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CASE REPORT

Gallbladder cancer harboring *ERBB2* mutation on the primary and metastatic site: A case report

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Author contributions: Inagaki C and Satoh T collected the patients' clinical data, reviewed the literature and drafted the manuscript; Maeda D performed pathological examination and clinical annotation of NGS sequence data and drafted the manuscript, Kimura A and Otsuru T collected the patients' clinical data and contributed to manuscript drafting, Shirotsuki R and Yachida S performed clinical annotation of NGS sequence data and drafted the manuscript; Iwagami Y, Nishida N, Sakai D and Doki Y were contributed for the revision of the manuscript for important intellectual content, all authors issued final approval for the version to be submitted.

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Abstract

BACKGROUND

Bile duct cancer constitutes gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (ICA), and extrahepatic cholangiocarcinoma (ECA). These three entities show morphological and immunohistochemical resemblance so that it is difficult to differentiate between primary ICA and liver metastasis of GBC, which sometimes becomes a point of discussion in clinical practice. Although these cancers demonstrate significant differences in their mutational landscape, several reports demonstrated shared genomic alteration in paired primary and metastatic site aids in distinguishing metastatic recurrence from second primary cancers.

CASE SUMMARY

We present a 73-year-old female patient who underwent curative resection for GBC harboring epidermal growth factor receptor 2 (ERBB2) activating mutation on next-generation sequencing (NGS)-based genomic testing. One year later, a

Satoh reports other from Merck Serono Co., Ltd, other from Takeda Pharmaceutical Company, other from Eli Lilly and Company, other from Bristol Myers Squib, other from Yakult Honsha, other from Ono Pharmaceutical Co., Ltd, other from Chugai Pharmaceutical Co., Ltd, from null, other from Takara Bio INC, outside the submitted work.

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hepatic lesion was observed on follow-up imaging and she underwent surgical resection for a pathological diagnosis. The histological findings of the hepatic lesion were similar to those of the primary lesion. Additionally, using NGS panel testing, the hepatic lesion was found to have *ERBB2* activating mutation, which is the identical mutation detected in the sequencing result of the primary site. ERBB2 activating mutation occurs more frequently in GBC than ICA and ECA. Therefore, in the present case, we think this molecular finding potentiated the diagnosis of the liver mass toward a metastatic recurrence. Additionally, this patient underwent *HER2*-targeted treatment with lapatinib in combination with capecitabin and obtained clinical benefit.

CONCLUSION
This case illustrated NGS panel usefulness in distinguishing GBC recurrence from second primary cancer and *HER2*-targeted agent efficacy on *ERBB2* mutated GBC.

Key words: Gall bladder cancer; Bile duct cancer; *ERBB2* mutation; Precision medicine; Mutation-driven targeted treatment; Case report

Core tip: We present a case report of a patient with gallbladder cancer (GBC) harboring epidermal growth factor receptor 2 (*ERBB2)* hotspot extracellular domain mutation (Ser310Phe) on both the primary site and metachronous liver metastasis. Given that pathological differentiation between hepatic metastasis and primary cancer of the liver is often difficult, next-generation sequencing panel could be a novel option for patients who need to distinguish a metastatic lesion from a second malignancy, which would affect staging and the treatment strategy. This case also illustrated the benefit of the *HER2*-targeted agent in the treatment of GBC harboring *ERBB2* activating mutation.

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INTRODUCTION

Gallbladder cancer (GBC) is an uncommon malignancy with an aggressive clinical course. Its prevalence varies among geographical areas and is higher in Asia and the Andes region[1]. GBC constitutes bile duct cancer along with intrahepatic cholangiocarcinoma (ICA) and extrahepatic cholangiocarcinoma (ECA). However, these are distinct entities with significant differences in their mutational landscape[2]. For example, isocitrate dehydrogenase 1 or 2 mutations, breast cancer *1* associated protein-1 mutations, and fibroblast growth factor receptors fusions are frequently seen in ICA, whereas Kirsten rat sarcoma viral oncogene homolog and, mothers against decapentaplegic homolog 4 mutations are more likely to occur in ECA. However, GBC has a high frequency of avian erythroblastosis oncogene B2 (ERBB2), transformation-related protein 53 (TP53), and cyclin-dependent kinase inhibitor 2A mutations.

