

Case Report

Alpha-fetoprotein-producing Colon Carcinoma with Rapidly Increasing Liver Metastases That Resulted in Death: A Case Report

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Abstract

Alpha-fetoprotein (AFP) has been widely used as a tumor marker for detecting hepatocellular carcinoma and yolk sac tumors. Recently, cases of gastrointestinal cancer with elevated serum AFP levels have been reported. However, AFP-producing colon cancer is considered rarer than other AFP-producing gastrointestinal cancers. In this study, we report on a case of a 47-year-old woman who was diagnosed with sigmoid colon cancer and underwent sigmoidectomy and lymph node dissection. Postoperative adjuvant chemotherapy (AC) was performed after the curative surgery. After the seventh course of AC, multiple liver masses and enlarged systemic lymph nodes were detected; these were later diagnosed as liver metastases from sigmoid colon cancer. Laboratory examination revealed high AFP levels (14,657.8 ng/mL). After confirming the recurrence, her condition worsened rapidly, and she eventually died 8 months after the operation. Autopsy and histopathological findings showed that the liver mass was positive for AFP staining, but the sigmoid colon cancer tissue was not. We then determined that liver metastases of the colon cancer were more likely than germ cell carcinoma according to the clinical course and pathological findings. We assumed that colon cancer cells can rapidly expand by dedifferentiation, and we diagnosed AFP-producing colon cancer with liver metastases. Despite curative surgery and AC for AFP-producing colon cancer, the patient died of liver and systemic lymph node metastases.

Keywords

AFP, colon cancer, liver metastases

J Anus Rectum Colon 2021; 5(1): 100-106

Introduction

Alpha-fetoprotein (AFP) is determined as a tumor marker for hepatocellular carcinoma and yolk sac tumors. Recently, cases of gastrointestinal cancer with elevated serum AFP levels have been reported. AFP production from tumors of the stomach, bile duct, and pancreas has also been re-

ported[1,2]. Although the number of AFP-producing colorectal cancer case reports is increasing, the disease is still considered to be rare[1,3].

Here, we report on a case of a patient with AFP-producing colon cancer in which liver and systemic lymph node metastases developed during postoperative adjuvant chemotherapy (AC) after curative therapy. Additionally, an

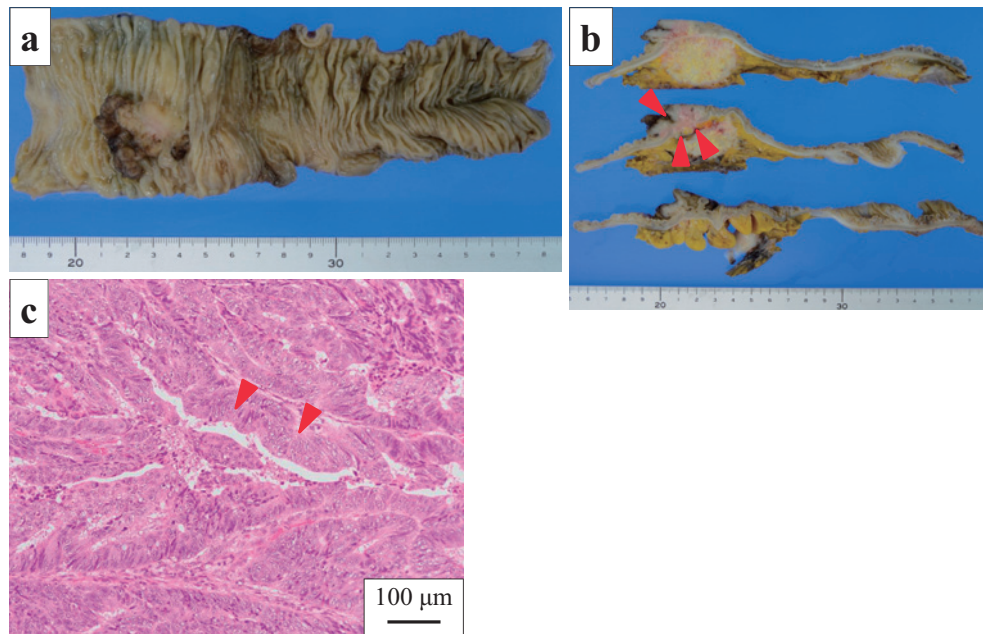


Figure 1. Macroscopic and microscopic findings.

