Surgical Resection for Liver Metastases Developing 10 and 21 Years After Primary Surgery for Mucinous Colon Adenocarcinoma: A Case Report

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Optimal management for liver metastases from colorectal mucinous adenocarcinoma is still controversial. Here, we report such a case of liver metastases that developed twice with 10-year intervals after curative resection. An 84-year-old man had undergone a radical left hemicolectomy for descending colon cancer at age 63 years. The histopathologic diagnosis was mucinous adenocarcinoma. Ten years later, he was found to have a cystic tumor in liver and underwent partial hepatectomy of segment 5. Moreover, 10 years after that hepatic resection, computed tomography showed a low-density tumor with calcification in remnant liver, and partial hepatectomy of segment 8 was performed. Histopathologic and immunohistochemical findings of each liver tumor indicated metastasis from primary colon mucinous adenocarcinoma. It is rare for colorectal mucinous adenocarcinoma to recur twice after long intervals of 10 years. However, in a patient with a history of colorectal mucinous adenocarcinoma, possibility of recurrence more than 10 years after curative surgery also must be kept in mind. Long-term clinical follow-up after curative surgery for primary colon cancer or liver metastases may be necessary to detect early signs of recurrence of colorectal mucinous adenocarcinoma.

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Colon cancer is one of the most common types of cancer and is the cause of much cancer-related death worldwide.[1] Metachronous secondary tumors affect 30% to 40% of colon cancer patients and are usually detected within 2 years of resection of the primary tumor.[2,3] Therefore, the surveillance protocols currently proposed are based on active surveillance during the first 5 years after curative surgery. However, several recent studies demonstrated the possibility of late recurrence in colon cancer and suggested a necessity for long-term follow-up after curative resection.[4–6]

On the other hand, colorectal mucinous adenocarcinomas, accounting for 10% to 15% of all colorectal adenocarcinomas,[7] have been associated with a worse prognosis than classic nonmucinous adenocarcinoma.[8–10] In a previous report, liver resection of colorectal metastases from mucinous adenocarcinoma was found to be associated with worse survival and lower chemotherapy response than in nonmucinous adenocarcinoma.[11,12] Optimal management for liver metastases from colorectal mucinous adenocarcinoma (Muc-CRLM) is still controversial.

Here, we report a case of descending colon mucinous adenocarcinoma with liver metastases 10 and 21 years after the resection of the primary lesion. Long-term clinical follow-up and surgical resection of these liver metastases resulted in the patient's long-term survival.

Case Report

An 84-year-old man with descending colon cancer underwent radical left hemicolectomy with lymph node dissection at age 63 years. The pathologic findings were mucinous adenocarcinoma classified as T4aN1aM0 (stage IIIB) according to the Union for International Cancer Control TNM classification (Fig. 1A). This patient did not receive neoadjuvant and adjuvant chemotherapy. The postoperative course was uneventful.

Although there had been no signs of recurrence for the first 5 years after colon surgery, thereafter the serum level of carcinoembryonic antigen (CEA) continued to increase gradually (Fig. 2). We maintained clinical follow-up, and at 73 years of age, 10 years after the primary colectomy, computed tomography (CT) showed a hypodense lesion in the

right liver lobe, with a peripheral high-intensity lesion suspected to be calcification measuring approximately 60 mm in diameter at segment 5/6 (Fig. 3A). Peripheral rim enhancement was identified by CT during arteriography (Fig. 3B). In magnetic resonance imaging (MRI), the signal was low in T1-weighted sequences and very high in T2-weighted sequences (Fig. 3C and 3D). The tumor biopsy did not reveal malignancy. Chest CT scan, esophagogastroduodenoscopy, and colonoscopy revealed no malignant lesions. At this point our diagnosis was hepatic cyst, but malignancy could not be completely excluded. Therefore, we performed partial hepatectomy. This laparotomy revealed only the hepatic tumor detected by the CT scan. There were no additional tumors (either primary or recurrent lesions). Histologic examination showed metastasis from mucinous adenocarcinoma of colon (Fig. 1D). The postoperative course was uneventful.

