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Case Report

Toxic Epidermal Necrolysis in a Patient with Autoimmune Limbic Encephalitis with Anti-Glutamate Receptor Antibodies

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Keywords
Anti-glutamate receptor antibodies · Autoimmune limbic encephalitis · Toxic epidermal necrolysis (TEN)

Abstract
We report on a 44-year-old woman who was diagnosed with toxic epidermal necrolysis (TEN) during the recovery phase from autoimmune limbic encephalitis with anti-glutamate receptor antibodies. Both, autoimmune limbic encephalitis and TEN are very rare diseases. The co-existence of the two diseases has not yet been reported. We speculate that the total of 18 drugs needed for the treatment of encephalitis might have increased the risk of TEN. Similar reports would be required to elucidate the pathophysiology of the co-existence.

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Introduction

Toxic epidermal necrolysis (TEN) is a rare life-threatening disease characterized by drug-induced skin eruptions. The incidence of TEN is estimated to be 0.4–1.2 per million person-years. Stevens-Johnson syndrome is one spectrum of the same disease; >30% detached body surface area is defined as TEN, whereas <10% detached body surface area is defined as Stevens-Johnson syndrome. The precise immunological background of TEN is still unknown. However, it has been proposed that cytotoxic T cells activated by drugs induce apoptosis of the epidermis, and human leukocyte antigen alleles related to specific drugs play important roles in TEN [1].

Autoimmune limbic encephalitis is also a rare life-threatening disease characterized by working memory deficits, seizures, or psychiatric symptoms suggestive of the involvement of the limbic system. The incidence of autoimmune limbic encephalitis is estimated to be <0.5–1.0 per million person-years [2]. In autoimmune limbic encephalitis, antibodies against a glutamate receptor (GluR) subunit have often been detected [3–6]. Generally, in anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, not only anti-NMDA receptor antibodies but also anti-GluR antibodies, such as anti-GluN1 antibodies and anti-Glu N2B antibodies, can be detected in the cerebrospinal fluid (CSF) [7]. Although the significance of anti-GluR antibodies for autoimmune limbic encephalitis has not been established compared to that of the anti-NMDA receptor antibodies, the detection of anti-GluR antibodies can usually imply autoimmune mechanisms in limbic encephalitis. The precise immunological background of autoimmune limbic encephalitis with anti-GluR antibodies has not yet been revealed. However, anti-GluR antibodies produced by preceding infection or seizure are supposed to induce infiltration of CD8+ T cells in the central nervous system. Cytotoxicity of the T cells might result in neuronal damage [8].

Here, we report on a patient who was diagnosed with TEN during the recovery phase from autoimmune limbic encephalitis with anti-GluR antibodies. To our knowledge, this is the first report on the co-existence of these two diseases.

Case Report

A 44-year-old woman with a precedent infection visited the hospital with her family, because she had become unable to communicate with her family. On admission, her body temperature was 38.2°C, percutaneous oxygen saturation was 95% in room air, blood pressure was 129/83 mm Hg, and her heart rate was 83 beats/min and regular. Neurological examinations showed consciousness disturbances during which she was not able to comply to any commands. Her ocular position, posture, and muscle tone were normal, and there were no involuntary movements, seizure, or hypersalivation. Soon after admission, she started to shout and jump on her bed.

Routine blood examinations returned normal, including negative anti-HIV antibody. Liquor examinations showed slight pleocytosis (25/μl; monocytes 76%) and an elevated protein level (64 mg/dL). CSF culture was negative. Brain magnetic resonance imaging (MRI) revealed abnormal hyperintensities in the bilateral medial temporal lobes on T2-weighted imaging and fluid-attenuated inversion recovery. Body computed topography and pelvic MRI showed no tumors. Electroencephalography (EEG) showed diffuse slow waves on irregular basic activity.

Based on the patient's age, gender, consciousness disturbances, her abnormal behavior, CSF pleocytosis, and the findings of MRI and EEG, we considered autoimmune limbic encephalitis. We administered steroid pulse therapy (methylprednisolone: 1 g/day for 3 days, every week, for 4 times) on day 1 and added intravenous immunoglobulin (IVIg: 0.4 g/kg/day for 5 days) on day 4 (Fig. 1). Polymerase chain reaction tests of the pretreatment CSF were negative for herpes simplex virus and varicella zoster virus. Therefore, acyclovir, which had been administered from day 1 for the possibility of herpetic encephalitis, was discontinued on day 3.

