

Case Report

Maffucci Syndrome with Intrahepatic Cholangiocarcinoma: A Case Report

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Keywords

Maffucci syndrome · Cholangiocarcinoma · Isocitrate dehydrogenase 1

Abstract

Maffucci syndrome is characterized by multiple hemangiomas and enchondromas. Somatic mutations in *IDH1* and *IDH2* are associated with the development of Maffucci syndrome, and these patients develop various malignant nonskeletal tumors in addition to malignant skeletal tumors. We report a case of Maffucci syndrome with *IDH1* mutation complicated by intrahepatic cholangiocarcinoma. The patient was a 35-year-old woman who was diagnosed with Maffucci syndrome in childhood. She was referred to our department because of a large hepatic tumor. Serum carcinoembryonic antigen was 27.1 ng/mL upon laboratory examination. CT scanning showed a large low-density tumor (90 × 70 mm) in the right lobe of the liver, and MRI revealed a multilobulated and fibrous tumor, which was observed as high signal intensity on T2- and diffusion-weighted images and low signal intensity on T1-weighted images. Positron emission tomography-CT revealed peritoneal dissemination and cancer spread to the muscles of the back. Finally, she was diagnosed with intrahepatic cholangiocarcinoma with dissemination and metastases. We performed a tumor biopsy to determine a treatment plan for chemotherapy. Sanger sequencing of a tumor biopsy identified a mutation in *IDH1* at c.394C>T (R132C), but the patient died of rapid cancer progression before the chemotherapy could be initiated. Although rare, malignant tumors can develop in patients with Maffucci syndrome; therefore, it is necessary to monitor these tumors through careful and periodic observation.

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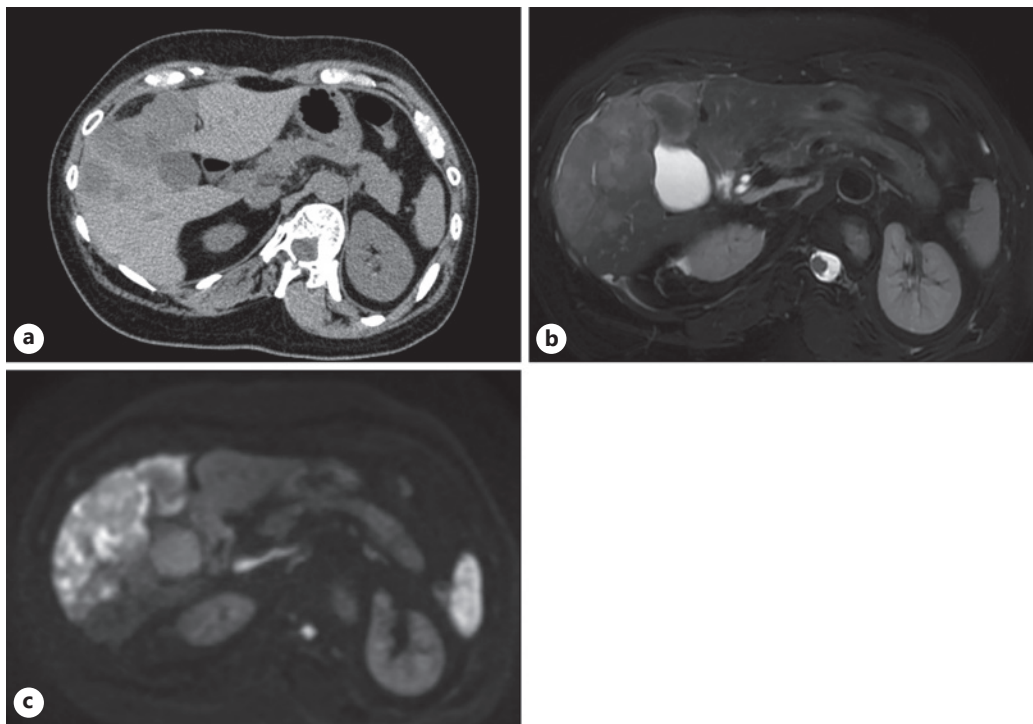


Fig. 1. **a** CT showing a large low-density tumor (90 × 70 mm) in the right lobe of the liver. **b, c** MRI showing a multilobulated and fibrous tumor, which was observed as high signal intensity on T2- (**b**) and diffusion-weighted (**c**) images.

