Case report: Secondary sclerosing cholangitis induced by lapatinib and vinorelbine in a metastasis breast cancer patient

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Abstract
Secondary sclerosing cholangitis (SSC) is a rare cholestatic liver disease that may have a severe clinical course. A 61-year-old woman with a history of metastasis breast cancer was admitted to our hospital for the second cycle of chemotherapy with lapatinib and vinorelbine. The patient had no reports of elevated liver function tests (LFTs) in the previous multiple chemotherapies or history of liver disease. However, the admission laboratory results showed severe cholestatic liver injury with the possibility of SSC by magnetic resonance cholangiopancreatography. Although chemotherapy was discontinued and patient was treated with hepatoprotective drugs, the LFTs did not improve and liver biopsy indicated mild injury of intrahepatic bile duct epithelium and hepatocyte. We added ursodeoxycholic acid and prednisolone to protect the liver, and laboratory data showed a response. To prevent the progression, lapatinib and vinorelbine were reintroduced and transient increases in alanine aminotransferase and γ-glutamyl transpeptidase were observed. With no evidence of viral or autoimmune liver disease, SSC induced by lapatinib and vinorelbine was diagnosed. This is the first case report of tyrosine kinase inhibitors and vinorelbine induced SSC and clinicians should be aware of the possibility of it. More case reports about this adverse drug reaction are needed to delineate optimal management.

KEYWORDS
case report, cholestatic drug-induced liver injury, lapatinib, secondary sclerosing cholangitis, vinorelbine

INTRODUCTION
Lapatinib is an orally small molecule epidermal growth factor receptor and human epidermal growth factor-2 (HER2) tyrosine kinase inhibitor (TKI), which has been approved in combination with chemotherapy for the treatment of HER2-overexpressing metastatic breast cancer (MBC).\(^1\) Cancer treatment-associated drug-induced liver injury (DILI) is widely reported, but clinically serious idiosyncratic DILI is rare.\(^2\) Secondary sclerosing cholangitis (SSC) is a rare, cholestatic liver disease that can be induced by infectious, immune-mediated, obstructive, ischemic injury or toxic and may have a severe clinical course.\(^3\) A variety of drugs have been reported to be associated with SSC,\(^3\)–\(^9\) but there is no report on TKIs or vinorelbine-induced SSC.
CASE REPORT

Our patient is a 61-year-old woman with a diagnosis of HER2-overexpressing MBC. The patient had no reports of elevated liver function tests (LFTs) and abnormal contrast-enhanced computed tomography (CT) imaging of bile ducts (Figure 1(a),(b)) in the previous chemotherapies (Table 1). However, in October 2018, before the second cycle of lapatinib and vinorelbine injection, the admission laboratory results showed obvious liver injury: alanine aminotransferase (ALT) 219 IU/L, aspartate aminotransferase (AST) 809 IU/L, alanine aminotransferase (ALP) 606 IU/L, \( \gamma \)-glutamyl transpeptidase (GGT) 748 IU/L, and total bilirubin (TBIL) 23.9 \( \mu \)mol/L. Physical examination was unremarkable and liver-protecting treatment with reduced glutathione, polyene phosphatidylcholine, ursodeoxycholic acid (UDCA), and compound glycyrrhizin was initiated. In serial laboratory tests, LFTs did not decline and showed a trend of fluctuation (Figure 2). Hepatitis virus markers, Alpha-fetoprotein, protein induced by vitamin K absence or antagonist-II, serum immunological markers, hematology, coagulation, and tuberculosis-spot were in the normal range. A CT scan on hospital day 5 revealed multiple lesions at intrahepatic and extrahepatic bile ducts and swelling of the intrahepatic Glisson’s sheath (Figure 1(c)). Lapatinib was discontinued. Magnetic resonance imaging (MRI) (Figure 1(e)) and magnetic resonance cholangiopancreatography (MRCP) (Figure 1(f)) on hospital day 15 showed dilation of intrahepatic duct, thickening of the common, left, and right hepatic duct wall and bile duct wall, stenosis in

FIGURE 1  Imaging of the patient. Contrast-enhanced computed tomography scan (a) before neoadjuvant chemotherapy in August 2015, (b) during the eight cycles of weekly nab-paclitaxel and trastuzumab for metastasis, (c) on hospital day 5 and (d) after the termination of lapatinib and vinorelbine. (e) Upper abdominal magnetic resonance imaging and (f) magnetic resonance cholangiopancreatography on day 15.
ducts, and dilation of distal bile duct, with the appearance of SSC. Percutaneous ultrasonography-guided liver biopsy revealed mild injury of intrahepatic small bile duct epithelium and hepatocyte (Figure 3), which were likely to be chemotherapy-related. Given no improvement in hepatic enzymatic indices, mostly with elevated ALP and GGT, prednisolone (30 mg/day orally) was added to protect liver, together with UDCA dose increased (from 250 mg twice a day to 500 mg twice a day). After LFTs improved, the patient began chemotherapy again with lapatinib (1000 mg/day) and vinorelbine capsule (80 mg on days 1 and 8, every 3 weeks) on 49 and 71 days after admission, respectively. However, ALP and GGT increased again with no evidence of viral or autoimmune liver disease. According to the above findings, DILI induced by lapatinib and vinorelbine was diagnosed, with the possibility of SSC. Following the intensive liver protecting treatment and continuing chemotherapy, LFTs were controlled acceptable. The progression in brain metastases was observed after 5 months from the first cycle of lapatinib and vinorelbine, and the patient received whole brain radiotherapy with trastuzumab added to the prior treatment. In April 2020, lapatinib and vinorelbine were stopped (Figure 1(d)), and the LFTs were determined: ALT 33 IU/L, AST 49 IU/L, ALP 222 IU/L, GGT 177 IU/L and TBIL 19.0 μmol/L.