Macroscopic findings of the resected specimen revealed a semicircular raised tumor of the sigmoid colon with dimensions of 38 × 33 mm (a). As shown by the red arrows, the cancer reaches deep into the serosal muscle layer. A large lymph node attached to the colonic wall could also be seen (b). Microscopic findings show a moderately differentiated tubular adenocarcinoma with invasion of the serosal muscle layer. Tumor cells line the lumen of the colon (c, red arrows, hematoxylin, and eosin).

autopsy was also performed. In this case, immunostaining of the primary lesion was determined to be AFP-negative, whereas the metastatic lesion was AFP-positive. In the past, there has only been one case report with such immunostaining results; therefore, we also reviewed the related literature.

Case Report

A 47-year-old woman visited the hospital complaining of bloody stools. She had no family history of cancer. However, colonoscopy revealed a protruding tumor in the sigmoid colon. Biopsy specimens from the tumor suggested the presence of a moderately differentiated tubular adenocarcinoma. Laboratory examination revealed no remarkable abnormalities. The carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels were determined to be 6.0 ng/mL (normal range, <5.0 ng/mL) and ≤2.0 U/mL (normal range, <37.0 U/mL), respectively.

Contrast-enhanced computed tomography (CT) has showed that the primary tumor was in the sigmoid colon, and a few neighboring lymph nodes were clumped together, leading to a swollen mass measuring 40 mm × 30 mm. However, no distant metastases were found. The clinical diagnosis was T4aN1bM0 Stage IIIB sigmoid colon cancer, as per the Union for International Cancer Control tumor node

metastasis classification for colorectal cancer.

Sigmoidectomy and lymph node dissection were then performed. The tumor was a semicircular raised lesion, having a size of 38 mm × 33 mm. Histopathological examination has revealed a moderately differentiated tubular adenocarcinoma that had invaded the serosal muscle layer. The final pathological diagnosis was T3N1bM0 Stage IIIB sigmoid colon cancer according to the TNM classification (Figure 1).

The patient was discharged on postoperative day (POD) 11 without any postoperative complications. CAPOX therapy (body surface area 1.42 m², capecitabine 1000 mg/m², oxaliplatin 130 mg/m²) was introduced as AC from POD 35. After the seventh course of AC (POD 197), high fever (38.9 °C), anorexia, epigastric tenderness, and right back pain were noted. On examination, the abdomen was found to be flat and soft, but a lump was noted in the upper right abdomen. Laboratory examination revealed that CEA, CA19-9, and AFP levels were 4.9 ng/mL, ≤2.0 U/mL, and 14,657.8 ng/mL (normal range, <10.0 ng/mL), respectively. She did not have a history of HBV or HCV hepatitis.

CT revealed a 9 cm low-density area in the anterior segment of the right lobe of the liver and a 3 cm tumor on the caudate lobe of the liver. Enlarged lymph nodes around the inferior vena cava, hepatic portal system, common hepatic artery, and mediastinum were also noted (Figure 2a). The

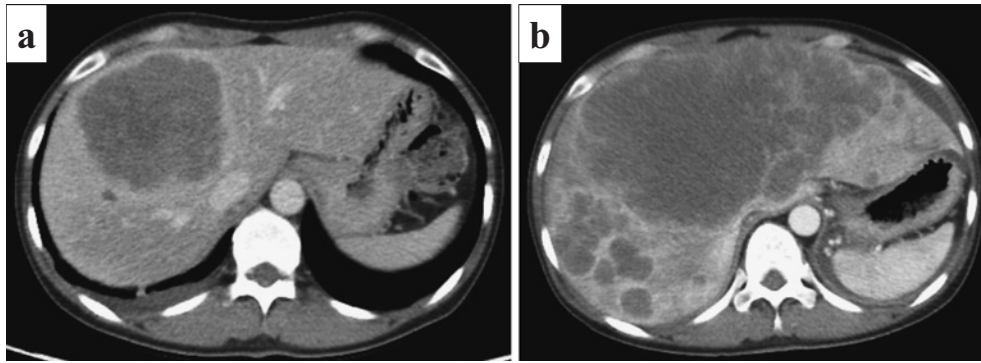


Figure 2. Contrast-enhanced computed tomography (CT) findings.

CT revealed a low-density tumor with a 9 cm diameter in the anterior segment of the right lobe of the liver and a tumor with a 3 cm diameter on the caudate lobe of the liver (a, POD197). The liver tumor was growing rapidly (b, POD225).

