Agranulocytosis following injection of inactivated Japanese encephalitis vaccine (Vero cell): A case report

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Abstract

BACKGROUND
Japanese encephalitis virus (JEV), a mosquito borne flavivirus, is the leading cause of viral encephalitis in Asia, in terms of frequency and severity. JEV infection is thought to confer lifelong immunity. With the near eradication of poliomyelitis, JEV is now the continent’s leading cause of childhood viral neurologic infection and disability. The most common clinical manifestation of JEV infection is acute encephalitis, and currently there is no specific antiviral therapy. Japanese Encephalitis Vaccine (JE-VC) is an effective prevention measure, including JE-VC, Live (JE-MB), and Inactivated JE-VC.

CASE SUMMARY
A 9-mo-old girl received injection of Inactivated JE-VC (Vero cell) (Liaoning Chengda, batch number 201611B17) on August 31, 2017. On that night, she developed a fever with the body temperature up to 38.5 °C, for which Ibuprofen Suspension Drops 1.25 mL was given as antipyretic treatment. On September 1, the patient developed apocleisis, and her parents noticed herpes in her oral cavity. The patient was sent to our hospital on September 3. Physical examination led to a
diagnosis of herpetic stomatitis, for which Stomatitis Spray 1 puff, tid, Kangfuxin Liquid 2 mL, tid, and vitamin B 0.5 tablet, tid, were prescribed. Routine blood tests for low fever on September 6, 2017 revealed an absolute neutrophil count (ANC) of $0.62 \times 10^9$ /L, hemoglobin (Hb) of 109 g /L, and platelet count (PLT) of $308 \times 10^12$ /L, and the tests were monitored regularly thereafter. The patient was followed until July 26, 2020, when routine blood tests revealed ANC $1.72 \times 10^9$ /L, Hb 138 g /L, and PLT $309 \times 10^12$ /L, indicating that the neutropenia count had normalized.

CONCLUSION
This report attempts to bring to clinical attention that Inactivated JE-VC (Vero cell) might cause prolonged granulocytopenia or even agranulocytosis.

Key Words: Inactivated Japanese Encephalitis Vaccine (Vero cell); Neutropenia; Agranulocytosis; Japanese Encephalitis virus; Case report

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Core Tip: So far, there has been no report of vaccine-induced neutropenia that persisted for 2 years until recovery. Japanese Encephalitis virus, a mosquito borne flavivirus, is the leading cause of viral encephalitis in Asia, in terms of frequency and severity. This report attempts to bring to clinical attention that Inactivated Japanese Encephalitis Vaccine (Vero cell) might cause prolonged neutropenia or even agranulocytosis.

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INTRODUCTION
Japanese Encephalitis virus (JEV), a mosquito borne flavivirus, is the leading cause of viral encephalitis in Asia, in terms of frequency and severity[1].

JEV infection is thought to confer lifelong immunity. With the near eradication of poliomyelitis, JEV is now the continent’s leading cause of childhood viral neurologic infection and disability[2]. The most common clinical manifestation of JEV infection is acute encephalitis, and currently there is no specific antiviral therapy. Japanese Encephalitis Vaccine (JE-VC) is an effective prevention measure, including JE-VC, Live (JE-MB), and Inactivated JE-VC[2]. Inactivated Vero cell culture-derived JE-VC is the only JE vaccine licensed and available in the United States. In 2009, the U.S. Food and Drug Administration licensed JE-VC for use in persons aged > 17 years. In 2013, licensure was extended to include children aged > 2 mo. The studies on adverse events with JE-VC have reported fever ($\geq 38$ °C) within 7 d after the first dose or second dose [3].

CASE PRESENTATION
Chief complaints
A 9-mo-old girl received injection of Inactivated JE-VC (Vero cell) on August 31, 2017. On that night, she developed a fever with the body temperature up to 38.5 °C.

History of past illness
No special history of past illness.

