HHS Public Access

Author manuscript

Hepatology. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Hepatology. 2018 May ; 67(5): 2051–2054. doi:10.1002/hep.29682.

Acute acalculous cholecystitis during Zika virus infection in an immunocompromised patient

Suzane Kioko Ono[*,1], **Leda Bassit**[*,2], **Victor Van Vaisberg**[*,1], **Venâncio Avancini Ferreira Alves**[3], **Elia G. Caldini**[3], **Brian D. Herman**[2], **Reed Shabman**[4], **Nadia B. Fedorova**[4], **Denise Paranaguá-Vezozzo**[1], **Caroline Torres Sampaio**[1], **Rafael Bandeira Lages**[1], **Débora Terrabuio**[1], **Wellington Andraus**[1], **Raymond F. Schinazi**[2], and **Flair José Carrilho**[1]

[1]Department of Gastroenterology, Division of Clinical Gastroenterology and Hepatology, Hospital das Clinicas - University of São Paulo School of Medicine, São Paulo, SP, Brazil

[2]Center for AIDS Research, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University School of Medicine, Atlanta, GA 30322, USA

[3]Department of Pathology, University of São Paulo School of Medicine, São Paulo, Brazil

[4]J. Craig Venter Institute, Rockville, MD 20850, USA

Keywords

Infectious Diseases; Electron Microscopy; Hepatobiliary Diseases; Cholecystectomy; Flavivirus

Introduction

The focus of the Zika virus (ZIKV) outbreak has been on the predilection for infection of the central nervous system (CNS) (1). Broader impact of ZIKV including non-CNS involvement are not well understood. We report a patient with acute acalculous cholecystitis (AAC) which occurred during ZIKV acute infection.

Case Presentation

A 54-year-old male sought medical care with complaint of mild right hypochondrium abdominal pain lasting for 7 days with concomitant three days intermittent fever and one day non-pruritic maculopapular rash on torso and arms. One week prior to the onset of symptoms, the individual presented with aqueous diarrhea. Previous medical history included diabetes, rheumatoid arthritis and large granular lymphocytic leukemia for which he was treated with methotrexate, neutropenia and past episodes of intermittent unconjugated hyperbilirubinemia due to Gilbert's Syndrome [homozygous for the (TA)7TAA-allele].

Corresponding author: Suzane Kioko Ono, MD, PhD, Department of Gastroenterology, University of Sao Paulo School of Medicine, Av. Dr. Enéas Carvalho de Aguiar, 255 ICHC - 9th floor - room 9159, São Paulo –SP, Brazil, ZIP code: 05403-000, Tel/fax: +55-11-2661-7830, suzane.ono@fm.usp.br.

*contributed equally

The patient was found to be dehydrated and febrile (38.3°C). He appeared to have mild abdominal discomfort, with a positive rebound tenderness sign but a negative Murphy's sign. Laboratory work-up is shown in Table 1. Ultrasound and CT findings were compatible with AAC (Figure 1 A–B). A comprehensive screening for infectious disease was conducted with negative results, but serum positive by polymerase chain reaction (RT-PCR) for ZIKV. Similarly, tests confirmed ZIKV in bile and gallbladder tissue *via* RT-PCR, with a 100% homology to a ZIKV sequence (see Supplementary Materials).

The patient received empiric intravenous antibiotic therapy including ceftriaxone (2 g/day) and metronidazole (2.25 g/day). Nonetheless, the patient's general condition continued to deteriorate, and thus a laparoscopic cholecystectomy was performed. No Murphy's sign developed during disease course. Surgical exploration (lasting 290 mins) was difficult due to numerous adhesions and pericholecystic plastron. In addition, the patient was hyperthermic and hypotensive. Fluids and noradrenaline were administered and vital parameters stabilized. Intraoperative findings comprised an enlarged gallbladder with thickened walls, and viscous bile inside with no calculi. Gallbladder histology revealed large portions of organizing inflammation and necrosis, and small vessels were obliterated by fibrin thrombi (Figure 1 E–G), and electron microscopy showed Flavivirus-like particles in both intra and extracellular compartments, and emerging out of an endothelial cell into a vessel (Figure 2).