Generally, surgical resection is the only curative option for localized GBC, and chemotherapy is the primary treatment for unresectable or recurrent disease. Despite recent advances in the treatments, more than half of the patients have experienced a recurrence after radical resection and prognosis of metastatic disease is very poor with 5-year survival around 5%[3,4]. The liver is the most common site of recurrence in GBC[4]. The histological differentiation between primary ICA and liver metastasis of GBC is often difficult owing to morphological and immunohistochemical resemblance, whereas the distinction between the metastasis of the primary malignancy and newly developed second primary malignancy is clinically important for accurate staging and tailoring treatment strategies[5]. Reflecting recent technical

advances in high-throughput next-generation sequencing, there are several reports describing the utility of genomic profiling in the differential diagnosis of a metastatic recurrence and distinguishing it from second primary malignancy[6].

Here, we present a case report of a patient with GBC harboring *ERBB2* activating mutation on both the primary site and metachronous liver metastasis, which aids in the differentiation from secondary malignancy. Additionally, this patient was treated with human epidermal growth factor receptor-2 (*HER2*)-targeted agent, lapatinib, and achieved clinical benefits.

CASE PRESENTATION

Chief complaints

The patient was a previously healthy 73-year-old female who underwent curative resection for GBC (pT2N0M0 according to the eighth International union against cancer TNM classification). We performed next-generation sequencing (NGS)-based genomic profiling of the resected specimen using the NGS gene panel, Oncomine® Comprehensive Assay version 3 (OCA v.3, Thermo Fisher Scientific), which revealed *ERBB2* Ser310Phe (c.929C>T; VAF, 18%) and *TP53* Ser241Tyr (c.722C>A; VAF, 19%) mutations. One year later, a hepatic lesion was observed on follow-up imaging and she underwent surgical total biopsy for a pathological diagnosis.

History of present illness

A patient had no symptoms and was in good health at the time of total biopsy.

History of past illness

The patient had no previous medical history.

Physical examination and laboratory testing

The patient's physical examination was not remarkable and laboratory testing was within normal limits, including tumor markers, such as *CA19-9* and *CEA*.

Imaging Examination

Contrasted computed tomography (CT) showed an ill-defined low attenuation lesion in the posterior lobe of the liver (Figure 1).

Further diagnostic work-up

The hepatic lesion was histologically diagnosed as well-differentiated adenocarcinoma and the histological findings of the hepatic lesion were similar to those of GBC (Figure 2). Therefore, the lesion was considered a metastasis. Moreover, we performed genomic profiling from the liver tumor using the NGS panel, Oncomine® Target Test system (OTT, Thermo Fisher Scientific). This revealed *ERBB2* Ser310Phe (c.929C>T; VAF, 26%), which was identical to the mutation detected in the sequencing result of the primary site; thus, the liver tumor was the most consistent with a metastasis of GBC rather than localized ICC. To evaluate *HER2* overexpression in tumor cells, we performed immunohistochemistry of *HER2*, which was negative (*HER2* score 0). Since *TP53* was not included in the gene list of OTTs, *TP53* mutation status at the metastatic site was not assessed.

FINAL DIAGNOSIS

The final diagnosis of the presented case is hepatic recurrence of GBC.

TREATMENT

After the total biopsy of liver metastasis, she was treated with two standard chemotherapy regimens, namely gemcitabine and cisplatin, and TS-1; however, her disease did not obtain clinical benefit from these treatments. After six months from hepatic resection, she was confirmed to have a progressive disease during second-line chemotherapy. At that time, she had liver and pulmonary recurrence, as well as pulmonary and inferior vena cava tumor embolism, which caused tachycardia and peripheral edema.