Introduction

Maffucci syndrome is characterized by multiple hemangiomas and enchondromas. Somatic mutations in *IDH1* and *IDH2* are associated with the development of Maffucci syndrome and are not familial [1]. Although it is well known that various malignant tumors are complicated by *IDH1* gene mutations in Maffucci syndrome, only 2 cases of Maffucci syndrome with intrahepatic cholangiocarcinoma have been reported [2, 3]. We herein report a case of Maffucci syndrome with intrahepatic cholangiocarcinoma that resulted in rapid cancer progression and a deteriorated outcome, with a review of the literature.

Case Report

A 35-year-old woman was referred to our department for a large hepatic tumor. In childhood, she was diagnosed with Maffucci syndrome that was characterized by the presence of multiple enchondromas and hemangiomas in soft tissues and multiple organs. None of her family had a history of cancer.

The results of laboratory tests were as follows: aspartate transferase 40 U/L, alanine amino transferase 32 U/L, γ -glutamyl transpeptidase 173 U/L, lactate dehydrogenase 312 U/L, alkaline phosphatase 562 U/L, total bilirubin 0.47 U/L, serum carcinoembryonic antigen 27.1 ng/mL, and des-gamma-carboxy prothrombin 56 mAU/mL. Blood cell count and coagulation test were all within normal limits.

CT, which was performed because the patient had an allergy to iodinated radiocontrast media, showed a large low-density tumor (90 × 70 mm) in the right lobe of the liver (Fig. 1a).

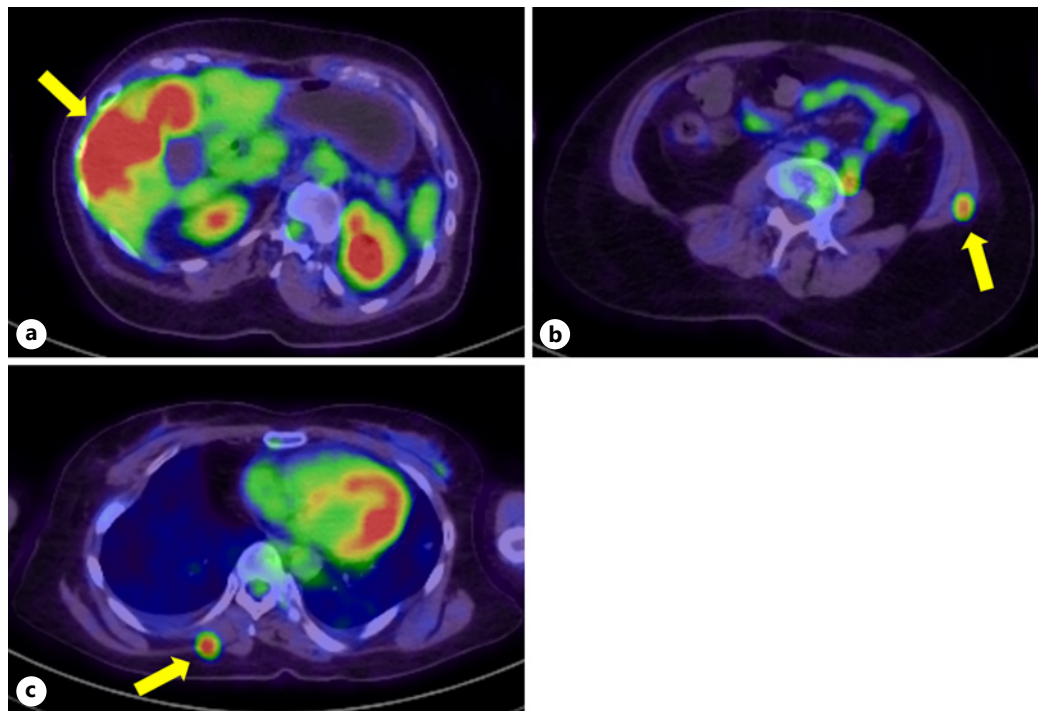


Fig. 2. Positron emission tomography-CT showing abnormal uptake in the tumor (a) and disseminations that had spread to muscles (b, c).

MRI revealed a multilobulated and fibrous tumor, which was observed as high signal intensity on T2- (Fig. 1b) and diffusion-weighted (Fig. 1c) images and low signal intensity on T1-weighted images. Upper gastrointestinal endoscopy and colonoscopy did not reveal any other tumors. Positron emission tomography-CT revealed peritoneal dissemination (Fig. 2a) and cancer spread to the muscles of the back (Fig. 2b, c). From the imaging findings, the patient was diagnosed with intrahepatic cholangiocarcinoma developing dissemination and metastases. We performed a liver biopsy to obtain a tissue diagnosis for chemotherapy.

