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CASE REPORT-MOLECULARLY TARGETED THERAPY

Intrahepatic cholangiocarcinoma with FGFR2 fusion gene positive that responded to pemigatinib and caused hypophosphatemia

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Abstract
Intrahepatic cholangiocarcinoma is a condition with a poor prognosis. Traditionally, there was no cure unless important drugs such as gemcitabine, cisplatin, and tegafur/gimeracil/uracil potassium showed efficacy. Pemigatinib has recently become accessible for the treatment of intrahepatic cholangiocarcinoma with FGFR2 fusion or rearrangement gene abnormalities. Hyperphosphatemia is typically linked to pemigatinib. In the current case, pemigatinib was used to effectively treat a 48-year-old woman, and hypophosphatemia was observed. Patients with intrahepatic cholangiocarcinoma should undergo aggressive cancer multigene panel testing as well as careful monitoring of serum phosphorus levels.

Keywords Intrahepatic cholangiocarcinoma · Fibroblast growth factor receptor 2 fusion gene · Chemotherapy · Pemigatinib

Introduction

Cholangiocarcinoma, cancer of the intrahepatic and extrahepatic bile ducts, is chiefly distinguished by late diagnosis and fatal results. Cholangiocarcinoma, which makes up approximately 10–15% of all hepatobiliary malignancies, is the second most prevalent primary liver tumor [1]. Conventionally, there were no effective drugs after the key drugs, namely, Gemcitabine (GEM), Cisplatin (CDDP), and Tegafur/gimeracil/oteracil potassium (S-1). However, recently, durvalumab in combination with GEM plus CDDP (GC) therapy was approved. [2].

In Cholangio-cellular carcinoma (CCC), the fibroblast growth factor receptor 2 (FGFR2) gene is a crucial driver gene for the oncogenic process. In 10–15% CCCs, fusion or rearrangement of FGFR2 is seen. Pemigatinib is a potent ATP competitive selective inhibitor of FGFR1, FGFR2, and FGFR3 [3, 4]. As a result, in June 2021, pemigatinib received insurance approval in Japan.

Hyperphosphatemia has been linked to pemigatinib. There are currently no detailed case reports on the efficacy and adverse events of pemigatinib. Here, we present a hypophosphatemia case that developed after successful pemigatinib treatment.

Case report

In April 2019, a 48-year-old woman presented with intrahepatic bile duct dilatation on computerized tomography (CT) for a follow-up of type 2 diabetes at another hospital, and magnetic resonance imaging (MRI) revealed a 35-mm large mass in the right lobe of the liver (S6). In June, the patient was referred to our hospital with suspicions of having CCC. As a result of fluoroscopic bile duct biopsy, adenocarcinoma was discovered and para-aortic lymph node metastasis was found, resulting in Stage IV diagnosis. In July 2019, we began GC therapy. The patient maintained a partial response (PR) by CT and MRI but was switched to S-1 monotherapy in April 2020 because of itchiness experienced during CDDP administration in March 2020. However, the drug-induced lymphocyte stimulation test for S-1

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was positive, because the patient also had a liver disorder and stomatitis. Therefore, we switched to GEM monotherapy in August 2020. The diagnostic imaging revealed that while CA19-9 increased from October 2020, efficacy was maintained. Because the aortic lymphadenopathy did not increase by PET, hepatic resection was performed in February 2021. Macroscopic and microscopic images of resected tumors are shown in Fig. 1. Macroscopic findings revealed a grayish-white mass with indistinct borders in the posterior right lobe of the liver (Fig. 1a). HE stains of the mass area showed small atypical cells with rounded nuclei, forming an adenoductal structure and proliferating (Fig. 1b). Azan staining revealed fibrous liver tissue associated with pericholangitis (Fig. 1c). Therefore, the resected pathological findings were well to moderately differentiated adenocarcinoma (small duct type), im(-), e.g., fc(-), fc-inf(-), sf(-), s0, n1, vp2, vv1, va1, b2, p0, sm(-), and f3.

