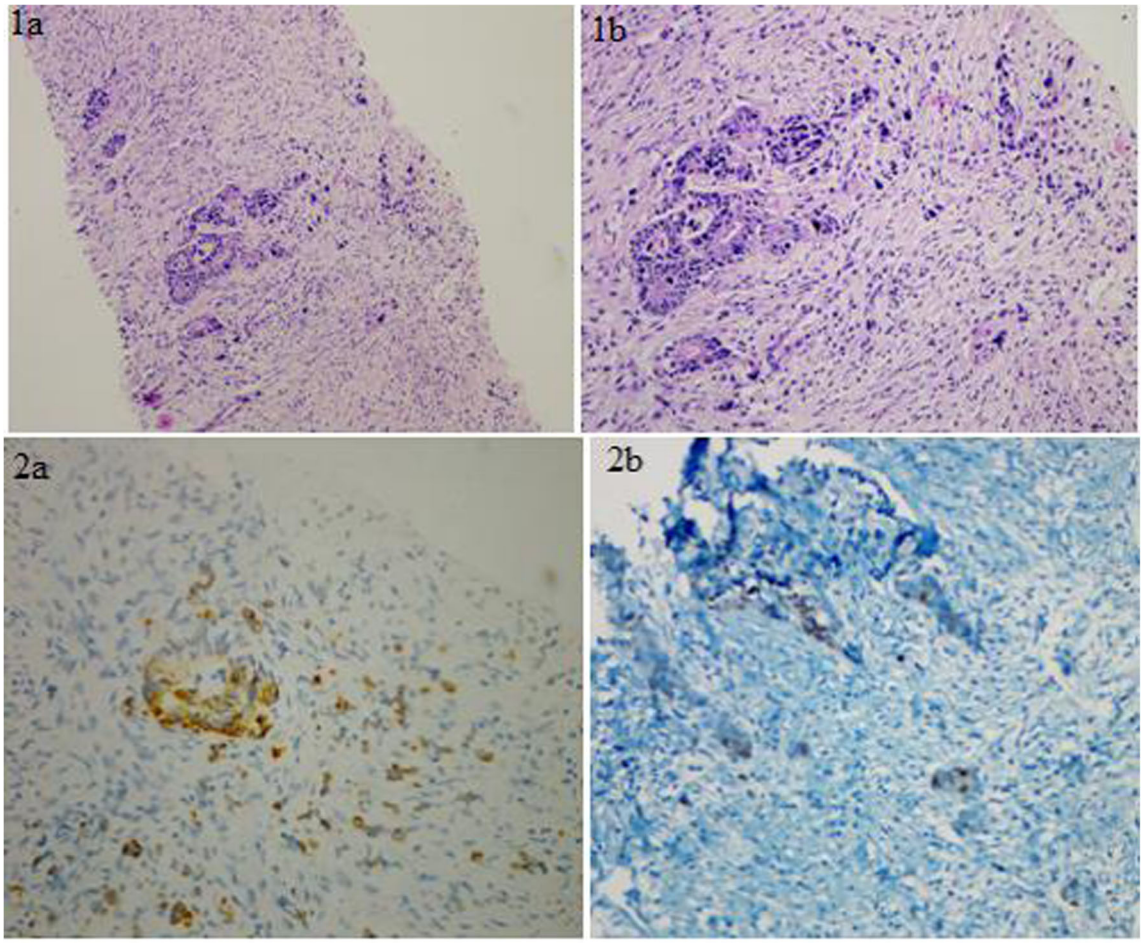

Fig. 2 (1) Malignant glandular structures embedded in dense desmoplastic stroma ((1a) HE × 100, (1b) HE × 200). (2a) Positive staining for cytokeratin 20 (CK20), immunohistochemistry × 100. (2b) Positive nuclear staining for CDX2, immunohistochemistry × 100