The patient was discharged on day 4 with full recovery/improvement in vital parameters. During disease course, the patient did not develop any changes in mental status or neurological impairment, suggesting that dissemination of ZIKV disease had unlikely occurred. As of February 2017, he is alive and underlying pathologies are under control.

Discussion

AAC physiopathology is poorly defined, and appears to be multifactorial. It can be caused by a variety of infectious disease agents, or a resultant complication during disease course (2). Reports have linked AAC to other *Flavivirus* infections, such as dengue fever (3). In the current case, ZIKV detection in the gallbladder endothelium suggested ZIKV-induced microangiopathy. Several AAC cases have been associated with gallbladder microangiopathy, potentially leading to decreased emptying of the stimuli, cell death and ultimately secondary bacterial growth.(4)

Recent reports suggest the potential for more severe infections and complications in immunocompromised hosts during ZIKV infection (5, 6). Mechanistic insights and the full clinical spectrum of ZIKV infection is unclear and further studies are required.

In this case, AAC may have resulted from multiple factors, including viral infection and host factors. We hypothesize that ZIKV-related microangiopathy induced by endothelium infection may have led to cell death and gallbladder necrosis. Finally, the patient's immunocompromised status might have impaired his ability to fight against both viral and bacterial infections. This report provides a cautionary warning for clinicians to consider the potential increased risk and disease severity and/or atypical presentations with ZIKV infections in immunocompromised patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the patient in this case for his willingness to provide detailed medical and biological samples; Hui-Mien Hsiao for technical assistance; Cristina Takami Kanamura for the immunohistochemistry reactions; James Kohler for writing assistance and Marcia Lea Wajchenberg for illustration assistance.

Financial Support: NIH sponsored Center for AIDS Research grant P30 AI050409 (to RFS); Alves de Queiroz Family Fund for Research sponsored Department of Gastroenterology. RFS and NF report grants from the National Institute of Allergy and Infectious Diseases for Zika virus research, outside the submitted work.

List of Abbreviations

AAC	acute acalculous cholecystitis
CNS	central nervous system
GS	Gilbert Syndrome
RT-PCR	reverse transcription polymerase chain reaction
NGS	Next-Generation sequencing
TA	thymine-adenine
UGT1A1	UDP-glucuronosyltransferase 1A1
ZIKV	Zika virus

References

1. Dos Santos T, Rodriguez A, Almiron M, Sanhueza A, Ramon P, de Oliveira WK, Coelho GE, et al. Zika Virus and the Guillain-Barré Syndrome - Case Series from Seven Countries. N Engl J Med. 2016; 375:1598–1601. [PubMed: 27579558]
2. Poddighe D, Tresoldi M, Licari A, Marseglia GL. Acalculous Acute Cholecystitis in Previously Healthy Children: General Overview and Analysis of Pediatric Infectious Cases. Int J Hepatol. 2015; 2015:459608. [PubMed: 26640715]
3. Nimmagadda SS, Mahabala C, Boloor A, Raghuram PM, Nayak UA. Atypical Manifestations of Dengue Fever (DF) - Where Do We Stand Today? J Clin Diagn Res. 2014; 8:71–73. [PubMed: 24596727]
4. Hakala T, Nuutinen PJ, Ruokonen ET, Alhava E. Microangiopathy in acute acalculous cholecystitis. Br J Surg. 1997; 84:1249–1252. [PubMed: 9313705]
5. Nogueira ML, Estofolete CF, Terzian AC, Mascarin do Vale EP, da Silva RC, da Silva RF, Ramalho HJ, et al. Zika Virus Infection and Solid Organ Transplantation: A New Challenge. Am J Transplant. 2017; 17:791–795. [PubMed: 27629942]
6. Sarmiento-Ospina A, Vasquez-Serna H, Jimenez-Canizales CE, Villamil- Gomez WE, Rodriguez-Morales AJ. Zika virus associated deaths in Colombia. Lancet Infect Dis. 2016; 16:523–524.