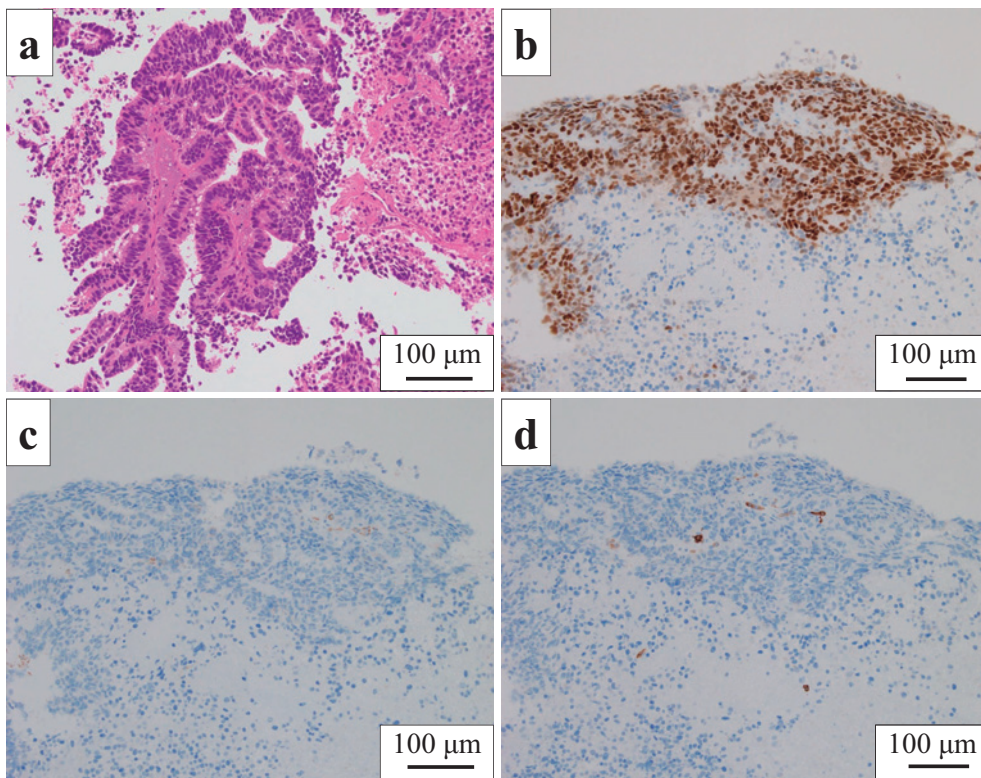


Figure 3. Liver biopsy findings.

Biopsy revealed adenocarcinoma showing irregular papillary tubular structure with massive necrosis inside the tumor mass (a, hematoxylin, and eosin). CDX-2 (+++) (b), CK20 (-) (c), CK-7 (-) (d).

differential diagnoses of malignant lymphoma, hepatocellular carcinoma, or recurrence of sigmoid colon cancer were then considered, and liver biopsy was performed in order to have a definite diagnosis. Liver biopsy revealed an intestinal type of tubular adenocarcinoma (Figure 3). We diagnosed the liver mass as a metastatic tumor originating from the sigmoid colon cancer, which was initially treated with surgery.

On molecular analysis, both the RAS and BRAF genes were of the wild type in sigmoid colon cancer tissue and the biopsy specimens from the liver tumor. She had a persistent high fever of 38-39°C and a poor oral intake. Therefore, we considered that she failed to adapt to the standard chemotherapy including oxaliplatin or irinotecan; thus, we opted to administer panitumumab monotherapy. Abdominal bloating and pain developed on day 15 after starting this treatment