We continued clinical follow-up, and at age 83 years, CEA started to increase again. At age 84 years, 11 years after liver surgery, CT showed a small, hypodense lesion in the remnant liver with growing calcification and a mucous plug (Fig. 4A). Angiography was performed, and CT during arterial portography (CTAP) showed a perfusion defect in segment 8, and CT of arterial phase showed delayed enhancement of the tumor (Fig. 4B and 4C). MRI showed low intensity in T1-weighted sequences and high intensity in T2-weighted sequences. Fluorodeoxyglucose–positron emission tomography showed no uptake in the liver (Fig. 4D). We diagnosed a recurrence of descending colon cancer resected 21 years earlier, and therefore partial hepatectomy of segment 8 was performed. Histology of the resected tumor was mucinous adenocarcinoma again (Fig. 1G), with infiltration into the middle hepatic vein and portal venous branch. By immunostaining examination, cancer cells were negative for cytokeratin 7 (CK7) but positive for CK20, indicating the same pattern as the primary resected colon cancer (Fig. 1). Finally, we diagnosed 2 liver tumors as metastases from the descending colon mucinous adenocarcinoma. This patient recovered uneventfully after surgery and has remained recurrence-free 4 months after the last surgery without any postoperative chemotherapy.
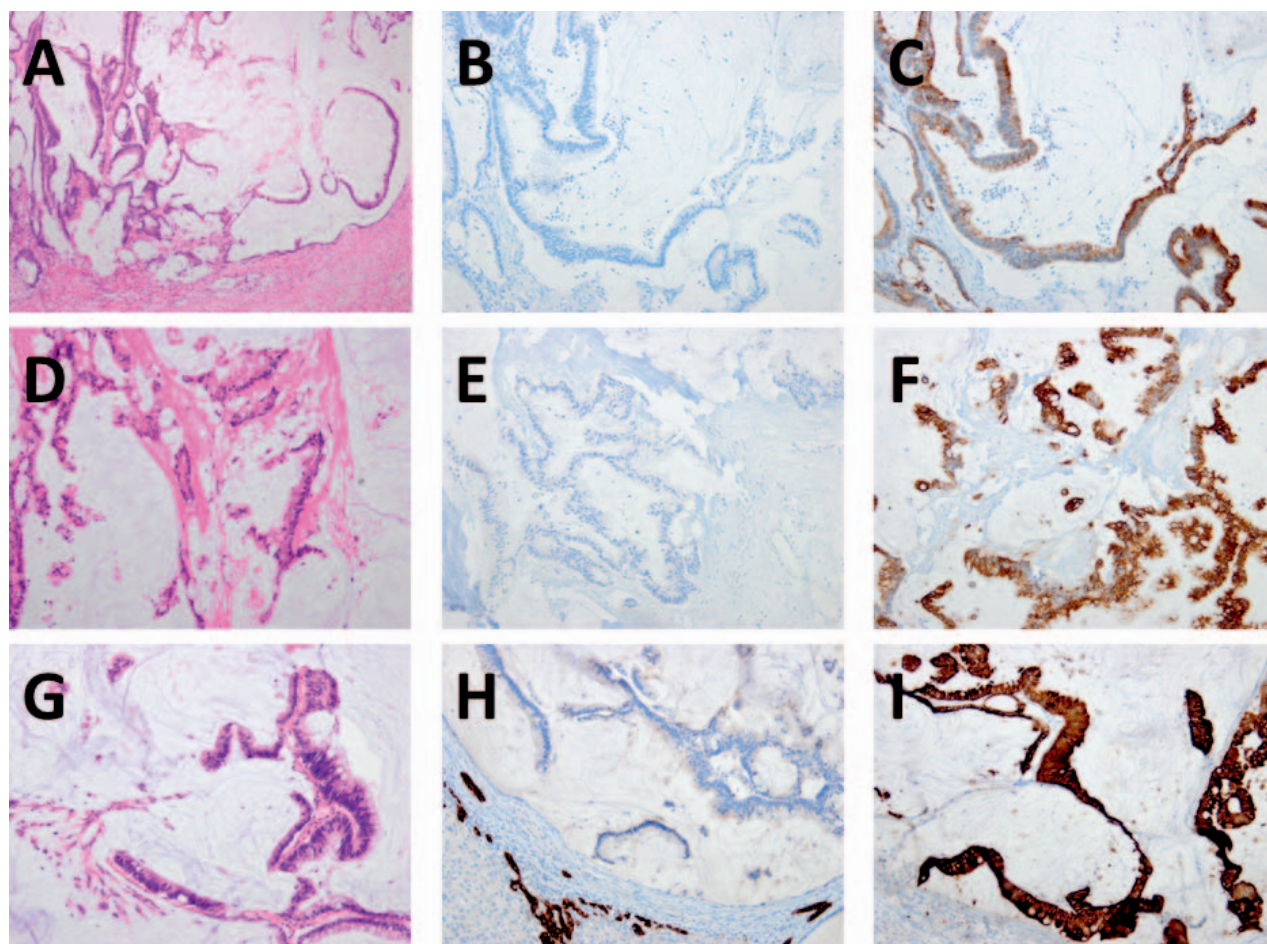
Fig. 1 Photomicrographs of the resected colon (A, B, and C), and first (D, E, and F) and second (G, H, and I) recurrence of liver tumor. (A, D, and G) The entire tumor shows signs of mucinous adenocarcinoma (hematoxylin-eosin stain). Tumors were negative for CK7 (B, E, and H), and they were positive for CK20 (C, F, and I). The findings suggest that the recurrent liver tumors are metastases from the primary colon cancer.
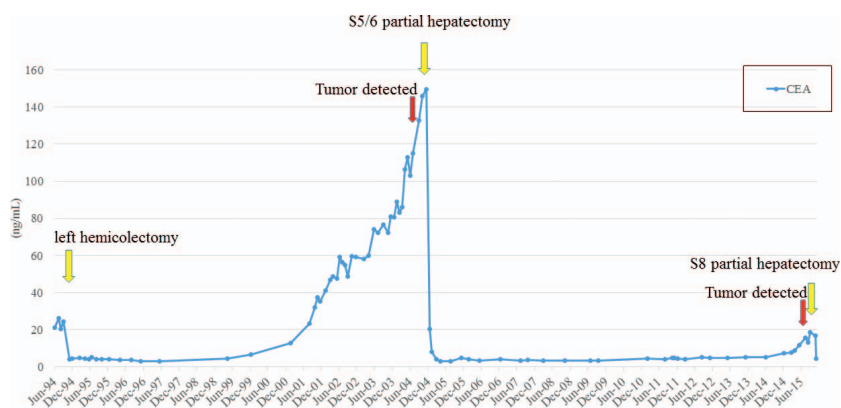