Considering no standard treatment beyond second-line for GBC, we treated the patient with lapatinib with a combination of capecitabine (lapatinib at a dose of 1250 mg per day continuously plus capecitabine at a dose of 2000 mg per square meter of

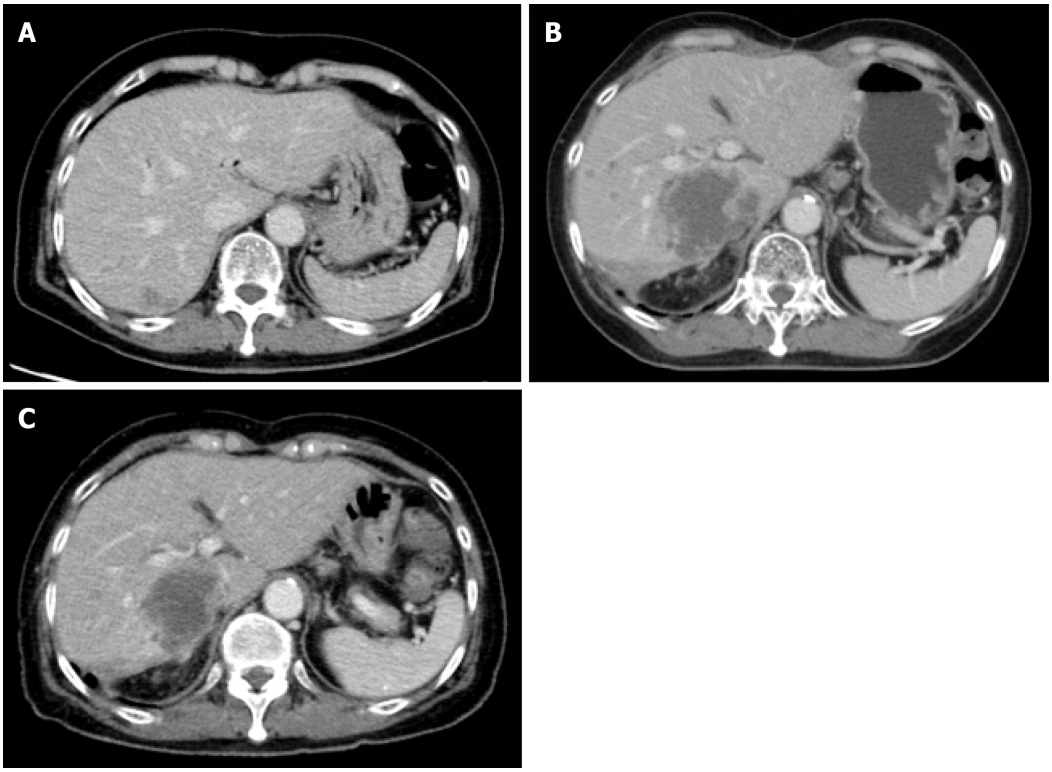

Figure 1 Contrasted computed tomography images. A: Contrasted computed tomography scan before surgical biopsy. A hypoattenuating lesion with ill-defined margins was observed in the posterior lobe of the liver; B and C: Comparative contrasted computed tomography scan before (B), and after (C) 2 cycles of lapatinib and capecitabine treatment. Hepatic metastases were reduced in size and tumor emboli in inferior vena cava (arrow heads) was mostly disappeared with the therapy.

body-surface area on days 1 through 14 of a 21 d cycle) based on the accumulating preclinical and clinical evidence that tumors with *ERBB2* mutation benefit from *HER2*-targeted treatment.

OUTCOME AND FOLLOW-UP

Within a week of treatment, she experienced major subjective clinical improvement, which included resolution of peripheral edema. After 2 cycles of treatment, contrasted CT imaging showed a decrease in the size of tumor emboli and hepatic lesions (Figure 1). However, after 4 cycles of treatment, the patient discontinued treatment due to grade 3 mucositis. Mucositis was gradually subsided over two weeks after discontinuation of the treatment. One month after discontinuation, her disease progressed, and she chose best supportive care.

DISCUSSION

We observed the same *ERBB2* Ser310Phe mutation in the primary tumors, as well as the metachronous hepatic lesion of this patient using NGS panels. We believe this molecular finding potentiated the diagnosis of the liver mass toward a metastatic recurrence. In addition, this patient exhibited a favorable effect of the *HER2*-targeted agent on GBC with *ERBB2* activating mutation.