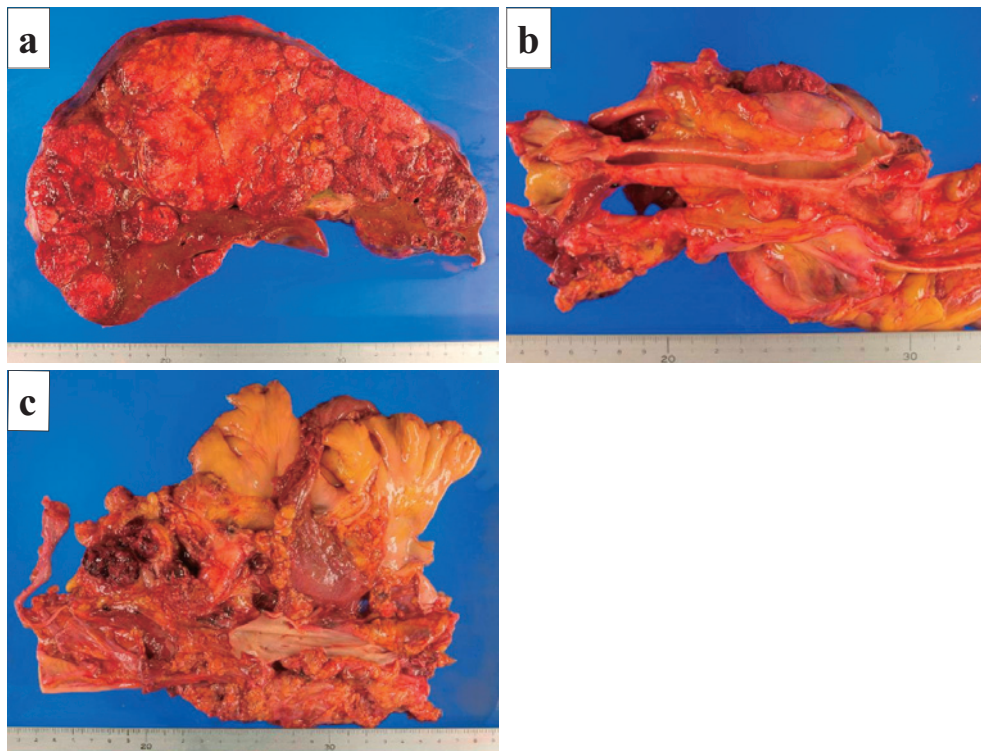


Figure 4. The autopsy findings.

In the liver, 4/5 or more had been replaced with both large and small metastatic nodules (a). Many enlarged lymph nodes were found in the neck, subclavian triangle, mediastinum, aorta, and abdominal cavity. Peri-tracheal lymph nodes (b). Peri-aortic lymph nodes (c).

(POD 225), and symptoms have continued to worsen. On performing a laboratory examination, we found that the serum AFP level had markedly increased to 66,100.0 ng/mL, and abdominal radiography and CT showed an enlarging liver tumor along with the development of ascites (Figure 2 b). Subsequently, a second course of panitumumab monotherapy was administered. However, the rapidly progressive disease showed no improvement, and the patient died on POD 240.

The patient then underwent autopsy after obtaining an informed consent from her family. Autopsy showed that the hepatic capsule was taut, with bulging metastatic nodules on the surface; $\geq 4/5$ of the hepatic parenchyma had been replaced with large and small metastatic nodules. Many enlarged lymph nodes were found from the neck down to the abdominal cavity (Figure 4). We could not find neoplastic lesions in the stomach, pancreas, or biliary tract and further speculated that as an AFP-producing tumor, the characteristics of the primary lesion were consistent with those of surgically resected sigmoid colon cancer.

The pathological examination showed that findings such as tumor cells lined up in blood vessels similar to the Schiller-Duval body, mixed large bizarre nuclei, and pathological nuclear fission images were obtained. Similar findings were also seen in the enlarged lymph nodes. These

findings were suspicious of germ cell tumors and were different from those of a typical colorectal adenocarcinoma (Figure 5). Immunostaining of the liver metastatic tissue was also performed. CK7 (-), CK20 (-), and CDX-2 (+30%) were the findings that did not rule out colorectal adenocarcinoma. Malignant lymphoma was ruled out because CD30 was negative; a germ cell tumor was ruled out because OCT-4, CD117, and hCG were all negative. AFP (+20%) suggested that the tumor cells have acquired AFP-producing ability. From these results, liver metastases of AFP-producing colorectal cancer were suspected (Figure 5). Tissue specimens of the surgically excised sigmoid colon cancer were immunostained again. CK7 (-), CK20 (+), and CDX-2 (+100%) were then judged to be typical colon adenocarcinoma findings. Based on being AFP (-) by immunostaining, AFP-producing tumor cells were not detected in the resected colon cancer or in the lymph nodes.

Based on the clinical course, the fact that the liver tumor had a gastrointestinal histology, and that CDX-2 was positive together with the sigmoid colon cancer, we can conclude that she died of multiple liver metastases from sigmoid colon cancer. Written informed consent was obtained from the patient's family head and other relevant members for the publication of this case report, including some photographs.