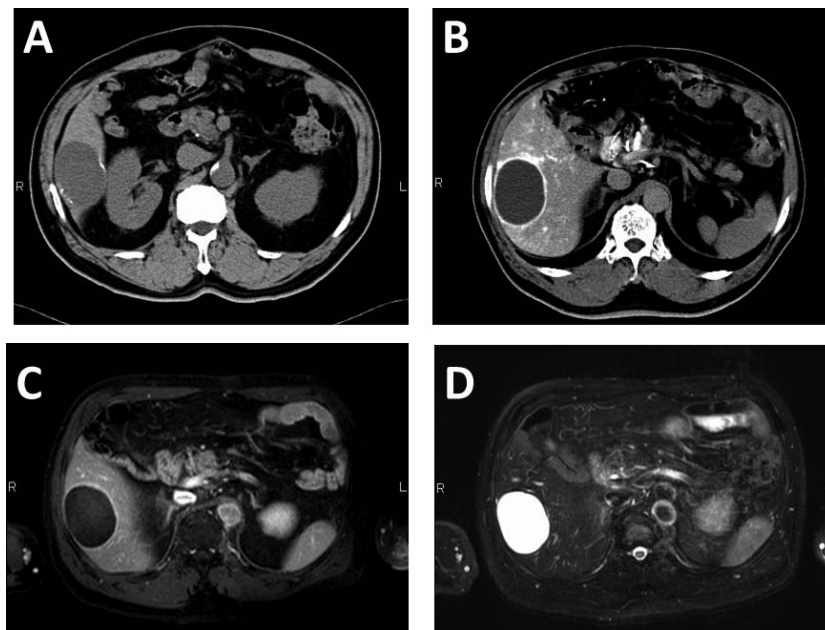**Fig. 2** Sequential changes in serum CEA.

Fig. 3 (A) CT showing first recurrence of cystic lesion with calcification in segment 5/6 liver. (B) CTA showing peripheral rim enhancement of the cystic lesion. (C, D) MRI showing low T1-weighted signal and very high T2-weighted signal of the lesion.

