Lactic Acidosis during Entecavir Antiviral Treatment in a Patient with Hepatitis B Virus-related Decompensated Cirrhosis

The Editor,

Sir,

Hepatitis B virus (HBV)-related decompensated cirrhosis is an end-stage liver disease; antiviral therapy can improve the prognosis in these patients (1). Entecavir (ETV) is considered an ideal drug for nucleotide and nucleoside-naïve patients with decompensated cirrhosis due to its rapid and potent antiviral effects and low risk of resistance, but clinical data on the safety in these patients with severely impaired liver function are limited.

A 58-year old Chinese male was diagnosed with chronic HBV in 2009, but he had not received any treatment for HBV at that time. He presented with HBV-related decompensated cirrhosis, including ascites and splenomegaly. The initial laboratory tests showed elevated liver tests and the serum HBV DNA level was 4.15×10^7 copies/mL. He was diagnosed with HBeAg-positive chronic HBV-related decompensated cirrhosis and his model for end-stage liver disease (MELD) score was 18. He was treated with 0.5 mg ETV daily and was evaluated for liver transplantation.

After one month of therapy with ETV, he had a significant reduction in serum HBV DNA (9.70×10^3 copies/mL) and the MELD score remained stable. After receiving two months of ETV therapy, he was admitted to hospital with diarrhoea, abdominal pain, vomiting and fever. His body temperature was 37.2 °C, his pulse 120 beats per minute, respiratory rate 20 breaths per minute and blood pressure 110/70 mmHg. The physical examination revealed yellow sclera, abdominal tenderness and rebound pain, shifting dullness and active bowel sounds. The white blood cell count was 4.15×10^9/L, the neutrophil ratio 85.1%, haemoglobin 104 g/L, and the platelet count 71×10^9/L. The arterial pH value was 7.17, the oxygen pressure 23.3 kPa, the carbon dioxide pressure 3.2 kPa, the oxygen saturation 99%, the base excess -18.1 mmol/L, and the lactate level > 15 mmol/L. Empiric medical treatment for infection, prevention of further insult to the liver, and maintaining water, electrolyte and acid base balance was initiated, but the patient's condition rapidly deteriorated, and he eventually died 15 hours after admission. Two days later, the blood culture showed the presence of *Escherichia coli*.

All of the approved oral nucleotide and nucleoside analogues for HBV carry a 'black box' warning in their labelling regarding potential mitochondrial toxicity that can manifest itself as lactic acidosis, myopathy, neuropathy, or even hepatotoxicity (1).The MELD score has been reported in association with lactic acidosis during ETV treatment (2). However, some recent studies observed only one adverse event of lactic acidosis in an ETV treated patient, and the event was resolved without interruption of drug. It is worth noting that two of these studies included patients with a worse liver function (median MELD score 17.1 and 15.3, respectively in the study by Liaw *et al* (3); 16.1 ± 4.3 and 16.7 ± 4.1, respectively in the report by Hyun *et al* (4)). Moreover, a small study found that the risk of lactic acidosis was not increased in patients with HBV decompensated cirrhosis with high MELD score who received ETV, compared with patients with non-HBV decompensated cirrhosis (5). The report from Germany also showed that the white blood counts of the patients with MELD scores ≥ 20 were significantly higher than those with MELD scores ≤ 17 (9.28 ± 3.06/nL *vs* 5.87 ± 2.43/nL, $t = 2.41$, $p < 0.05$, using SPSS version 13.0). Thus the patients with high MELD scores could have some unrevealed infections.

In conclusion, even if more high-quality and well-designed studies are needed to confirm the correlation between ETV and lactic acidosis, prevention of infection in patients with HBV-related decompensated cirrhosis and severely impaired liver function should be more emphasized. Once these patients develop lactic acidosis, infection must be first excluded or controlled in a timely manner.

Keywords: Entecavir, hepatitis B virus, lactic acidosis, liver cirrhosis

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REFERENCES

1. Fontana RJ. Entecavir in decompensated HBV cirrhosis: the future is looking brighter. J Hepatol 2010; **52:** 147−9.
2. Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S et al. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. Hepatology 2009; **50:** 2001−6.

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3. Liaw YF, Raptopoulou-Gigi M, Cheinquer H, Sarin SK, Tanwandee T, Leung N et al. Efficacy and safety of entecavir versus adefovir in chronic hepatitis B patients with hepatic decompensation: a randomized, open-label study. Hepatology 2011; **54:** 91−100.
4. Hyun JJ, Seo YS, Yoon E, Kim TH, Kim DJ, Kang HS et al. Comparison of the efficacies of lamivudine versus entecavir in patients with hepatitis B virus-related decompensated cirrhosis. Liver Int 2012; **32:** 656−64.
5. Marzano A, Marengo A, Marietti M, Rizzetto M. Lactic acidosis during entecavir treatment in decompensated hepatitis B virus-related cirrhosis. Dig Liver Dis 2011; **43:** 1027−8.