On day 3, she did not respond to any stimuli. Later, her breathing spontaneously became shallow and, 3 h later, she stopped breathing. Her arterial blood gas analysis showed carbon dioxide retention, suggestive of central hypoventilation. She required a ventilator. She also presented complex partial seizures of the face and arm on the right side, and levetiracetam and lacosamide were administered in addition to propofol. On day 23, she started to breath spontaneously again and was, therefore, withdrawn from the ventilator. She suffered from short-term memory impairment; her mini-mental state examination (MMSE) score was 17/30.

On day 30, erythema abruptly appeared on her upper body. We immediately discontinued any drugs which had recently been started. However, her body temperature rose to approximately 39°C, and the erythema extended to the whole body with black bullae and skin detachment (Fig. 1a). Skin biopsy revealed necrotizing keratinocytes and a liquefactive degeneration of the basal cells, suggestive of TEN (Fig. 1b). After all drugs had been discontinued, steroid pulse therapy and IVIg were resumed for TEN. Her skin condition started to improve on day 41, and re-epithelialization was completed on day 51. Prednisolone (1 mg/kg/day) which had been started on day 32 was tapered from day 45 and discontinued on day 69. Based on the skin improvement after discontinuing the drugs, we diagnosed her with TEN. A lymphocyte transformation test was performed for 9 of the 18 drugs used before the onset of TEN. However, the lymphocyte transformation test showed no positive results (Fig. 2). Therefore, we considered that drug-induced hypersensitivity syndrome was not responsible for her skin rash, because her IgG antibody titer of human herpesvirus 6 did not change between paired sera, and she had no organ failure such as liver dysfunction.

On day 57, she was transferred to a rehabilitation hospital, because her cognitive functions had improved (MMSE 28/30), and the findings on brain MRI and EEG had also normalized. After discharge, it was revealed that anti-GluN1 antibodies and anti-GluN2B antibodies were positive in the pretreatment CSF using enzyme-linked immunosorbent assay. In contrast, anti-NMDA receptor antibodies were negative in the pretreatment CSF using a fixed cell-based assay. Finally, we diagnosed her with autoimmune limbic encephalitis [9] with anti-GluR antibodies. On day 103, she was discharged and can do housework independently using memoranda. Her modified Rankin Scale score was 1.

Discussion

Our young female patient developed autoimmune limbic encephalitis with anti-GluR antibodies and started to get better after immune-mediated therapies. During the recovery phase, she also suffered from TEN. The co-existence of these two diseases has not yet been reported. A total of 18 drugs had been used for autoimmune limbic encephalitis, although the causal drugs for TEN have not been identified.

We speculated that the mechanism of the co-existence of autoimmune limbic encephalitis and TEN is as follows: many drugs needed for the treatment of encephalitis might increase the

risk of TEN additively or synergistically. For the intensive therapy of autoimmune limbic encephalitis, various types of drugs are usually required. Here, we used a total of 18 drugs before TEN. The additive or synergistic effects of the drugs might have contributed to the development of TEN. On the other hand, we cannot deny the possibility that some immunological changes induced by autoimmune limbic encephalitis might have been the basis for TEN, because both autoimmune limbic encephalitis and TEN are immune-mediated disorders in a broad sense. In the supporting literature on systemic lupus erythematosus (a representative immune-mediated disorder), TEN has been noted to develop more frequently in patients with this disorder compared to in patients with other non-immune-mediated disorders. Therefore, it has been postulated that lupus-associated TEN may exist [10]. Based on the literature, we can speculate that an immune-mediated disorder, e.g., autoimmune limbic encephalitis, might have some immunological mechanisms in common with those in TEN.

Further supportive literature suggests that cutaneous adverse reactions to antiepileptic drugs develop more frequently in patients with epilepsy after infectious encephalitis or encephalopathy compared to in patients with general epilepsy. It has also been proposed that a serum chemokine called RANTES (regulated on activation normal T cell expressed and secreted), secreted by immune cells such as natural killer cells, CD4+T cells, CD8+T cells, and eosinophils, might be a biomarker for susceptibility to cutaneous adverse reactions in patients with epilepsy after infectious encephalitis or encephalopathy [11]. Based on the literature, we can speculate that RANTES could newly occur even after infectious encephalitis or encephalopathy. In other words, cutaneous adverse reactions could develop even during the recovery phase from an immune-mediated disorder, just like in the present case. To date, the common immunological mechanisms underlying both autoimmune limbic encephalitis and TEN are still unknown. However, in the present case, some immunological changes common to TEN might have occurred during the recovery phase from autoimmune limbic encephalitis. To clarify the pathophysiology of the co-existence, further similar reports would be needed.