metastasis ($n = 10$). In this study, the longest time to recurrence was 8 years [15]. In a study conducted by Broadbridge et al. in 750 patients with resected colorectal cancer, the rate of late recurrence (> 5 years) was found to be 11.6%. In this study, the follow-up period was less than 10 years and the rate of liver metastasis was found to be higher than the rate of lung metastases in the group of late recurrences (25.3% vs 9.2%) [18]. In a study investigating the incidence of late recurrences (recurrences occurring between 5 and 10 years) in 1222 patients with rectal cancer, 8.4% of the patients developed late recurrences (4.6% distant metastases and 3.8% local metastases). The most common site of distant metastases was the liver (36.8%) which was followed by the lungs (16.5%). As the length of follow-up in this study was 10 years, it is not known if recurrences have occurred after 10 years of follow-up [10]. In a study conducted in patients with only rectal cancer, Tan et al. reported a late recurrence rate of 1.2% in 326 patients with rectal cancer. The lung (34.7%) was the most common site of distant metastases [8]. In a study of 835 patients with resected colorectal cancer, the late recurrence (> 5 years) rate was found to be 4.3% and the lung (40.5%) was also the most common site of distant metastases. In this study, the longest time to recurrence was 11 years, and this patient had undergone an abdominoperineal resection procedure [19]. The time to recurrence in our patient (10 years) was one of the longest time periods reported for late recurrences in the literature. Considering the incidence of colorectal cancer, although the rate of recurrence is high within the 5 years after the treatment, recurrence rates after the first 5 years are too high to be ignored. Although cases of recurrences are very rare, particularly after 10 years, recurrences may still occur, and therefore, a surveillance longer than 10 years may help detect recurrences earlier in this patient group.

Recurrence rates may vary based on the location of primary tumor in rectal cancer. The rate of lung metastases is higher in patients with a primary tumor located in the lower parts of the rectum while the rate of liver metastasis was higher in patients with a primary tumor located in the middle or upper parts of the rectum. In a study conducted by Lee et al. in patients with resected rectal cancer, the rates of liver metastases to lung metastases in patients with a primary tumor located in the lower (the first 5 cm), middle (> 5 to ≤ 8 cm), and upper (>

8 cm) parts of the rectum were 0.49, 0.58, and 0.94, respectively [5]. In a study conducted by Watanabe et al. in 41 patients with lung metastases from rectal cancer, the location of primary tumor was the anal canal + lower rectum (0 to 10 cm) in 24 (58.6%) patients and upper rectum (10 to 15 cm) in 17 (41.4%) patients [20]. The higher rates of lung metastases in lower rectal tumors may be explained by the venous drainage of this region into systemic circulation while the higher rates of liver metastases in upper rectal tumors may be explained by the venous drainage of the upper rectal area into the portal circulation [20]. However, the lack of a standard cutoff value to determine the location of primary rectal tumors in abovementioned studies can lead to confusion.

The rates of late recurrences may vary in colorectal cancer based on the location of primary tumor. In a study of 1136 patients, only one patient with right colon cancer developed recurrence after the first 5 years [15]. In another study of 418 patients, none of the patients with right colon cancer developed a recurrence [17]. In studies on a possible relationship between the location of the tumor and recurrence patterns, authors reported that left colon and rectal cancers progressed slower than the cancers of the other parts of the colon [15, 21]. As a consequence, late recurrences may occur in tumors located in the left colon and rectum; therefore, the follow-up duration can be longer in this patient group.

There is risk for a secondary malignancy in patients who receive chemotherapy or radiation therapy for the treatment of any cancer. Considering prior history of chemotherapy and radiation therapy, a second primary cancer was taken into consideration in the differential diagnosis of this patient who presented with clinically symptomatic, refractory cough and a central 6-cm mass in the left lung, mediastinal lymphadenopathy, and pulmonary nodular lesions. However, the results of the histological examination of the biopsy specimens obtained during bronchoscopy were consistent with metastatic rectum cancer. Therefore, in case of the detection of a mass lesion in the lung in a patient who has received treatment for rectal cancer, a metastasis should be considered in the first place, even 10 years after the curative treatment.

In conclusion, the lung is the common site of the late recurrences in patients with rectal cancer. Metastatic rectal cancer should be considered in the first place in a patient who presents with a primary pulmonary mass lesion and mediastinal lymphadenopathy, many years (10 years) after primary rectal cancer treatment.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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