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Letter to the Editor

Hepatitis B flare during osimertinib targeted therapy in a lung cancer patient with a resolved hepatitis B virus infection

Po-Hsin Lee [a], Teng-Yu Lee [d,e], Gee-Chen Chang [a,b,c,*]

[a] Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan
[b] Faculty of Medicine, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Institute of Biomedical Sciences, National Chung Hsing University, Taichung, Taiwan
[d] Division of Gastroenterology & Hepatology, Taichung Veterans General Hospital, Taichung, Taiwan
[e] Department of Medicine, Chung Shan Medical University, Taichung, Taiwan

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To the Editor,

Chronic Hepatitis B Virus (HBV) infection is concerning public health issue worldwide. Acute HBV reactivation may occur and cause the development of fulminant hepatitis flare, hepatic failure, and death. Cytotoxic chemotherapy has been known to be a risk factor for HBV reactivation, in which 20–50% of patients may suffer from abrupt hepatitis flare [1]. In addition to chemotherapy, Tyrosine Kinase Inhibitors (TKIs), such as BCR–ABL TKI Imatinib and nilotinib, are also reported to be risk factors surrounding HBV reactivation [2]; therefore, TKI has been categorised and placed into a class of moderate risk of reactivation [3]. Fortunately, HBV reactivation after TKI therapy is rarely reported in patients with resolved HBV infection [4]. However, not only has the chimeric oncogene (BCR–ABL) TKI, and Epidermal Growth Factor Receptor (EGFR)-TKI been reported to be a risk factor in HBV reactivation for HBV carriers [5]. In this case report, we focus on a lung cancer patient with resolved HBV infection (positive hepatitis B core antibodies [anti-HBc], negative surface antigen of hepatitis B virus (HBsAg), and undetectable serum HBV DNA) [6] who experienced HBV reactivation during epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR-TKI) therapy. To the best of our knowledge, this is the first case of EGFR-TKI-induced HBV reactivation in a patient with resolved HBV infection.

1. Case report

The 69-year-old male is an ex-smoker who had smoked for 40 years and had quit for 10 years. He was found to

* *Corresponding author*: Division of Chest Medicine, Department of Internal Medicine, Taichung Veterans General Hospital, No. 1650, Sect. 4, Taiwan Boulevard, Taichung, 407 Taiwan.fax: +886 4 23741320.
E-mail addresses: berry7bo@gmail.com (P.-H. Lee), tylee@vghtc.gov.tw (T.-Y. Lee), august@vghtc.gov.tw (G.-C. Chang).

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have stage IV lung cancer in September 2017, when tumour metastasis to the bone and brain was discovered. The pathology of the lung tumour revealed adenocarcinoma harbouring L858R substitution in exon 21 of the EGFR gene. Before initiating any cancer treatment, hepatitis B serologic tests uncovered positive anti-HBc, negative HBsAg, negative hepatitis B surface antibodies (anti-HBs), along with undetectable serum HBV DNA, all of which met the criteria for a resolved HBV infection [6]. Afatinib, a second-generation EGFR-TKI, had been used as treatment since October 2017. In March 2019, due to the progression of the disease to the brain, along with leptomeningeal metastasis, we shifted the targeted therapy to osimertinib, a third-generation EGFR-TKI. During this period, the liver function tests of this patient all revealed him to be within normal limits. However, at the patient's regularly scheduled clinical check-up in November 2019, asymptomatic hepatitis with an elevation in levels of alanine aminotransferase (ALT) (111 U/l) was accidently found. The levels of bilirubin and alkaline phosphatase however remained within normal limits. An abdominal sonography revealed only mild fatty liver change, without any evidence of liver cirrhosis or splenomegaly. After a series of tests for differential diagnosis, including hepatitis A virus, hepatitis C virus, Cytomegalovirus (CMV), Epstein–Barr Virus (EBV), Herpes Simplex Virus (HSV), the results of all the tests showed negative findings, except those for HBV. Positive HBsAg and a marked elevation in HBV viral load (245,000 IU/ml) in the blood were revealed, which indicated HBV seroreversion (HBsAg reappearance and/or loss of anti-HBs). In addition, no new medications or health food supplements were prescribed during the complete course of cancer treatment. The peak level of blood ALT was 529 U/l after a 2-week follow-up, therefore the oral antiviral therapy for HBV, lamivudine, was prescribed. The patient's ALT level gradually decreased after initiating lamivudine therapy.

2. Discussion

Careful monitoring, prevention and treatment for HBV reactivation during cytotoxic chemotherapy and/or immunosuppressive therapy have been recommended in the international guidelines; however the recommendations for the use of targeted therapy have not been updated. In this case report, we first reveal a patient who suffered from HBV reactivation during EGFR-TKI therapy, in a status of resolved HBV infection. Importantly, prompt antiviral therapy may help to control hepatitis flare in patients. This case report can help to enforce in clinicians that HBV reactivation should be monitored in cancer patients who receive targeted therapies, and that care still needs to be taken even in patients with resolved HBV infection.

EGFR-TKI is now the first-line of treatment for lung cancer patients with activating EGFR mutations. EGFR-TKI therapy is particularly valuable in Asia, due to the reason that mutations in the EGFR gene occur in at least 50% of Asians with Non-small Cell Lung Cancer (NSCLC) [7]. However, TKI has been reported to be with a moderate risk of HBV reactivation with an incidence rate of 1–10% [3]. Until now, 8 cases of HBV reactivation have been documented in HBsAg-positive patients under imatinib or nilotinib treatment, with a high mortality rate of 38% [2]. Yao *et al.* retrospectively analyzed 171 patients who were diagnosed with NSCLC and chronic HBV infection during the period 2011 to 2017, with 9.36% of the patients suffering from HBV reactivation during EGFR-TKI therapy, and having an annual incidence rate of 7.86% [5]. However, whether EGFR-TKI treatment increases the risk of HBV reactivation in patients with resolved HBV infection has not yet been reported. Our case report may provide clinicians with the valuable information that EGFR-TKI can be a risk factor of HBV reactivation in patients with resolved HBV infection.

The mechanisms of TKI-induced HBV reactivation remain unclear. HBV-specific cytotoxic T lymphocyte and B lymphocyte may play a role in the control of HBV infection [8]. Kinase signalling pathways are crucial for immune activation and the proliferation of lymphocytes. TKIs have been developed to target these critical pathways which lead to lymphocyte dysfunction and concomitant HBV reactivation. For example, imatinib, a non-receptor PTK inhibitor is known to induce HBV reactivation, possibly through inhibiting T-cell activation and proliferation in *in vitro* studies [9]. Erlotinib, an EGFR-TKI targeting receptor PTK inhibitors, may block T-cell proliferation and Th1/Th2 cytokine production, and also induce T cell anergy *in vitro* [10]. However, further biological studies are mandated for determining the exact mechanisms.

In conclusion, EGFR-TKI therapy can be related to an increased risk of HBV reactivation in cancer patients, and hepatitis B flare was even discovered in this particular case report of resolved HBV infection. Routinely screening the status of HBV infection should be recommended prior to EGFR-TKI prescription, and regularly monitoring a patient's liver function and HBV viral load for those with resolved HBV infection should be still be taken notice of during EGFR-TKI therapy.

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Conflict of interest statement

None declared.

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