Histologically, metastatic adenocarcinoma of the biliary tract cannot be distinguished from ICA or pancreatic origin owing to similarities in appearance and immunohistochemical staining patterns[5]. In addition, there is no particular method established to assess genetic relationships and clonality in primary and metastatic sites in malignancy. However, limited studies have shown the potential of genetic profiling to distinguish between a metastatic recurrence of the primary cancer and newly developed second primary cancer in several malignancies[6-8]. Previous reports demonstrated shared genomic alteration in paired primary and metastatic sites was useful in differentiating multifocal non-small cell lung cancer from intrapulmonary metastasis[7,8]. Moreover, Vignot *et al*[9] showed that genomic profiles of the first metastatic recurrent sites are highly concordant to the primary site in colorectal

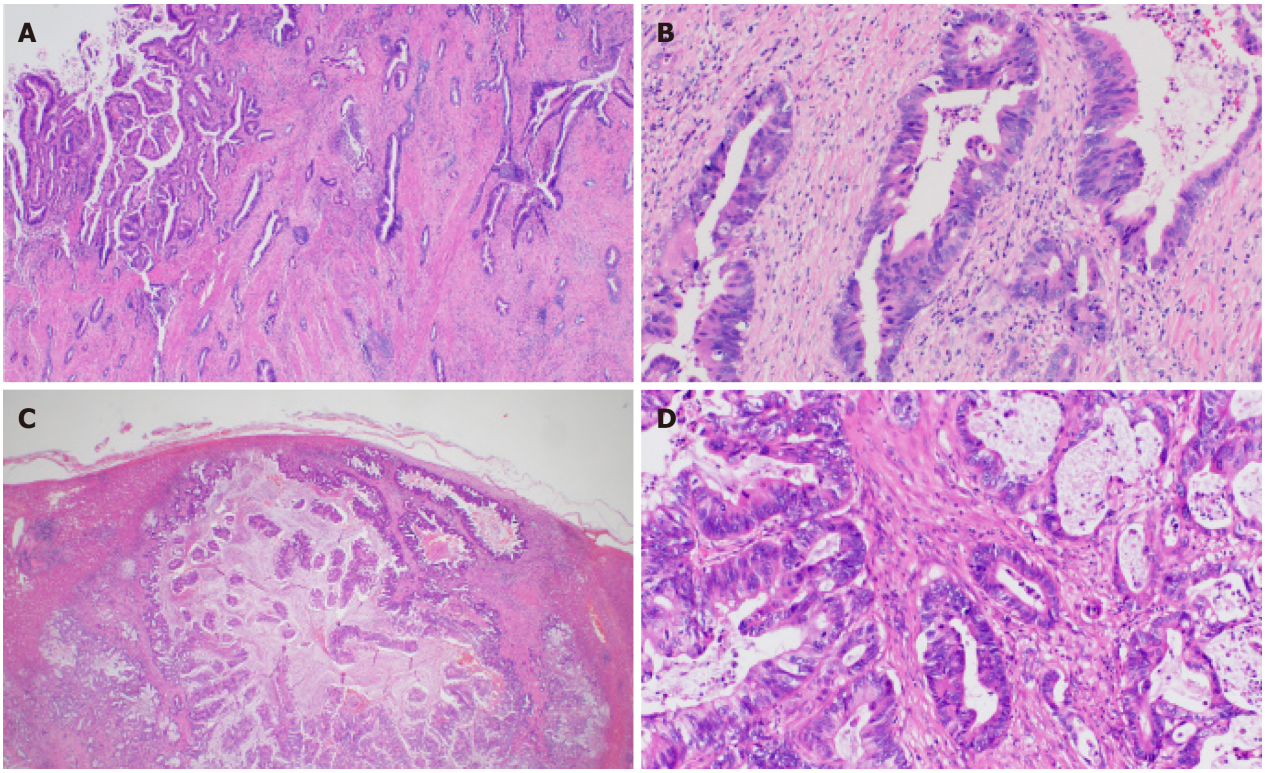

Figure 2 Tumor histology. A: Low-power microscopic view of the gallbladder cancer. The tumor cells form tubules of variable sizes. The tumor infiltrates deeply into the gallbladder wall; B: High-power microscopic view of the gallbladder cancer. Atypical columnar cells with enlarged nuclei grow in tubular structures. Stromal fibrosis and inflammation are also observed; C: Low-power microscopic view of the hepatic lesion. Adenocarcinoma with vaguely nodular contour involves the liver parenchyma; D: High-power microscopic view of the hepatic lesion. Glandular structure is predominant. The tumor cells have enlarged nuclei with coarse chromatin. Multiple mitoses are observed.