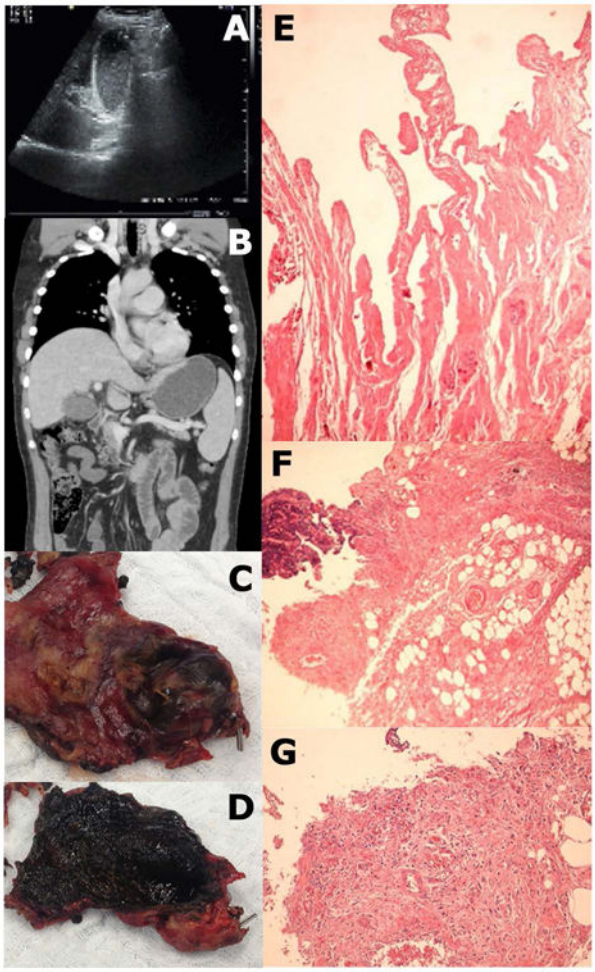

Figure 1.

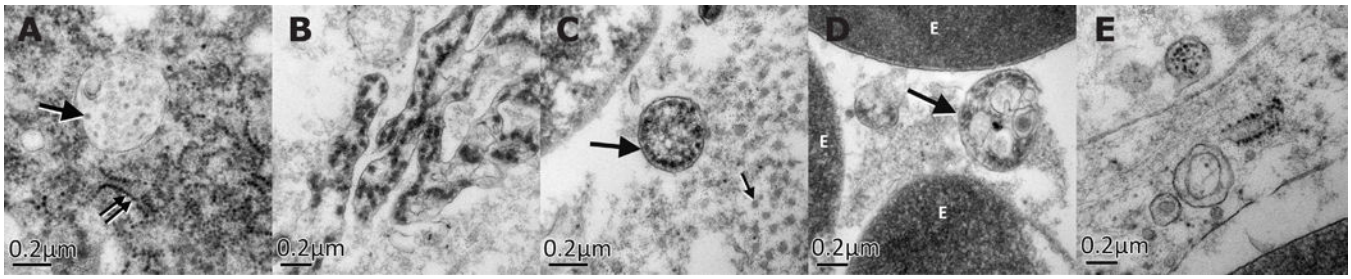

Figure 2.

Table 1

Laboratory results at admission

	Laboratory results	Normal range
Hemoglobin	12.6 g/dL	13.0 – 18.0 g/dL
WBC	5,060 /mm3	4000 – 11000 /mm3
Neutrophils	1,380 /mm3	1,600 – 7,000 /mm3
Platelets	129,000 /mm3	140,000 – 450,000 /mm3
Creatinine	1.16 mg/dL	0.7 – 1.2 mg/dL
ALT	16 U/L	< 41 U/L
AST	17 U/L	< 37/UL
GGT	43 U/L	8 – 61 U/L
ALP	59 U/L	40 – 129 U/L
Indirect bilirubin	1.08 mg/dL	0.1 – 0.6 mg/dL
Direct bilirubin	0.61 mg/dL	< 0.3 mg/dL
C-reactive protein	34 mg/L	< 5.0 mg/L
Urinalysis	No abnormalities	No abnormalities

WBC: White blood cell count; ALT: Alanine aminotransferase AST: Aspartate aminotransferase GGT: Gamma-glutamyl transferase; ALP: Alkaline Phosphatase