The patient had received GEM monotherapy for postoperative adjuvant chemotherapy since April after the operation; however, a CT scan in September 2021 revealed the recurrence of liver metastasis. A cancer multigene panel testing was performed using surgical specimens. The findings showed TP53–STK11, VUS, GATA6, and FGFR2–EBF3 fusion as actionable gene abnormalities, and FGFR2–EB3 fusion was suggested as a druggable gene abnormality. As a result, we began pemigatinib treatment (13.5 mg/days 1–14, q21 day) in November 2021.

Table 1 displays the blood and biochemical data obtained before pemigatinib administration, and the course after pemigatinib administration is depicted in Fig. 2. The patient had increased C-reactive protein, elevated hepatobiliary enzymes, elevated blood glucose and HbA1c levels, occult hematuria due to chronic urinary tract infection, and urinary glucose and proteinuria due to diabetic nephropathy. The serum phosphorus level decreased to 1.9 mg/dl at the beginning of the treatment, but no subjective symptoms were observed. Hepatobiliary enzymes rapidly improved during treatment, while proteinuria tended to worsen. The patient was hospitalized for renal biopsy as proteinuria due to pemigatinib has been reported in 0.9% of patients [5]. While the patient was admitted, pemigatinib was discontinued. Pathological findings on renal biopsy showed doughnut lesions with a progressive increase in the mesangial matrix, suggestive of diabetic nephropathy. Based on these findings, the patient was diagnosed with diabetic nephropathy Cless IIa, and proteinuria improved with subsequent glycemic control. After the resumption of pemigatinib treatment, the serum phosphorus level remained within the normal range, but it decreased to 1.3 mg/dl in the late stage of treatment.

Figure 3 shows the enhanced MRI late-phase images used to assess the efficacy of pemigatinib. Liver metastases observed before treatment (Fig. 3a, b) indicated a shrinking

Table 1 Blood and biochemistry data before Pemigatinib administration

Blood biochemistry		Blood cell count
CRP: 3.0 mg/dl	T-bil: 1.7 mg/dl	WBC: 7000/μl
Na: 131 mM	D-bil: 1.0 mg/dl	RBC: 3.84×10^6/μl
K: 4.1 mM	UN: 11 mg/dl	Hb: 11.6 g/dl
Ca: 9.0 mg/dl	Cre: 0.63 mg/dl	PLT: 207×10^3/μl
P: 3.1 mg/dl	eGFR: 77.3	General urine
Fe: 106 μg/dl	AST: 66 U/L	pH: 5.0
UIBC: 192 μg/dl	ALT: 33 U/L	Occult hematuria: (+)
TIBC: 298 μg/dl	LD-IF: 301 U/L	Urinary glucose: (3+)
TP: 6.8 g/dl	BS: 377 mg/dl	Proteinuria (qualitative): (3+)
Alb: 2.9 g/dl	HbA1c: 7.9%	Proteinuria (quantitative): 4.3 g/gCr

CRP C-reactive protein, *UIBC* unsaturated iron binding capacity, *TIBC* total iron binding capacity, *TP* total protein, *Alb* albumin, *T-bil* total bilirubin, *D-bil* direct bilirubin, *UN* urea nitrogen, *Cre* creatinine, *eGFR* estimated glemerular filtration rate, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LD-IF* lactate dehydorogenase, *BS* blood sugar, *HbA1c* hemoglobin A1c, *WBC* white blood Cell, *RBC* red blood cell, *Hb* hemoglobin, *PLT* platelet

