
Carbamazepine-Induced Stevens-Johnson Syndrome Sparing the Skin Previously Affected by Herpes Zoster Infection in a Patient with Systemic Lupus Erythematosus: A Reverse Isotopic Phenomenon

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Key Words

Carbamazepine · Stevens-Johnson syndrome · Systemic lupus erythematosus · Herpes zoster · Reverse isotopic response

Abstract

The reverse isotopic response is a rarely encountered phenomenon. The spared lesions are various and mainly inflammatory in nature, with herpes zoster infection being the most common. A novel case of Stevens-Johnson syndrome triggered by carbamazepine sparing the skin area previously affected by herpes zoster infection in a 39-year-old Indian female with systemic lupus erythematosus is documented. Several features as well as possible pathomechanisms that bear discussion have emerged from this case documentation. These may be related to the virus immunity, the underlying autoimmune disease (systemic lupus erythematosus) and/or drug metabolism.

Introduction

Infections are common in patients with systemic lupus erythematosus (SLE) throughout the course of their disease and remain a source of morbidity and mortality [1, 2, 4].

Apart from the host genetic predisposition which may determine the general susceptibility to both infections (i.e. herpes zoster) and SLE, a defective cell-mediated immunity, a hyperactive humoral immunity associated with polyclonal B-cell activation and the adverse effects of immunosuppressive treatment have been demonstrated by immunological studies [1, 2, 6].

Well-documented cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis occurring at the site of resolved herpes zoster (isotopic response) have been reported since the first recognition of this dermatological phenomenon by Wolf et al. [3, 4] in 1985.

However, a dermatosis sparing another unrelated and already healed skin disease (reverse isotopic response) is a rarely encountered phenomenon [5].

The spared lesions are various, with the majority being inflammatory in nature [5].

Case Report

A 39-year-old Indian woman with SLE diagnosed in 2003 developed right thoracoabdominal herpes zoster in December 2007. The vesicular eruption was preceded by a prodrome of dermatomal pain and constitutional symptoms lasting for about 4 days. The patient was treated appropriately with acyclovir for 7 days and the herpes zoster resolved uneventfully.

However, a burning sensation persisted in the affected area and carbamazepine (CBZ) was started for postherpetic neuralgia 3 weeks following the clearance of the lesions. Eleven days later, the patient developed painful erosions of the oral mucosa, conjunctival hyperemia, purpuric macules and patches, and flaccid blisters. Further, the skin detachment was patchy. The striking feature of this new eruption was the distinct sparing of the area previously affected by the herpes zoster (fig. 1).

Serum and lesional skin tissue samples were collected at the time of presentation and a complete blood count with differential analysis was normal. A comprehensive metabolic panel revealed hypercholesterolemia. Acute phase proteins, liver enzymes, urea/electrolytes/creatinine levels, thyroid functional tests, rheumatoid factor and urinalysis were within normal limits. An antinuclear antibody titer as well as antibodies to ds-DNA, anti-Ro, and anti-La were negative at the time of presentation. Histopathological examination of the lesional skin showed features in keeping with SJS (epidermal necrosis, marked dermal edema and sparse perivascular lymphocytic infiltrate; fig. 2). Chest X-ray and ECG revealed no abnormalities, and the PPD test was negative. Furthermore, abdominal echography disclosed an uncomplicated cyst of the left kidney. The patient's medical history was relevant for bronchial asthma with many recurrent infectious episodes in the past. A remote history of pulmonary tuberculosis in 2003 was one of note.

Taking into consideration her Asian ancestry and under the impression of CBZ-induced SJS, we attempted to perform genotyping, but the patient declined the test due to the cost involvement. The offending drug was withdrawn and oral prednisone was increased from the maintenance dose of 10 mg/day she was receiving for her SLE during the past 3 years to 1 mg/body weight/day. She continued with azathioprine 100 mg/day along with antibiotics and supportive measures. This led to complete resolution of the eruption.

The patient remained clinically stable during the subsequent 4 months although she had a flare-up of SLE in May 2008, which was well controlled with immunosuppressive therapy. One year later in August 2009, her condition deteriorated rapidly. The patient was admitted with respiratory distress, pneumonia/pleuritis, and active SLE. She soon died of complications (septicemia, disseminated intravascular coagulation).

Discussion

Based on the clinical presentation and the pathology report, a diagnosis of CBZ-induced SJS with a reverse isotopic phenomenon was established in a patient with SLE. In

agreement with other authors reports [6], it was found that herpes zoster reactivation occurred when SLE was inactive. The presence of varicella-zoster virus DNA in the early lesions after herpes zoster eruption has been inconsistently demonstrated by PCR analysis [2]. Negative findings in the current case were in line with this statement. Additionally, the negative PPD skin test confirmed the low positive rate for PPD results observed in patients with SLE as described previously, suggesting a depressed cell-mediated immunity or anergy [7].

Allodynia is common in the acute phase of herpes zoster infection and predicts a higher likelihood of developing postherpetic neuralgia [7]. CBZ is widely used in the treatment of postherpetic neuralgia along with NSAID, opioid analgesics, local anesthetics and antiviral therapy [8]. Skin reactions induced by CBZ are usually mild, reversible and dose related [8, 9]. Severe idiosyncratic drug reactions can also occur [9]. They are more likely to occur during the first 8 weeks of the treatment, when the starting dose is high or when CBZ is administered with other anticonvulsants [9]. In the case presented herein, SJS developed after 11 days of taking CBZ.