After general anesthesia, we performed a laparoscopic biopsy using 3 ports. When observing the intra-abdominal cavity, a large, white, hard tumor was observed on the surface of the right hemiliver. Additionally, small white nodules, which were suspected as dissemination, were observed around the liver. We took a biopsy of the tumor and the disseminated nodule.

Histologically, the liver biopsy specimen showed atypical glands infiltration with desmoplastic reaction (Fig. 3a, b). These glands were focally immunoreactive for cytokeratin 7 (Fig. 3c, d) and cytokeratin 19, whereas cytokeratin 20, hepatocyte, arginase1, and p63 were negative and diagnosed as cholangiocellular carcinoma. The small white nodule which was identified on the liver surface also showed the same atypical glands proliferation and interpreted as disseminated cholangiocellular carcinoma. Furthermore, isocitrate dehydrogenase 1 (IDH1) gene analysis was performed by Sanger sequencing in paraffin-embedded tumor tissue, and heterozygous IDH1 mutation with c.394C>T Arg132Cys (R132C) was detected (Fig. 4). After surgery, the patient recovered uneventfully and was discharged from the hospital on postoperative day 32. Unfortunately, the patient died of rapid cancer progression before the chemotherapy could be administered.

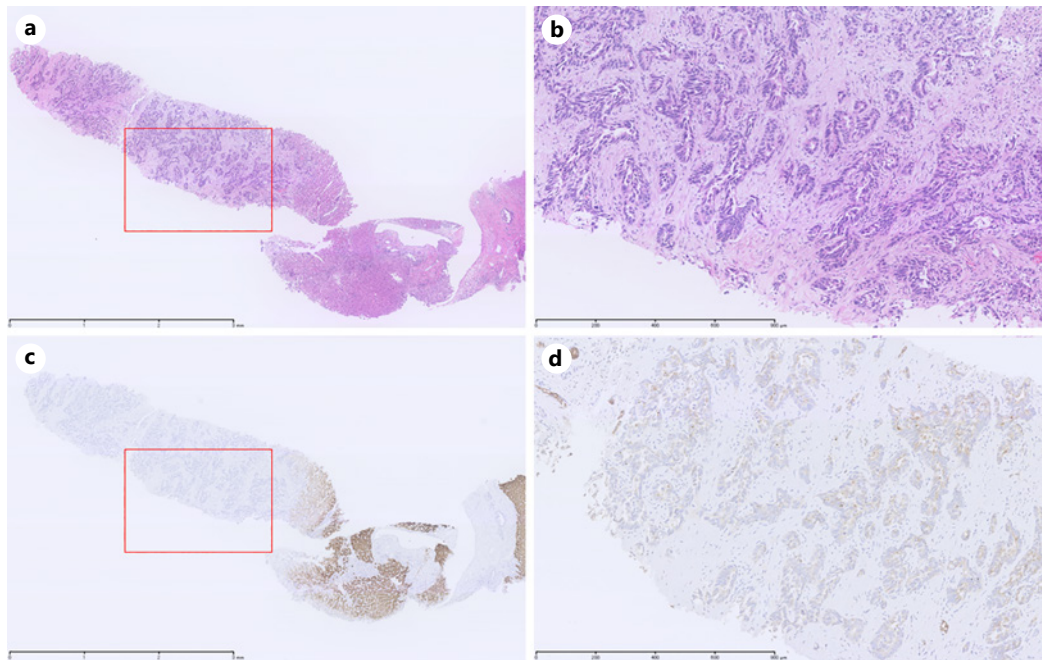


Fig. 3. Histopathological examination showed atypical glands infiltration with desmoplastic reaction (a, b). These glands were focally immunoreactive for cytokeratin 7 (c, d).