A Bullous Pilomatricoma Developed after Hepatitis A Vaccination

The Editor,

Sir,

Pilomatricomas originate from hair matrix cells and usually appear as firm, solitary and asymptomatic nodules beneath the skin. These tumours occur mostly in children. They are generally located on the face and neck (1). Bullous pilomatricoma is an uncommon lesion and only few cases of this variant have been reported in the literature (1, 2).

We report a 7-year old girl with a pilomatricoma showing bullous appearance. The patient suffered from a dome shaped, bullous mass on the left arm. The 1.5 × 1.5 cm lesion presented one month previously and progressively enlarged. In the history of the patient, there was a hepatitis A vaccination to the same area with the bullous lesion, about four months earlier. Two days after the vaccination, severe inflammation occured in the same region. The patient did not have any family history of such or mechanical trauma. On dermatologic examination, a dome shaped, red-brown coloured, semi-translucent bullae was noted (Fig. 1A).

The bullae collapsed inward with palpation and a firm, small, painless mass was felt at the bottom of the lesion. When the lesion was pressed with the tip of a pen, it had a wrinkled-atrophic appearance (Fig. 1B). The other physical and systemic examination findings were normal and there was no lymphadenopathy. Routine haematological and biochemical examinations of the patient were within the normal limits. With dermatoscopy, red-coloured tortuous small vessels on an irregular white opacity, which settled on a livid-red background, were observed (Fig. 1C).

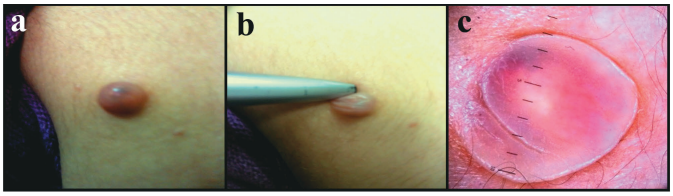

Fig. 1: (A) Clinical appearance of the bullous pilomatricoma; (B) pressed and wrinkled appearance of the lesion and (C) dermatoscopic appearance of the lesion.

Needle aspiration material of the bullae was haemorrhagic and its microbiological culture was sterile. With these findings, the diagnosis of the lesion was made as a "bullous pilomatricoma". The mass was totally removed with surgical excision. On histopathological examination, the tumour nests were composed of eosinophilic shadow cells, basophilic cells and surrounded by a fibrous capsule in the deep dermis. Calcium salt depositions were observed in the tumour mass. In the superficial dermis, marked lymphoedema and increased numbers of dilated lymphatics filled with eosinophilic lymph fluid were observed (Fig. 2).

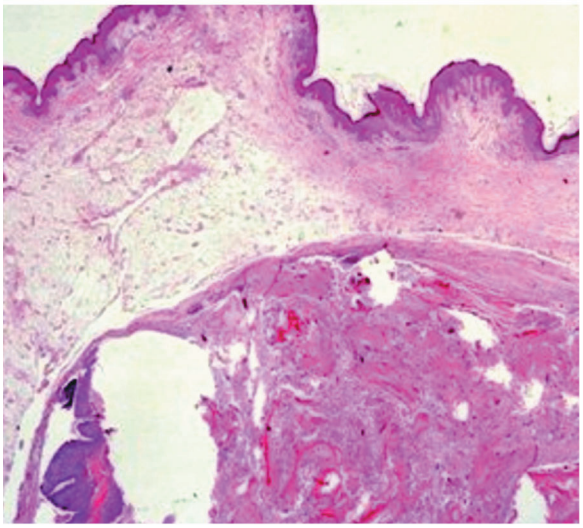

Fig. 2: Histopathologic appearance of the lesion (HE × 40).

Bullous pilomatricoma is a very rare form of pilomatricoma (3). Their incidence is between 3% and 6% (1). Although pilomatricomas can be associated with other genetic disorders such as myotonic dystrophy and Gardner's syndrome, the bullous variant is not associated with these syndromes (2). The bullous lesions are located mostly in the shoulder and upper extremity and predominantly in females. They are usually asymptomatic lesions (1, 2). Clinical characteristics reported include semi-transparent, erythematous, bluish or skin-coloured, heavily folded or striae-like, flaccid blisters overlying a solitary, firm-to-hard nodule (2, 4). Mechanical irritations such as continuous mechanical stimulation, scratching and pinching trauma and continuous pressure play an important role in the development of bullous pilomatricomas (2, 5).

The common dermatoscopic findings of bullous pilomatricomas are reddish homogenous areas, irregular white structures and hairpin-like atypical vessels (6). In the histopathology of pilomatricomas can be seen eosinophilic shadow cells, basophilic cells, foreign body cells, calcified focus or even ossification (2). In a bullous pilomatricoma, in addition to these findings, lymphoedema and dilated lymphatic vessels in the superficial dermis were found in most cases (1–3). These lymphatic findings have been described as common pat-