| Time point  | Measures |
|-------------|----------|
| 08/2015     | Diagnosed with HER2-overexpressing breast invasive ductal cancer (T2N1M0) with middle grade DCIS. |
| 08–12/2015  | 6 cycles of neoadjuvant chemotherapy with docetaxel, carboplatin, and trastuzumab. |
| 12/2015     | Modified radical mastectomy. Response evaluation: pathological complete response (ypT0N0M0). Histological examination: scattered middle grade DCIS with HR-positive, HER2-positive (3+), and 10% of cells Ki67-positive. |
| 01/2016–01/2018 | Finished 1-year trastuzumab therapy followed by radiation and letrozole. |
| 01/2018     | Metastases in bone, brain, and lung. |
| 03–06/2018  | Gamma knife. 8 cycles of weekly nab-paclitaxel and trastuzumab. |
| 07–08/2018  | 2 cycles of lapatinib (1250 mg/day) and capcitabine (1500 mg twice daily on days 1–14, every 3 weeks). Discontinued because of grade 3 diarrhea. |
| 09/2018     | 1 cycle of lapatinib (1250 mg/day) and vinorelbine capsule (80 mg on days 1 and 8, every 3 weeks) |
| 09/2018     | 1 cycle of lapatinib (1250 mg/day) and vinorelbine injection (40 mg on days 1 and 8, every 3 weeks). |

Abbreviations: DCIS, ductal carcinoma in situ; HER2, human epidermal growth factor 2; HR, hormone receptor.

**TABLE 1** Previous diagnosis and treatments

**FIGURE 2** Treatments received and time course of liver function tests. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; TBIL, total bilirubin; PP, polyene phosphatidylcholine, 20 mL/day; RG, reduced glutathione, began with 1800 mg/day and increased to 2400 mg/day on hospital day 30; CG, compound glycyrrhizin, began with 40 mL/day and increased to 80 mL/day on hospital day 27; UDCA, ursodeoxycholic acid, began with 500 mg/day and increased to 1000 mg/day on hospital day 41; prednisolone, began with 30 mg/day and tapered off by 5 mg on hospital days 51, 65, 79, 99 and 127; MI, magnesium isoglycyrrhizinate, 200 mg/day; CT, contrast-enhanced computed tomography; MRCP, magnetic resonance cholangiopancreatography.
DISCUSSION

Lapatinib is associated with idiosyncratic DILI. During the treatment, hepatotoxicity exhibits a variable, typically late onset, and elevated ALT that usually resolves on lapatinib discontinuation. However, in our case, the patient developed a severe cholestatic pattern of DILI and continued to worsen even when lapatinib stopped, which prompted a MRCP that suggested as SSC. The time course of the DILI in our case suggests a link with lapatinib and vinorelbine, and other causes of liver injury were adequately excluded, thus our patient was diagnosed with drug-induced SSC.

There are various treatments for SSC, but the best way remains unclear. Among pharmacotherapies, UDCA and immunosuppressants have been used for primary sclerosing cholangitis and are thought to be useful in SSC. In our case, ALP and GGT showed a poor response to reduced glutathione, polyene phosphatidylcholine and compound glycyrrhizin. But we observed a wavelike decrease of laboratory data after UDCA (250mg twice a day) therapy and an obvious decrease of LFTs plus with the treatment of prednisolone and high dose of UDCA (500mg twice a day).

Although drug rechallenge should be avoided because of the possibility of more severe hepatotoxicity, controlled rechallenge is considered justified in relation to oncology therapy, especially targeted therapeutics. In our case, despite the fact that transient increases in ALP and GGT were observed after chemotherapy rechallenge, LFTs were controlled acceptable. Possible causes include: (a) reducing the dose of lapatinib like other successful rechallenge studies; (b) remarkable adaptive capacity of hepatocytes and the immune system to chemotherapy; or (c) coadministration with UDCA, prednisolone, and other hepatoprotective drugs.

The pathogenic mechanism of TKIs and vinorelbine-induced SSC remains unclear. Inhibition of hepatic transporters by lapatinib and its phenol metabolite may be a cause for cholestatic liver damage. Moreover, previous studies indicates HLA allele-DRB1*07:01 was a risk factor for lapatinib-induced DILI. The specific mechanism and the association between pharmacogenomics and SSC need further research.
To our knowledge, this is the first case report of TKIs and vinorelbine-induced SSC. Although our work does not allow drawing general conclusions, it is worth noting that patients with DILI can lead to SSC visualized on biliary imaging. The incidence of SSC linked to medications may be underestimated and clinicians should be aware of the possibility of it.

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DISCLOSURE
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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