**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 62000

**Manuscript Type:** CASE REPORT

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

Wang L *et al*. A case report

Li Wang, Xu Zhang, Yan-Tao Liu

**Li Wang, Yan-Tao Liu,** Department of Pharmacy, West China Second University Hospital, Sichuan University/Evidence-Based Pharmacy Center, West China Second University Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu 610041, Sichuan Province, China

**Xu Zhang,** Department of Pharmacy, West China Second University Hospital, Sichuan University/Evidence-Based Pharmacy Center, West China Second University Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu 610041, Sichuan Province, China/Department of Pharmacy, Dechang People's Hospital, Liangshan 615500, Sichuan Province, China

**Author contributions:** Wang L reviewed the literature and drafted the manuscript; Zhang X was responsible for the revision of the manuscript for important intellectual content; Liu YT reviewed the literature and contributed to manuscript drafting; all authors issued final approval for the version to be submitted.

**Corresponding author: Yan-Tao Liu, MSc, Associate Professor,** Department of Pharmacy, West China Second University Hospital, Sichuan University/Evidence-Based Pharmacy Center, West China Second University Hospital, Sichuan University/Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, No. 20, Section 3, South Renmin Road, Chengdu 610041, Sichuan Province, China. 2287083973@qq.com

**Received:** December 25, 2020

**Revised:** May 25, 2021

**Accepted:** July 16, 2021

**Published online:**

**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 B2 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 × 109/L, hemoglobin (Hb) of 109 g/L, and platelet count (PLT) of 308 × 1012/L, and the tests were monitored regularly thereafter. 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 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

Wang L, Zhang X, Liu YT. Agranulocytosis following injection of inactivated Japanese encephalitis vaccine (Vero cell): A case report. *World J Clin Cases* 2021; In press

**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.

**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 (≥ 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 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.

**ACKNOWLEDGEMENTS**

Heartfelt thanks to Miss DeAnn.

**REFERENCES**

1 **Halstead SB**, Jacobson J. Japanese encephalitis. *Adv Virus Res* 2003; **61**: 103-138 [PMID: 14714431 DOI: 10.1016/s0065-3527(03)61003-1]

2 **Hills SL**, Walter EB, Atmar RL, Fischer M; ACIP Japanese Encephalitis Vaccine Work Group. Japanese Encephalitis Vaccine: Recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep* 2019; **68**: 1-33 [PMID: 31518342 DOI: 10.15585/mmwr.rr6802a1]

3 **U.S. Food and Drug Administration**. Clinical review: Ixiaro. [cited 18 July 2020]. In: U.S. Food and Drug Administration [Internet]. Available from: https://www.fda.gov/vaccines-blood-biologics/vaccines/ixiaro

4 **Muturi-Kioi V**, Lewis D, Launay O, Leroux-Roels G, Anemona A, Loulergue P, Bodinham CL, Aerssens A, Groth N, Saul A, Podda A. Neutropenia as an Adverse Event following Vaccination: Results from Randomized Clinical Trials in Healthy Adults and Systematic Review. *PLoS One* 2016; **11**: e0157385 [PMID: 27490698 DOI: 10.1371/journal.pone.0157385]

**Footnotes**

**Informed consent statement:** Written informed consent was obtained from the patient’s parents for publication of this case and accompanying images.

**Conflict-of-interest statement:** The authors have no conflict of interest to declare.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** December 25, 2020

**First decision:** May 11, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Wang S **S-Editor:** Gao CC **L-Editor:** Wang TQ **P-Editor:**

**Table 1 Results of blood tests**

|  |  |  |  |
| --- | --- | --- | --- |
| **Date** | **ANC (× 109/L)** | **Hb (g/L)** | **PLT (× 1012/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.