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Case Report

A granulocytosis associated with rufinamide: A case report

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Abstract

Background: Rufinamide, a triazole derivative, is a novel antiepileptic drug (AED) chemically unrelated to other current AEDs. Previous studies on pediatric epilepsy treatment with rufinamide have demonstrated a frequency of leukopenia as an adverse event of 0.5%, and there has been no report of the development of agranulocytosis. Here, we report a patient with Lennox–Gastaut syndrome (LGS) who developed agranulocytosis associated with fever and skin rash with rufinamide. To the best of our knowledge, this is the first reported case of agranulocytosis induced by rufinamide. *Patient:* A 10-year-old boy with a history of herpes encephalitis at the age of 1 year developed LGS, and was administered rufinamide as add-on therapy to valproate, lamotrigine, and clonazepam because of difficulties in controlling tonic seizures. Eighteen days after initiation of rufinamide, agranulocytosis developed associated with high fever and skin rash, all of which resolved after withdrawal of rufinamide. Bone marrow aspiration demonstrated normocellular marrow with selective decrease of mature myeloid series, and suggested that agranulocytosis was not related to malignancy or serious infection. *Conclusion:* This case suggests that rufinamide may induce the potentially serious adverse effect of agranulocytosis. Patients should be monitored for clinical signs of agranulocytosis and consideration should be given to routine blood count determination for early detection of this.

Keywords: Drug-induced agranulocytosis; Rufinamide; Hypersensitivity reactions; Lennox–Gastaut syndrome

1. Introduction

Drug-induced agranulocytosis (DIAG) is a rare but serious adverse event evoked by drug administration [1]. Agranulocytosis is a severe form of neutropenia, defined as an absolute neutrophil count (ANC) less than 500/mm^3. Patients with agranulocytosis may develop severe infection or sepsis. The annual incidence of DIAG and acute neutropenia has been reported to range from 2.4 to 15.4 cases per million [1]. Many kinds of drugs, especially antipsychotics and antiepileptic drugs (AEDs), are associated with DIAG [2,3].

Rufinamide, a triazole derivative, is a novel AED chemically unrelated to other current AEDs. It has been postulated that the main mechanism of action is suppression of neuronal hyperexcitability by prolonging the inactivation phase of voltage-gated sodium channels [4,5]. It was recently approved in Japan as an adjuvant drug in patients with Lennox–Gastaut syndrome (LGS) older than four years of age. Previous studies have reported that common adverse effects are somnolence, vomiting, and headache, and that the majority of these adverse events are mild in severity and well

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tolerated [5]. The incidence of neutropenia during antiepileptic treatment with rufinamide has been reported to be infrequent (1/100–1/1000) according to the prescribing information approved by the U.S. Food and Drug Administration, and DIAG associated with rufinamide has not been reported so far. Agranulocytosis was not mentioned in Thome-Souza's study in 2014 [6]. Here, we report a patient with LGS who developed agranulocytosis associated with rufinamide administration.

2. Case

The patient was a 10-year-old boy with a history of herpes encephalitis at the age of 1 year who developed LGS. Due to difficulties in controlling tonic seizures, rufinamide (200 mg/day) was administered as add-on therapy to valproate, lamotrigine, and clonazepam. Laboratory studies immediately before starting rufinamide revealed a white blood cell (WBC) count of 6900 cells/mm^3 and a neutrophil count of 3200 cells/mm^3 with normal differential. The dose was increased to 400 mg at day 17 of rufinamide administration. Soon afterwards, he developed cheek rash and high fever. The rash gradually spread to the trunk and limbs, with the lesions fusing together. The high fever of 40 °C lasted for three days. Rufinamide was stopped on the third day of the rash. Because he lost appetite and he was very unwell, he was admitted to our hospital the next day. The high fever of 40 °C was already replaced with a low-grade fever in the region of 37 °C. At that stage the rash covered his face, trunk and limbs. It consisted of regular, round-shaped, characteristic target lesions less than 1 cm in diameter, consistent with erythema multiforme. There were no other abnormalities; in particular, there were no mucosal membrane lesions and there was no lymphadenoma or hepatosplenomegaly. Laboratory results revealed agranulocytosis, with WBC count of 5300 cells/mm^3. (see Figs. 1 and 2).