Physical examination
Physical examination led to a diagnosis of herpetic stomatitis.
Laboratory examinations
Routine blood tests for low fever on September 6, 2017 revealed an absolute neutrophil count (ANC) of 0.62 × 10⁹/L, hemoglobin (Hb) of 109 g/L, and platelet count (PLT) of 308 × 10¹²/L, and the tests were monitored regularly thereafter (Table 1). The patient was followed until July 26, 2020, when routine blood tests revealed ANC 1.72 × 10⁹/L, Hb 138 g/L, and PLT 309 × 10¹²/L, indicating that the neutrophil count had normalized. Routine blood tests revealed ANC 2.18 × 10⁹/L before injection of Inactivated JE-VC (Vero cell) on May 24, 2017 and ANC 2.12 × 10⁹/L on July 3, 2017, indicating a normal neutrophil count.

FINAL DIAGNOSIS
Neutropenia.

TREATMENT
No treatment was given for neutropenia, but treatment for complications such as fever was administered.

OUTCOME AND FOLLOW-UP
The patient developed neutropenia. After September 2017, regular tests were performed to monitor the neutrophil values, as shown in Table 1. The blood test showed that the lowest of ANC was 0.06 × 10⁹/L, indicating neutropenia developed agranulocytosis. The patient was followed until July 26, 2020, when routine blood tests revealed ANC 1.72 × 10⁹/L, Hb 138 g/L, and PLT 309 × 10¹²/L, indicating that the neutrophil count had normalized.

DISCUSSION
It is important to evaluate the safety profile of new vaccines. Abnormal hematological values, such as neutropenia, are often reported. We should not only identify potentially important safety signals but also understand their implications and clinical relevance.

In many cases, neutropenia occurs in people of African descent because they have a lower ANC compared to other ethnic groups. Neutropenia is not listed as a potential adverse reaction in the package insert of Inactivated JE-VC (Vero cell), nor have there been literature reports on neutropenia induced by inoculating such vaccine. There have been few literature reports on vaccine-induced neutropenia. Only one article on randomized, controlled clinical trials and systematic review[4] suggests that several cases of neutropenia were reported as post-inoculation adverse events within the first 2 wk after inoculation. However, such cases of neutropenia were generally transient, and expected to have favorable clinical outcome after receiving various novel or widely recognized licensed vaccines. Furthermore, vaccine recipients with neutropenia typically have a lower baseline ANC than those without neutropenia. Neutropenia is usually caused by a variety of diseases, including infections, drug treatments, autoimmune diseases, nutritional deficiencies, or hematological malignancies, but there is also genetic conditions such as benign ethnic neutropenia (BEN). Those of African descent are particularly affected by BEN which is believed to be caused by the regulatory variation of the chemokine gene Duffy Antigen Receptor and has no connection with the increase in the incidence of infection.

CONCLUSION
So far, there has been no report of vaccine-induced neutropenia that has persisted for 2 years until recovery. This report attempts to bring to clinical attention that Inactivated JE-VC (Vero cell) might cause prolonged neutropenia or even agranulocytosis.
Table 1 Results of blood tests

| Date             | ANC (× 10^9/L) | Hb (g/L) | PLT (× 10^12/L) |
|------------------|----------------|----------|-----------------|
| September 9, 2017| 0.52           | 113      | 459             |
| September 16, 2017| 0.13           | 118      | 460             |
| October 7, 2017  | 0.06           | 120      | 335             |
| October 27, 2017 | 0.34           | 110      | 311             |
| November 28, 2017| 0.15           | 113      | 353             |
| January 2, 2018  | 0.35           | 116      | 375             |
| February 12, 2018| 0.21           | 115      | 365             |
| April 22, 2018   | 0.11           | 118      | 313             |
| May 25, 2018     | 0.37           | 124      | 252             |
| November 15, 2019| 3.98           | 129      | 287             |
| June 2, 2020     | 1.49           | 131      | 297             |
| July 26, 2020    | 1.72           | 138      | 309             |

ANC: Absolute neutrophil count; Hb: Hemoglobin; PLT: Platelet count.

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