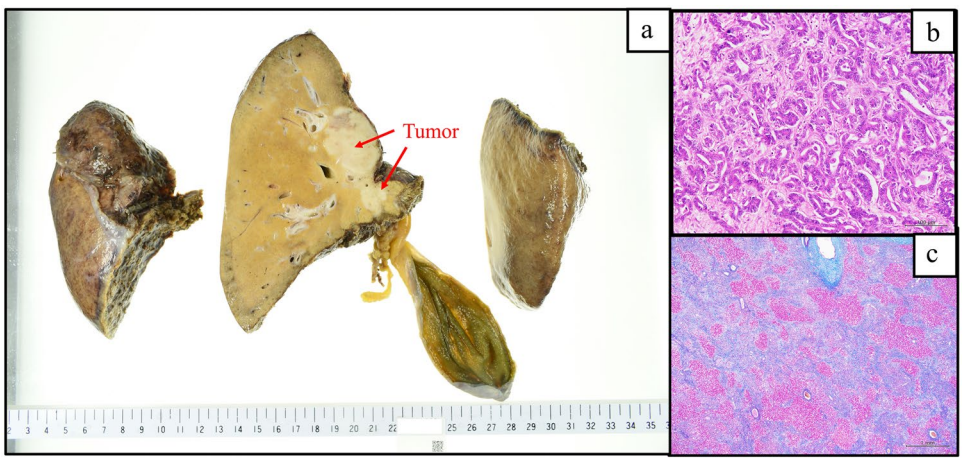

Fig. 1 Gross and pathological images of surgical specimen

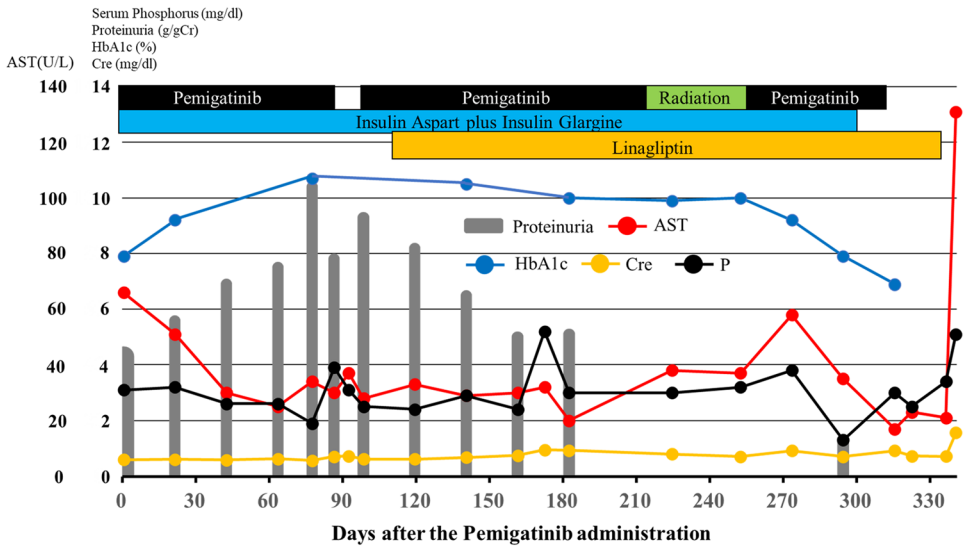

Fig. 2 Clinical course after the pemigatinib administration

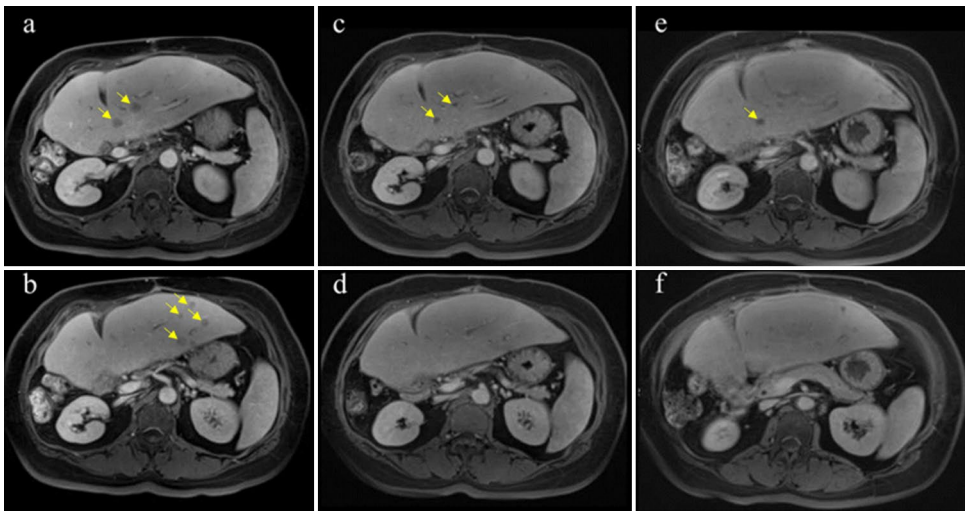

Fig. 3 Magnetic resonance imaging (MRI) findings before and after treatment. MRI pretreatment (**a**, **b**) imaging findings, 3 months (**c**, **d**), and 5 months (**e**, **f**) after Pemigatinib administration. There are some intrahepatic liver metastases (yellow arrow), but they improve after treatment