Blood examination revealed increased C-reactive protein (1.3 mg/dl; normal level is less than 0.2 mg/dl) and lactate dehydrogenase (606 IU/L; normal level is 124–226 IU/L) without any evidence of multiple organ involvement. Liver enzymes and coagulation parameters were within the normal range. Tests for Epstein–Barr virus, parvovirus B19, measles virus, rubella virus, herpes simplex virus, and mycoplasma were all negative. Autoantibodies were not detected. Bone marrow aspiration revealed normocellular marrow with complete absence of mature myeloid series (i.e., almost complete absence of segmented and band neutrophils with normal metamyelocytes or more immature myeloid cells), without any signs of malignancy or hemophagocytic syndrome. Erythropoiesis and thrombopoiesis were not affected. A drug patch test (DPT) for rufinamide was performed, but the result was negative.

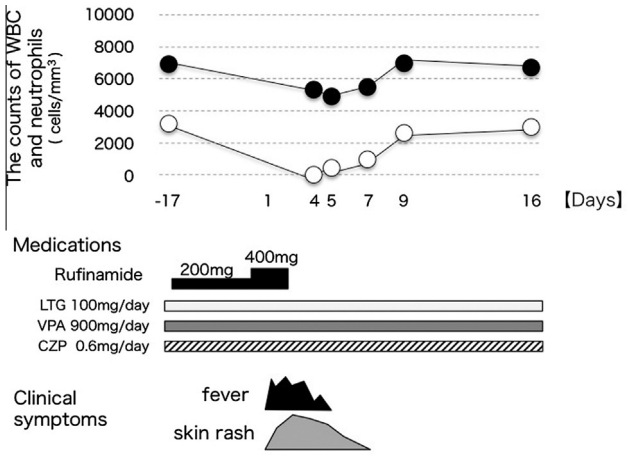

Fig. 1. Clinical course, white blood cell count (black), neutrophil count (white), and medications. In the record of the counts of white blood cells and neutrophils, black circles indicate white blood cells and white circles indicate neutrophils. Day 1 indicates the start of symptoms, including fever and skin rash. Abbreviations: LTG, lamotrigine; VPA, valproate; CZP, clonazepam.

Since his symptoms seemed to have improved after cessation of the drug on the third day, he was not treated with granulocyte colony-stimulating factor (G-CSF) or any other treatment, and was just observed. Fever did not recur after cessation of the drug. The rash did not worsen thereafter and resolved spontaneously. Mature neutrophils appeared in blood on the 5th day, with a count of 990 cells/mm^3 on the 7th day, and increased to normal range on the 9th day. All the symptoms resolved very soon after the rufinamide was withdrawn; therefore we concluded that they were all highly likely to have been induced by the rufinamide.

3. Discussion

Here, we reported a case of rufinamide-associated agranulocytosis. In this case, agranulocytosis developed two weeks after initiation of rufinamide add-on therapy, and resolved immediately after cessation of the drug. Furthermore, bone marrow aspiration demonstrated normocellular marrow with complete absence of mature myeloid series without any signs of malignancy. DPT, the diagnostic gold standard test in drug allergies, was negative in this case. However, the sensitivity of this test is not high, implying that a negative result does not exclude the possibility of DIAG. Since all the abnormalities resolved after cessation of the drug, we concluded that a causal relationship between rufinamide administration and agranulocytosis was highly likely in this case. A pooled analysis of 7 clinical studies on pediatric epilepsy treatment of rufinamide has demonstrated that the frequency of leukopenia defined as an ANC of $<$1500 cells/mm^3 as an adverse event is 0.5% (2 out of 391 cases), and there have been no reports of the