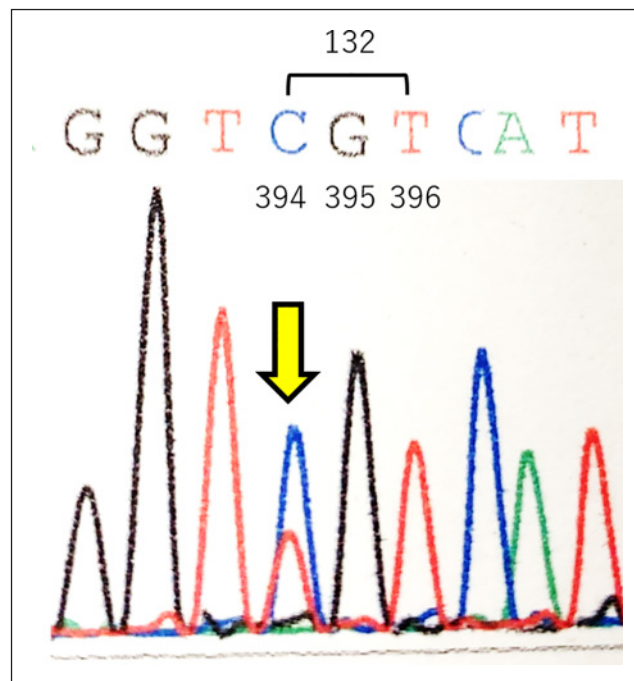


Fig. 4. IDH1 gene analysis was performed by Sanger sequencing in paraffin-embedded tumor tissue, and heterozygous IDH1 mutation with c.394C>T Arg132Cys (R132C) was detected. IDH1, isocitrate dehydrogenase 1.

Discussion/Conclusion

In Maffucci syndrome, 15.2% of enchondromas and 2% of hemangiomas are reported to cause malignant transformation and are associated with nonskeletal tumors such as glioma, astrocytoma, acute myeloid leukemia, and cholangiocarcinoma [4–6]. *IDH1/IDH2* mutations,

which are somatic mosaic mutations, are also associated with the development of these tumors [1]. Among them, only 2 cases of intrahepatic cholangiocarcinoma have been reported [2, 3]. Thus, the present case is extremely rare. According to a previous report, 77–93% of patients with Maffucci syndrome have *IDH1* somatic mosaic mutations, and c.394C>T (R132C) is sometimes described in cholangiocarcinoma.

Previously, Prokopchuk et al. [2] experienced a case of Maffucci syndrome with intrahepatic cholangiocarcinoma and reported mutant *IDH1*. In this case, Sanger sequencing revealed that the amino acid at position 394 was mutated from cysteine to arginine, resulting from a somatic mosaic mutation in *IDH1*. In a previous study, 88% of patients with Ollier disease and Maffucci syndrome had an *IDH1* mutation at c394C>T (R132C) in multiple tumors [1], whereas wild-type *IDH1* was detected in nontumor tissue. Therefore, it is considered that malignant tumors in Maffucci patients occur from somatic mosaic mutant cells [7]. However, the prognostic significance of *IDH1* in patients with Maffucci syndrome is unknown.

In the present case, in addition to cholangiocarcinoma, metastasis to soft tissue was detected by preoperative imaging. Hence, radical resection was considered impossible, and chemotherapy was selected. The biopsy results were consistent with intrahepatic cholangiocarcinoma, and the patient was scheduled to receive chemotherapy to treat the cholangiocarcinoma. In Japan, combination therapy with gemcitabine (GEM), cisplatin (CDDP), and S-1 is approved as chemotherapy for cholangiocarcinoma. Therefore, we planned to administer GEM + CDDP. Unfortunately, before the chemotherapy could be administered, the patient died of hypercalcemia and liver failure approximately 3 months after diagnosis.

Intrahepatic cholangiocarcinoma that develops in Maffucci syndrome has been reported to have a good prognosis [2], but in the present case, the disease progressed rapidly, and the patient died before the start of treatment. There is no consensus regarding the treatment of intrahepatic cholangiocarcinoma in Maffucci syndrome. In addition to the malignant transformation of enchondroma and hemangioma, Maffucci syndrome can cause various malignancies associated with *IDH1* somatic mosaic mutations. It is considered necessary for these patients to regularly undergo imaging tests such as CT and measurement of tumor markers to monitor for the presence of malignancies.

In conclusion, we experienced a patient with Maffucci syndrome in whom intrahepatic cholangiocarcinoma developed because of a somatic mosaic mutation in *IDH1*. Therefore, periodic and careful observation via tumor marker and imaging studies is considered crucial for patients with Maffucci syndrome because of the risk of malignancy.

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Statement of Ethics

We obtained written informed consent from the patient for the use of the specimens and information in this medical research, and we obtained written informed consent from the parent for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest directly relevant to the content of this article.

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Author Contributions

All authors were involved in the preparation of the manuscript. Ryoichiro Kobayashi, Koji Kubota, Tsuyoshi Notake, Shinsuke Sugeno, Kiyotaka Hosoda, Hikaru Hayashi, Koya Yasukawa, Yayoi Satoh, Mai Iwaya, and Kenji Sano collected the data, and Akira Shimizu, Mai Iwaya, and Yuji Soejima wrote the manuscript. Ryoichiro Kobayashi, Koji Kubota, Tsuyoshi Notake, Shinsuke Sugeno, Kiyotaka Hosoda, Hikaru Hayashi, and Koya Yasukawa were involved in the treatment of the patient. All authors read and approved the final manuscript.

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