trend after 3 months (Fig. 3c, d) and after 5 months (Fig. 3e, f) of treatment, and were analyzed as PR according to the RECIST guideline [6]. Table 2 lists adverse reactions to pemigatinib therapy. Despite not having any subjective symptoms, the patient had grade 3 hypophosphatemia. Other adverse effects included grade 2 anemia and grade 1 dry mouth, fever, and urinary infection, all of which were thought to be associated with diabetes mellitus or chronic urinary tract infection. At 6.5 months after treatment, the patient noticed an abdominal mass and a contrast-enhanced CT early phase scan of the abdomen revealed multiple liver metastases (Fig. 4a–d) and abdominal wall metastases (Fig. 4d, e). Radiotherapy (33 Gy in 11 fractions) was initiated for the abdominal wall metastases, but the metastases did not undergo shrinkage (data not shown). Pemigatinib was discontinued during radiotherapy. The patient insisted on continuing pemigatinib after the radiotherapy finished, but her quality of life deteriorated and she had difficulty taking the drug. Finally, the patient passed away 11.3 months after starting pemigatinib and 40 months (3.3 years) after starting initial therapy.

Discussion

The conventional first-line therapies for incurable biliary tract cancer in Japan include conventional, GC therapy [7, 8], GS (GEM plus S-1) therapy [9, 10], and GCS (GEM/CDDP/S-1) therapy [11]. For second-line therapy, modified FOLFOX [12] and *nal*-irinotecan plus 5-FU/LV [13] have both been found to be effective for second-line therapy; however, they are not approved in Japan. Nevertheless, in December 2022, durvalumab in combination with GC therapy was approved [2]. In the future, duruvalumab may play a significant role as a first-line therapy.

Table 2 Adverse events with Pemigatinib administration

Toxicity (CTCAE)	Grade 0	Grade 1	Graed 2	Grade 3	Grade 4
Hematological					
Leukopenia	●				
Thrombocytopenia	●				
Anemia			●		
Aspartate aminotransferase increased	●				
Alanine aminotransferase increased	●				
Hyperphosphataemia	●				
Hypophosphataemia				●	
Non-hematological					
Dry eye	●				
Dry mouth		●			
Fatigue	●				
Fever		●			
Nail disorder	●				
Skin toxicity	●				
Arthralgia	●				
Urinary tract infection		●			

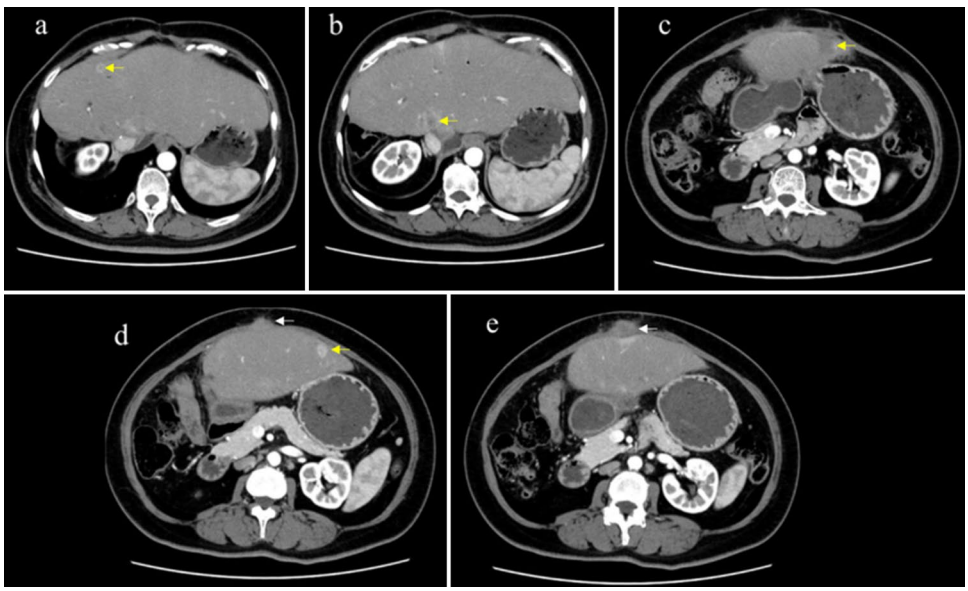

Fig. 4 Abdominal contrast-enhanced computed tomography findings 6.5 months after Pemigatinib administration. It revealed multiple liver metastases (yellow arrows) and abdominal wall metastases (white arrows)

