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CASE REPORT

A Granulomatous Drug Eruption Induced by Entecavir

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Entecavir (Baraclude®, Bristol-Myers Squibb) is a potent and selective antiviral agent that has demonstrated efficacy in patients with chronic hepatitis B. The most frequent adverse events attributed to entecavir include increased alanine aminotransferase, upper respiratory tract infection, headache, abdominal pain, cough, pyrexia, fatigue, and diarrhea. Although quite a few randomized double-blind studies including ones investigating adverse events along with these general symptoms have been reported, few cases of cutaneous adverse events have been described in detail. We demonstrate a case of granulomatous drug eruption as a cutaneous adverse event induced by entecavir. **(Ann Dermatol 25(4) 493～495, 2013)**

-Keywords-
Drug eruptions, Entecavir

INTRODUCTION

Entecavir (Baraclude®; Bristol-Myers Squibb, New York, NY, USA) is a deoxyguanosine analogue for the treatment of chronic hepatitis B viral infection in adults. With a 50% effective concentration, it has more than 300 times greater potency than lamivudine *in vitro*, which was the first oral anti-hepatitis B virus (HBV) nucleoside analog found to be effective for treating chronic hepatitis B when administered for the short[1,2]. The current phase II dose-ranging trial evaluated the good tolerability of 0.1 mg and 0.5 mg entecavir daily for 52 weeks in nucleoside-naive chronic hepatitis B patients[3]. Common entecavir-related toxicities are known to be diverse and include increased alanine aminotransferase, upper respiratory tract infections, headache, abdominal pain, cough, pyrexia, fever, fatigue, diarrhea, and dizziness[4]. We present a female patient who developed a granulomatous drug eruption induced by entecavir.

CASE REPORT

A 65-year-old woman was referred for consultation of a facial granulomatous facial eruption. The patient had a history of carrying the HBV for 35 years. Since her serum aspartate aminotransferase and alanine aminotransferase level were elevated for 3 months, she had been taking entecavir (Baraclude®) at a dose of 0.5 mg daily. Two months after initiating the antiviral therapy, she presented with multiple pruritic erythematous papules and telangiectasia on the forehead, both periorbital areas and the cheeks (Fig. 1). The patient did not show other accompanying systemic symptoms. She had not taken any other medication before starting the entecavir therapy, and there was no previous medical history. Routine laboratory examinations revealed increased serum aspartate transferase (83 IU/L), alanine transferase (99 IU/L), alkaline phosphatase (107 IU/L) and gamma-glutamyl transferase (49 IU/L). A skin biopsy was performed on her right cheek. Histopathologic findings showed granulomatous inflammatory reactions in the dermis and subcutaneous tissues (Fig. 2A). The prominent perivascular lymphocytic infiltrate, endothelioid histiocytic infiltrate, and some telangiectasia of the vessels were seen (Fig. 2B). Bacterial and fungal culture, and mycobacterial culture for *Mycobacterium tuberculosis* were all negative. She had no past

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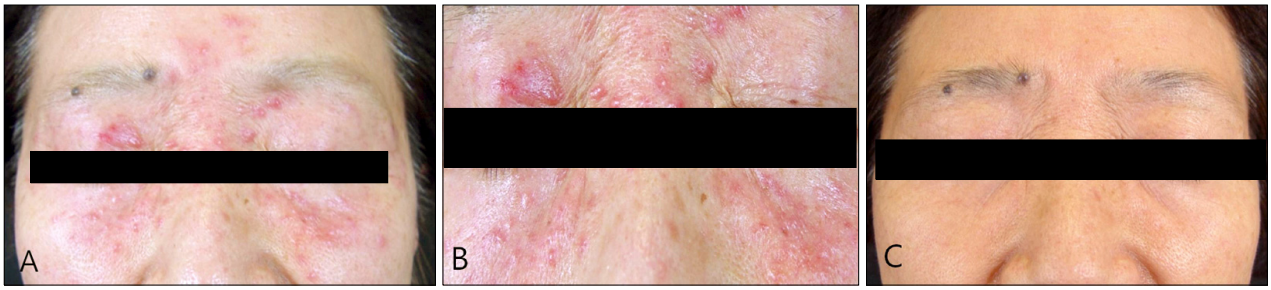

Fig. 1. (A) The patient presented with multiple pruritic erythematous papules on the forehead, both periorbital areas and cheeks 2 months after initiating entecavir therapy. (B) Closed view. (C) Resolved state after discontinuation of the entecavir.