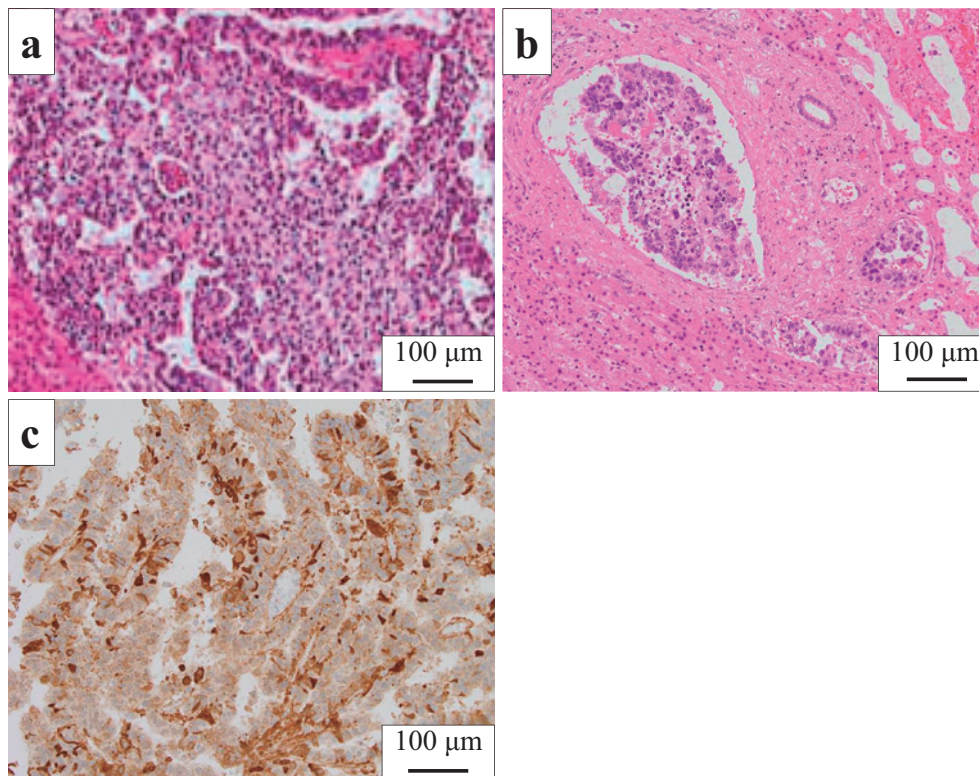


Figure 5. The pathological findings of the liver tumor on autopsy. The histological examination of the liver mass revealed the following findings. A hepatoid structure was recognized (a). Tumor cells lined up along the blood vessels, resembling the Schiller-Duval body findings (b). Alpha-fetoprotein-immunoreactivity was 20% (c). Similar histology was shown in metastatic lesions in the whole body.

Discussion

AFP is defined as a protein originating from the fetal liver and yolk sac with a molecular weight of approximately 70 kDa. Although AFP has been widely used as a tumor marker for primary hepatocellular carcinoma and yolk sac carcinoma[4,5], AFP production has been reported in neoplasms of several other organs such as the pancreas, gallbladder, and gastrointestinal tract[6]. The malignant tumors of these organs are derived from the same foregut system of the endoderm as the liver[1]. The colon is an organ derived from the hindgut system of the endoderm, and the phenomenon of AFP-producing cells appearing is rare. Therefore, fewer cases of AFP-producing cells have been reported in colorectal cancer than in gastric cancer[7].

AFP-producing gastric cancer is often associated with more aggressive clinical behavior and worse prognosis than AFP-negative gastric cancer. This is because of a higher incidence of vascular invasion and lymph node and liver metastases[8]. On the other hand, the amount of lymph node and liver metastases from AFP-producing colorectal cancer is as high as that from AFP-producing gastric cancer. Both AFP-producing colorectal cancer and AFP-producing gastric

cancer have been reported to have poor prognoses, and chemotherapy has not been found to be effective for both cancers[9].

The following are the potential mechanisms by which AFP is produced by tumor cells during carcinogenesis: a malignant change occurs in the gene expression of mature somatic cells, which then induce de-repression, or a phenotypic expression in the fetal stage by gene conversion occurs, thereby causing a retrograde differentiation to the embryonic stage[10,11]. In other words, tumor cells dedifferentiate into fetal gastrointestinal epithelial cells and acquire AFP-producing ability.