CCC is broadly classified into two types: large duct type and small duct type. It has been reported that FGFR2 fusion gene abnormalities are positive only in the small duct type, and this case was also a small duct type [14]. The liver surrounding the tumor was fibrotic, probably because of chronic cholangitis associated with bile duct obstruction.

A receptor-type tyrosine kinase called FGFR plays physiological roles in tissue formation, angiogenesis, tissue repair regulation, cell proliferation, and migration [15]. There are four different types of FGFRs (FGFR1, FGFR2, FGFR3, and FGFR4), each of which has the following three major domains: extracellular, transmembrane, and intracellular [16]. In genetically defined tumor models, the oral FGFR1-3 inhibitor pemigatinib, which is potent and selective, has demonstrated anticancer efficacy [17].

In the FIGHT202 study, a response rate of 35.5%, disease control rate of 82%, median progression-free survival of 6.9 months, and median survival of 21.1 months were reported for pemigatinib [5]. In this case, progression was confirmed at approximately 6.5 months and the patient passed away 11.3 months, after Pemigatinib administration. Despite the time to advancement being about the same as previously reported, the rapid decline in the quality of life thereafter did not prolong survival.

Hyperphosphatemia is a characteristic adverse event for FGFR inhibitors (Erdafitinib, Pemigatinib, Infigratinib,

Derazantinib) and is observed in 55–75% of patients. FGFR inhibitors block the catabolism of 1, 25 (OH) 2 vitamin D and sodium-phosphate co-transporters in proximal renal tubule cells, leading to hyperphosphatemia [18].

However, Grade 3 hypophosphatemia was present in this case. In the FIGHT-202 research, 7% of participants reported hypophosphatemia as a Grade 3 adverse event [5]. Serum phosphorus levels are generally affected by renal function. In the present case, proteinuria due to diabetic nephropathy was noted, but renal function was not compromised. Hypophosphatemia has been attributed to the continued use of a low phosphate diet or phosphate binders for hyperphosphatemia during the off-treatment week or from negative-feedback effects on phosphate homeostasis. However, negative feedback may be the cause in the present case, because no specific dietary restrictions were imposed In contrast, imatinib, dasatinib, and nilotinib, which are drugs for chronic myeloid leukemia, are known to cause hypophosphatemia, which is significantly improved by oral administration of monobasic sodium phosphate monohydrate [19]. Therefore, hypophosphatemia has few symptoms; however, oral phosphate preparations should be considered if it persists for a long period.

A phase III study (FIGHT-302) is being examined to evaluate the efficacy of pemigatinib in the first-line treatment of biliary tract cancer [20]. Depending on the outcomes, it might 1 day serve as a first-line therapy for CCC with FGFR2 fusion gene abnormalities.

In this case required conversion surgery due to GC therapy. In the KHBO1401 study, 8 out of 246 patients (2 with GC and 6 with GCS) underwent conversion surgery, and 5 patients experienced postoperative recurrence, with a 3-year survival rate of 75% and a significantly prolonged prognosis ($P=0.007$) [21]. Conversion surgery for biliary tract cancer is a topic for further research despite the minimal number of patients.

Unresectable intrahepatic cholangiocarcinoma with a diameter of 5 cm or less without metastases responds well to radiotherapy [22]. However, radiotherapy to the metastatic site in the abdominal wall, in this case, was ineffective. Future research should focus on the efficacy of radiotherapy for CCC with FGFR2 fusion gene abnormality.

In conclusion, this case is a CCC that responded to pemigatinib and induced hypophosphatemia. Aggressive multigene panel testing for FGFR2 fusion gene abnormalities should be performed on the CCC. Using a hypophosphate diet or phosphate-binding agents is to be avoided, because pemigatinib is typically linked with hyperphosphatemia but can also rarely result in hypophosphatemia.

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Data availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

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

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