cancer. In the present case, the primary site and hepatic lesion shared the identical *ERBB2* mutation. *ERBB2* mutations are relatively frequent (9%-10%) in GBC, in contrast to ICA, as shown in previous studies[10-12]. Currently, there are no reports evaluating the concordance between primary and metastatic sites in CA; however, we considered this molecular finding supported the diagnosis of metastatic recurrence rather than the primary carcinoma of liver origin.

Additionally, *ERBB2* Ser310Phe is a known activating hotspot mutation in the extracellular domain[13]. The growing body of preclinical evidence and early phase trials supports *HER2*-targeted therapy for cancers harboring *ERBB2* activating mutations, whereas standardized molecular treatment has not been determined for this population[14-16]. Furthermore, the efficacy of *HER2*-targeted treatment on *ERBB2*-mutated tumors seems to vary between tumor types and mutation loci. Neratinib is an irreversible pan-HER tyrosine kinase inhibitor and clinical efficacy of neratinib for various *ERBB2*-mutated cancers was evaluated in the basket trial[17]. Neratinib exhibited the greatest activity in patients with breast cancer [Overall response rate; ORR 32% (8/25)], followed by biliary tract cancer [ORR 22.2% (2/9)). When stratified by a mutant allele, response was greatest in patients with kinase domain hotspot mutation [ORR 21.4% (9/42)], followed by Ser310 mutation [ORR 10% (3/30)] and exon 20 insertion mutation [ORR 7.1% (2/28)]. Among two biliary tract cancer patients with *ERBB2* Ser310 mutation included in this trial, one patient responded to neratinib. Ado-trastuzumab emtansine, a *HER2*-targeted antibody-drug conjugate linking trastuzumab with emtansine, demonstrated ORR of 44% (8/18) for patients with lung cancer harboring *ERBB2* mutation, including Ser310, in phase II basket trial; however, to the best of our knowledge, there are no reports evaluating its benefit for GBC with *ERBB2* mutation[18]. Javle *et al*[19] reported a case series of biliary tract cancer harboring *ERBB2* mutations. In this report, one cholangial cancer patient with *ERBB2* Ser310 mutation treated with trastuzumab, a humanized monoclonal antibody directed to *HER2*, in combination with FOLFOX, was not effective. Our patient obtained clinical benefit from lapatinib and capecitabin combination treatment. Lapatinib is a dual tyrosine kinase inhibitor that targets epidermal growth factor receptor and *HER2* and the combination treatment of lapatinib and capecitabin was evaluated initially in *HER2* positive breast cancer patients and showed prolonged survival with tolerable toxicity[20]. A previous case report indicated substantial efficacy

of this combination treatment in a patient with metastatic extramammary Paget's disease harboring *ERBB2* Ser310 mutation[21]. Given that TS-1 monotherapy, which is oral fluoropyrimidine as with capecitabin, was prescribed as second line treatment and was not effective to this patient, modest benefit from this combination treatment would be attributed to lapatinib. As both lapatinib and capecitabin are off-label use in Japan for patients with cholangiocarcinoma, we prescribed these agents following patients' written consent.

CONCLUSION

This case highlighted the usefulness of NGS panels in distinguishing hepatic metastasis from primary cancer of the liver, which sometimes becomes a point of discussion in daily practice. Although we need a large cohort for verification, NGS panel may be a novel option for patients who need to distinguish a metastatic lesion from a second malignancy, which would affect staging and treatment strategies.

This case also illustrated the value of lapatinib in combination with capecitabine in the treatment of GBC harboring *ERBB2* activating mutation. We recognized *HER2*-targeted agent as a potential treatment for *ERBB2* mutated tumors. Further investigation of *HER2*-targeted agent in this population is warranted.

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