In our case, the tissue type of the resected sigmoid colon cancer lesion was moderately differentiated tubular adenocarcinoma, and we did not observe positive AFP staining. Postoperatively, an abnormally high serum AFP level was observed at the time of confirmation of the liver and lymph node metastases, and there was a positive AFP staining lesion in the liver tumor. The histopathological findings of the autopsy revealed that lymph node metastases were observed in the mass from around the abdominal aorta to the hepatic hilum and the mediastinum. We did not find the neoplastic lesions in the mediastinum or retroperitoneum on preopera-

tive CT examination and intraoperative findings. Therefore, it was extremely unlikely that germ cell tumors, which often originate in the midline, occurred metachronically. From the above clinical course, autopsy, and results of pathological examination, the liver tumor lesion was determined to be a metastatic tumor originating from the sigmoid colon cancer, and the metastatic tumor cells were assumed to have dedifferentiated into a primitive endodermal tumor. Additionally, although the patient in this case was a 47-year-old woman with colorectal cancer under the age of 50, we did not strongly suspect her to have Lynch syndrome in view of the revised Bethesda guidelines.

To augment our case, we conducted a literature review by searching PubMed using keywords such as “AFP-producing colon cancer.” In total, 13 English articles of AFP-producing colon cancer, including case reports and analytical reviews, were found. Among these case reports, there was only one case in which the primary lesion stained negative while the metastatic lesion stained positive for AFP. According to this case report, neuroendocrine changes were observed as pathological findings[11]. Cells with AFP-producing ability might be unevenly distributed in the tumor; it was possible that AFP non-producing cells were collected at the time of biopsy, and there were technical problems with staining. Several studies with patients diagnosed as having AFP-producing colorectal cancer reported that AFP-producing cells were found in only part of the tumor, instead of the whole tumor. Even if the number of cells is small in the early stage, the cells may proliferate and cause distant metastases, resulting in poor prognosis. At this point, serum AFP values are a good prognostic index. Immunostaining for AFP was not performed in all cases in the analytical reviews, and the authors diagnosed the patient as having AFP-producing colorectal cancer due to an increase in the AFP level after performing a blood test[11,12].

In our case, CAPOX therapy was administered as AC followed by panitumumab monotherapy later. Pathologically, the *RAS* and *BRAF* genes were both the wild type in the sigmoid colon cancer. The patient was in a poor state, making standard chemotherapy including irinotecan intolerable. Panitumumab was then chosen because of the *RAS* and *BRAF* gene mutation status as that is one of the indications in colorectal cancer with a chance of extending survival time and the occurrence of fewer adverse events. We could administer it only twice. A sharp increase in liver metastases and lymph node metastases was then observed; afterward, the patient was reported dead. Chemotherapy for AFP-producing colon cancer was not effective in most reported cases. Standard chemotherapy for colorectal cancer has then been described to be insufficient[7,13].

There were two limitations in this case report. First, we could not confirm the preoperative AFP value in this case. We assumed that the AFP level was within the normal range

at the time of the sigmoidectomy. The second is that the pathological specimen was evaluated in detail, but there is a possibility that AFP-producing tumor cells could be found slightly outside the observation range. It is suggested that an uneven distribution of AFP-producing cells in a tumor may make diagnosis difficult by pathological examination.

In conclusion, we report a case of AFP-producing colon cancer, in which primary tumor resection and lymph node dissection were performed; however, this was followed by the development of liver metastases and, eventually, death. It was a very rare case of AFP-producing colorectal cancer in which multiple liver metastases and AFP-producing cells were found in lymph nodes, although no AFP-producing cells were found in the resected primary lesion. It is necessary to perform tumor marker testing and biopsies promptly to confirm the pathological condition when colorectal cancer is growing rapidly. No clear treatment method for AFP-producing colorectal cancer has been established. Therefore, it is expected that an effective treatment will be determined from cumulative evidence obtained from further cases.

Conflicts of Interest

There are no conflicts of interest.

Author Contributions

NK participated in the concept/design and in drafting and revising the article. NK, KT, RK, AW, YS, MI, IO, KM, MI, SS, and TT participated in the treatment of the patient. KM participated in the interpretation of pathological data. TT is the chairperson of our department and supervised the writing of the manuscript. All authors read and approved the final manuscript.

Approval by Institutional Review Board (IRB)

Not applicable.

Informed Consent

Written informed consent was obtained from the patient and her family.

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