In conclusion, we reported the co-existence of autoimmune limbic encephalitis and TEN for the first time. This report must provide us with insights to solve the pathophysiology of the co-existence of these two diseases.

Statement of Ethics

Informed consent to publish her case was obtained from our patient.

Disclosure Statement

The authors declare no conflicts of interest.

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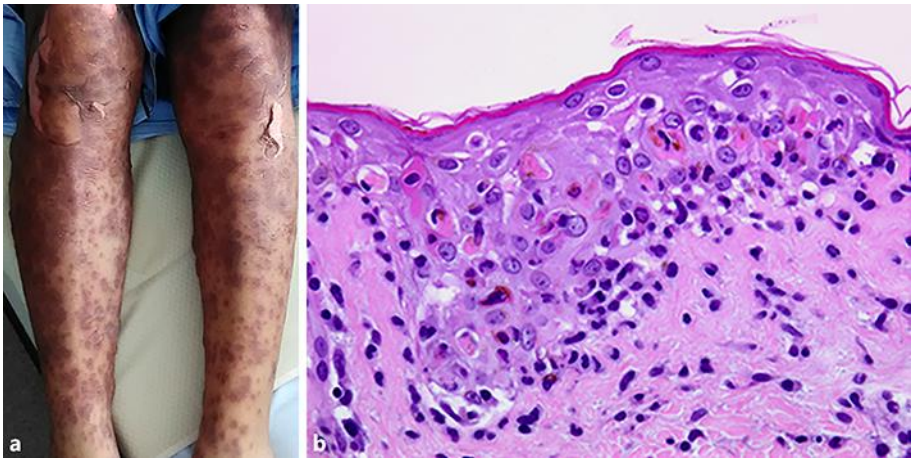

Fig. 1. A picture and histopathology of toxic epidermal necrolysis. **a** Diffuse black bullae and erosions on the patient's legs on day 35. **b** Histopathological findings showed necrotizing keratinocytes and a liquefactive degeneration of the basal cells (hematoxylin and eosin; original magnification ×40).

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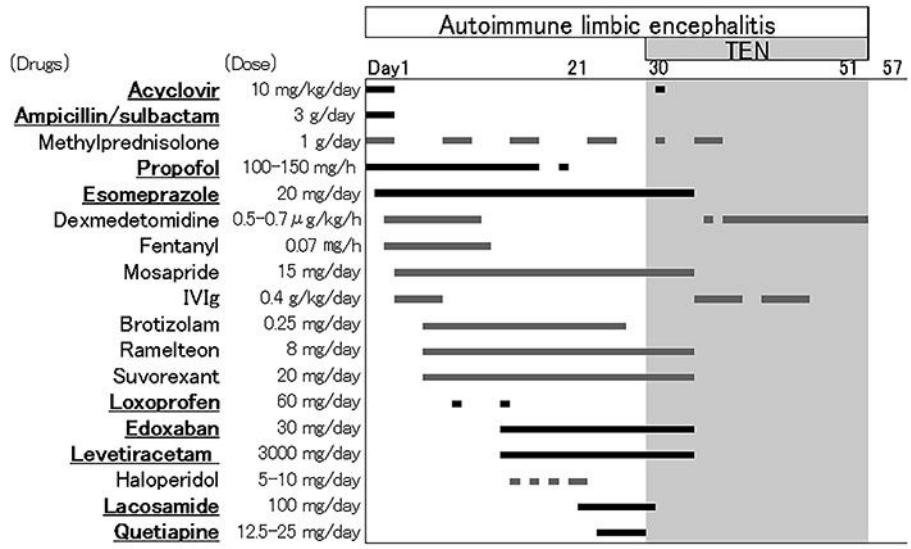

Fig. 2. Time course of autoimmune limbic encephalitis and all drugs administered before the onset of toxic epidermal necrolysis (TEN). Our patient suffered from autoimmune limbic encephalitis since day 1 and from TEN since day 30. Nine of the 18 drugs administered (in bold and underlined) were examined using a lymphocyte transformation test. However, the test produced no positive results. IVIg, intravenous immunoglobulin.