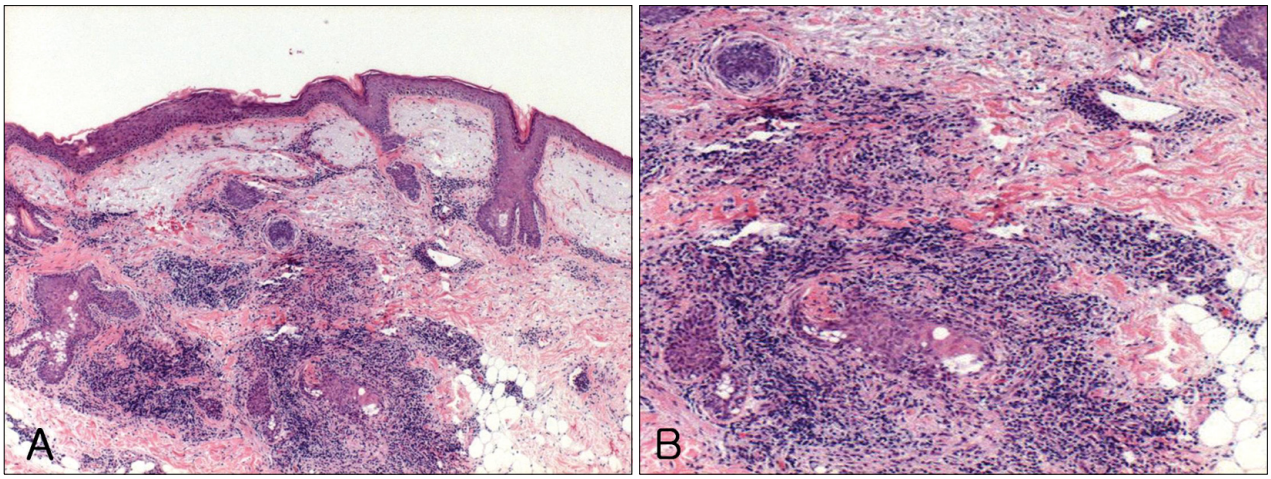

Fig. 2. (A) Histopathologic findings showed rosaceiform granulomatous inflammatory reactions in the dermis and subcutis (H&E, ×40). (B) The infiltration of lymphocytes and epithelioid histiocytes were seen in the perivascular area (H&E, ×100).

history of granulomatous disease such as rosacea, and no history of taking medications before the entecavir therapy, and she had a relatively acute onset of the clinical manifestations. The most important point in favor of the eruption being diagnosed as an entecavir induced drug eruption was that her skin lesions had which developed after retreatment in this case. Entecavir therapy was discontinued immediately and thisen was followed by treatment with 0.75% topical metronidazole and oral minocycline therapy (100 mg/d for 14 days), as well as sunscreens. Because of abdominal discomfort after taking minocycline, she discontinued the oral minocycline therapy herself. Within approximately two months of the skin lesions appearing, they completely resolved. However, the same cutaneous eruption recurred in the same site of her face after she started entecavir therapy again three months later (Fig. 1C). The entecavir was promptly discontinude and we check the photograph with patient's aggrement. The entecavir was promptly discontinued. A patch test was performed ten months after the drug eruption had disappeared completely. To the back area, entecavir (0.001%, 0.01%, 0.1%, 1%, 10%) in petrolatum was applied using an 8 mm Finn chamber (Smart Practice, Phoenix, AZ, USA) and Scanpor tape (Alpharma AS, Oslo, Norway). The patches were removed 48 hours later and a reading was done at 48 hours and 96 hours after the patch test, which was negative on both occasions according to the criteria of the International Contact Dermatitis Research Group.

DISCUSSION

Entecavir is a deoxyguanosine analog that has more than 300 times greater potency than lamivudine *in vitro*[1,2]. A number of phase II clinical trials demonstrated that entecavir was superior to lamivudine at a low dosage for HBV DNA reduction, and evaluated the good tolerability of 0.1 mg and 0.5 mg entecavir daily for 52 weeks in nucleoside-naive chronic hepatitis B patients[5,6]. Still, the current data has revealed safety problems and an increasing incidence of adverse events of entecavir[3]. The most common adverse events reported have been increased

serum alanine aminotransferase, upper respiratory tract infection, headache, abdominal pain, cough, pyrexia, fever, diarrhea, and dizziness[4].

Cutaneous adverse events attributed to entecavir have not been specifically reported. Sugiura et al.[7] recently reported a case of drug eruption induced by entecavir. In this case, the chronic hepatitis B patient presented with erythematous pruritic patches on his buttock and increased serum aspartate transferase (2,058 IU/L) and alanine transferase (3,219 IU/L) 2 days after the entecavir therapy. The diagnosis was confirmed by a skin provocation test.

Different from his case, our patient showed a granulomatous eruption two months after taking entecavir and the reaction was confirmed by retreatment. Granulomatous reactions are known to be associated with drugs. Granulomatous drug reactions (GDR) secondary to granulocyte colony-stimulating factor (G-CSF) treatment have been described[8]. Compared to that, interstitial granulomatous drug reactions (IGDR) have often been reported. Calcium-channel blockers, angiotensin-converting enzyme inhibitors, beta-blockers, lipid-lowering agents, and anticonvulsants have been described as drugs eliciting IGDR[9-11]. The mechanism of how entecavir induces a granulomatous reaction has not been described in detail. No relationship between GDR/IGDR and entecavir has been reported to date. Sugiura et al.[7] mentioned that the chemical structure of entecavir is similar to the antiviral drugs lobucavir, acyclovir and ganciclovir, and suggested that these nucleotide analogs possibly induce the same pattern of immunologic responses[7]. In our case, the GDR triggered by the entecavir clearly resolved with discontinuation of the possible causative drug and administration of oral minocycline. The physician should be aware of entecavir as a potential trigger for granulomatous drug eruptions.

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