Discussion

There is no consensus concerning the long-term follow-up of patients who have had colon cancer surgery. Most recurrences of colorectal cancer (89%–100%) were reported to develop within 5 years.[13] On the other hand, Bouvier and colleagues[6] reported that the overall cumulative recurrence rate between 5 and 10 years after initial surgery was 2.9% for local recurrence and 4.3% for distant metastasis. Furthermore, there are a few reports of the development of metastatic lesions a remarkably long time after primary colon cancer surgery.[4,5] To the best of our knowledge, this is the first report of a case that had liver metastases twice with such a long interval, 10 years after the primary colon surgery and another 11 years after the first liver surgery. Colorectal mucinous adenocarcinoma more frequently recurred in
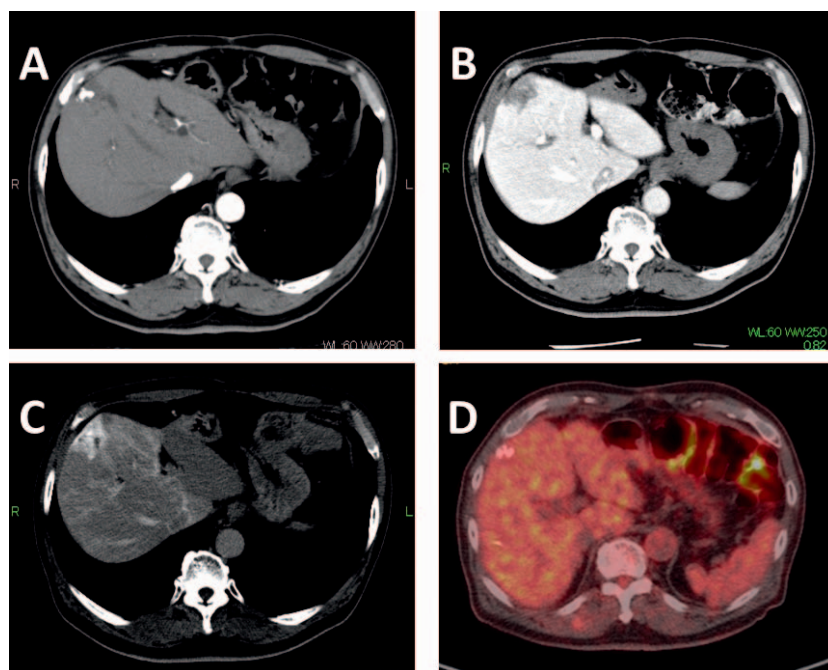

Fig. 4 (A) CT showing second recurrence of a lesion with growing calcification and mucous plug calcification in segment 8 liver. (B and C) CT during arterial portography showing a perfusion defect, and CTA showing the delayed enhancement of the tumor. (D) Fluorodeoxyglucose–positron emission tomography showed no uptake by the tumor.

atypical extrahepatic sites, especially the peritoneum. Half of the cases involved recurrences in multiple organs.[8,10,14] Because of these characteristics, Muc-CRLM has a very low re-resectability rate.[11] Intensive and long-term clinical follow-up more than 10 years after surgery for primary colon cancer or metastatic lesions may be necessary to detect early signs of the recurrence of colorectal mucinous adenocarcinoma. In our case, CEA played important roles in the diagnoses of recurrences as early prediction marker.

Some diagnoses of muc-CRLM are difficult to make accurately by preoperative examination.[15,16] The typical radiologic features of mucinous carcinoma are relatively unclear because they are largely dependent on the proportion of the mucinous component. In the present case, our preoperative diagnoses were hepatic cyst and biliary cystadenocarcinoma, respectively. However, they were, in fact, colorectal liver metastases (CRLMs), as shown by cytokeratin phenotyping for CK20 and CK7. Several studies reported that calcified liver metastases are more likely to develop in colorectal mucinous adenocarcinoma.[17,18] In a patient with a history of colorectal mucinous adenocarcinoma, a diagnosis of liver tumor should be made with caution, and the possibility of colon metastasis should be kept in mind.

Resection is the established gold standard treatment for CRLM.[19–21] It remains unclear how to stratify candidates for liver resection and select patients who can benefit from surgery. Muc-CRLM appears to be a separate disease, which is associated with worse survival and aggressive, rarely re-resectable recurrence.[11,12] Jimi and colleagues[22] suggested that liver metastasis was one of significant factors predicting the survival of patients with mucinous colorectal carcinoma. Although our case was of Muc-CRLM, early detection and surgery for the liver metastases may have been responsible for extending the patient's life.

Although recent advances in adjuvant chemotherapy have further improved the disease-free survival rate after curative surgery for colon cancer,[23] an effective regimen for colorectal mucinous adenocarcinoma has not yet been found. In addition, it is believed that preexisting noncycling dormant cells escape most chemotherapy.[24] It was anticipated that adjuvant chemotherapy after the first or second resection would not have made any difference in this case.

Some studies in humans have suggested the existence of two different tumor cell populations at the site of secondary tumor growth within the liver:

tumor cells growing to form metastases and tumor cells said to be dormant cells, which appear morphologically to be in a resting, nonproliferating state.[25–27] In our case, it took 10 years for each of the liver metastases to be detectable. Although the applicability of the concept of tumor dormancy to mucinous adenocarcinoma or liver metastasis is unknown, this is a potential explanation for the findings reported here. The dormant micrometastases may escape dormancy and begin to proliferate by increasing levels of angiogenic activity, such as when immunosuppression is induced by immunosuppressants or repeated surgical procedures.[5,27] However, there was no possible cause of the increasing level of angiogenic activity in our case. Further investigation into causes that make dormant cancer cells start forming metastases is warranted.

In conclusion, further investigations into surveillance and surgery for Muc-CRLM and dormant cancer cells are necessary to improve the possibility of restoring a good prognosis.

Acknowledgments

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