It is well known that because of genetic variations, humans differ in their response to treatments. Genetic markers vary in relation to the ethnicity and the offending drug [8, 10]. HLA-B*1502 as a marker for CBZ-induced SJS is well established in the Han Chinese population by different studies [10]. A significant association between CBZ-triggered SJS and HLA-B*1502 genotype has also been demonstrated among the Indians, particularly in the Hindu community [8, 10, 11].

What makes a lesional area protected by the original disease (herpes zoster) and resistant to the offensive of a secondary event (drug-induced SJS) remains speculative. Several possible pathomechanisms may be related to the virus (VZV) immunity, the underlying autoimmune disease (SLE) and/or drug metabolism. It has been hypothesized that the virus could alter the skin immune system locally and elicit a predominantly Th1 cytokine profile with overexpression of TNF- α , IFN- γ , IL-2, and IL-5 [7, 12]. It is possible that such cytokines locally inhibit the immunological aberrations responsible for SJS.

In addition, VZV has a variety of immune evasion mechanisms that limit the presentation of viral peptides by MHC class I and II; these may persist and remain hidden from the immune system [12]. These viral peptides and/or tissue antigens altered by the virus may induce an atypical immune response.

The concept of epitope spreading, whereby the tissue damage from a primary inflammatory process causes the release of previously sequestered antigen, leading to a secondary autoimmune response against the newly released antigen, may provide us with a possible explanation [13]. In this case, there were some configurational changes within the skin antigens, perhaps due to SLE or its treatment, which may have been sequestered, and it was only when another triggering event such as herpes zoster occurred that the secondary autoimmune response developed. The latter was probably altered by the concomitant use of immunosuppressive therapy.

A genetic or acquired defect in the drug metabolism (CBZ) in predisposed individuals, although plausible, does not explain the sparing of the area previously affected by an inflammatory condition.

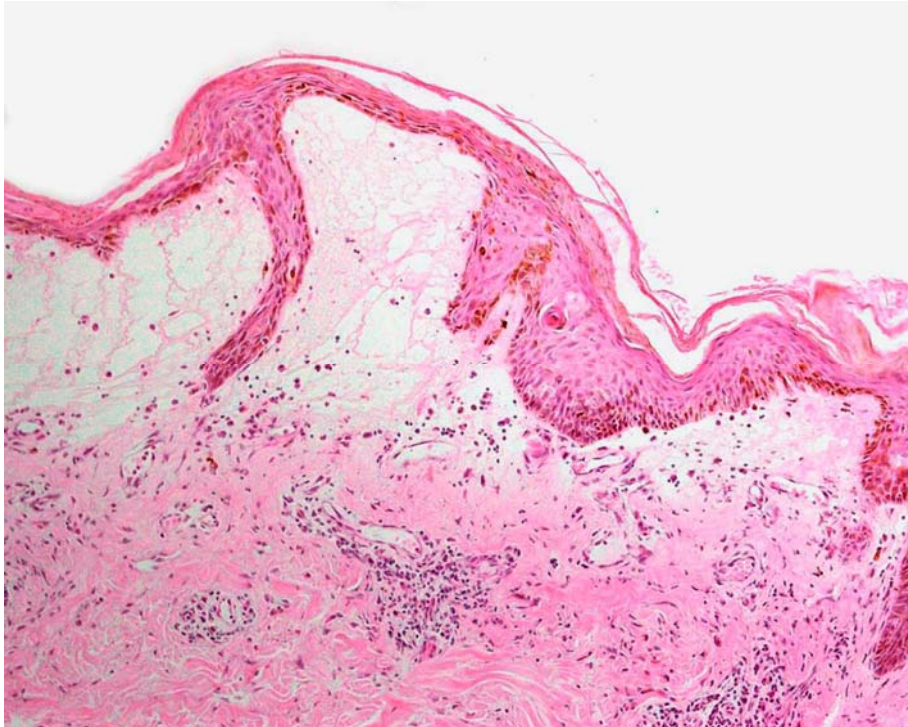
To conclude, we document a case of severe CBZ hypersensitivity following herpes zoster reactivation with a reverse isotopic phenomenon in a patient presenting an interaction of two unfavorable prognostic factors: an underlying autoimmune systemic disease (SLE) and a possible genetic predisposition.

The case presented in this paper provides some insight into the possible etiological mechanisms of this rare phenomenon and the complex interplay between antiviral and antidrug immune responses.

Fig. 1. Widespread purpuric macules and patches triggered by carbamazepine sparing the right thoracic (a) and upper abdominal quadrant (b) skin areas previously affected by herpes zoster.



Fig. 2. Histopathological examination of the lesional skin showing a thin epidermis with focal vacuolar alteration and scattered apoptotic keratinocytes, prominent edema of the papillary dermis, dilated capillaries and sparse perivascular lymphocytic infiltrate (HE, original magnification $\times 10$).



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