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Case Report

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Yellow fever vaccine-associated viscerotropic disease in a young patient evolving to death: a case report

Abstract

This article reports a case of yellow fever vaccine-associated viscerotropic disease (YEL-AVD).

Case presentation: A 26-year-old woman, with a history of recent vaccination for yellow fever, was hospitalized for investigation of febrile syndrome, evolving with significant thrombocytopenia and acute kidney injury, requiring intensive care on the third day in the hospital. Despite the care, she died three days after being admitted to the ICU. Liver immunohistochemistry and serology for IgM were, respectively, positive and reactive for the yellow fever virus. In addition, RT-PCR of collected samples confirmed the vaccination origin of the strain.

Conclusion: This report highlights the importance of the medical team being aware of the possibility of serious post-vaccination clinical events.

Keywords: yellow fever, vaccination, yellow fever vaccine-associated viscerotropic disease, adverse events, multiorgan system failure

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Introduction

Yellow fever (YF) is a disease caused by an RNA virus (YFV), a Flaviviridae family member, genus *Flavivirus*, transmitted by mosquitoes of the genera *Aedes* spp., *Haemagogus* spp. and *Sabethes* spp.[1] It has a high incidence in some regions of the world, mainly in Africa and South America, and is associated with high mortality rates. Its clinical picture can vary from asymptomatic to intense manifestation of systemic disease (*i.e.*, viscerotropic disease), with fever, jaundice, hemorrhage and acute kidney injury, being part of the spectrum of diseases that cause hemorrhagic fever.[2]

In an attempt to control the appearance of new outbreaks in regions with intense occurrence and high mortality, an effort was made to develop a vaccine against the disease, which was implemented in the 1930's. Although outbreaks still occur in Africa and South America regions, due to the low vaccination coverage of the population, this measure proved to be the most effective in reducing the YF mortality rate, associated with controlling the mosquitoes that transmit the virus and preventing their bites.[3]

Although the yellow fever vaccine has changed the disease's world scenario, it is not free of adverse events (AE). These can range from common local symptoms in the vaccine application area to rare but serious and potentially fatal systemic effects, which include yellow fever vaccine-associated neurotropic disease (YEL-AND), yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and anaphylaxis. The last three are classified as serious adverse events (SAEs).[4]

We report below the case of a patient who died as a result of viscerotropic disease associated with the yellow fever vaccine, confirmed by autopsy and histopathological study, in the city of Fortaleza, Ceará State, Brazil.

Case presentation

Female patient, white, 26 years old, sought the Emergency Care Unit in the city of Fortaleza, Ceará, on March 12, 2019, with fever, asthenia, myalgia and low back pain. She reported that these symptoms had started three days before, with lesser intensity, when she received vaccination against yellow fever, tetanus and hepatitis B due to a planned trip abroad. At the service, she was clinically diagnosed with dengue, receiving symptomatic treatment and discharge with medical guidance. Two days later, on March 14, she was admitted to a private hospital in Fortaleza with nausea, vomiting, diarrhea, dyspnea, abdominal distension, hematochezia and significant thrombocytopenia, requiring intensive care on March 17. Nevertheless, the case evolved with dialytic acute kidney injury, respiratory metabolic acidosis, liver failure, severe acute respiratory syndrome, respiratory shock and multiple organ failure. She died three days after admission to the Intensive Care Unit (ICU), being referred to the Death Verification Service (SVO) to clarify the cause of death. Bacterial superinfection, leptospirosis, disseminated histoplasmosis, melioidosis, severe visceral leishmaniasis and viscerotropic disease associated with the yellow fever vaccine were the diagnostic hypotheses raised by the medical team during the management of this case. The patient's relatives denied any chronic comorbidity, medication of continuous use, smoking habit or major surgery, as well as infectious diseases in contacted acquaintances or close relatives, but reported moderate and occasional consumption of alcoholic beverages.

At autopsy, the external physical examination showed anasarca, nail beds cyanosis, bilateral deep sclerotic hyperemia, as well as diffuse ecchymotic infiltrate. There was also the presence of accumulation of vomiting with a yellowish appearance in the upper airways. On internal examination, the craniotomy showed marked cerebral edema, without hemorrhages. The thorax presented massive bilateral hydrothorax

and mild pericardial effusion. The lungs had marked alveolar edema, without areas suggestive of hemorrhage or condensation. The heart, in turn, had mild left ventricular hypertrophy and right ventricular dilatation. Regarding the abdomen, there was moderate ascites, liver with friable consistency, suggestive of submassive necrosis (Figure 1), congested spleen, kidneys with numerous cortical scars and the presence of a small calculus in the left renal pelvis.

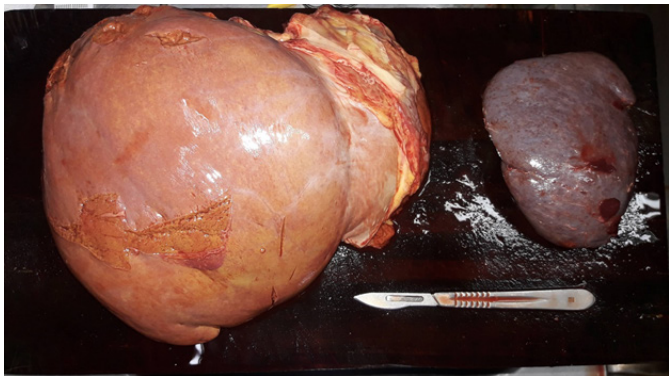

Figure 1 Liver with hepatic steatosis (left) and reactive spleen (right).

The macroscopic diagnosis at autopsy was respiratory failure due to pulmonary edema and bilateral hydrothorax by probable vascular permeability disorder resulting from hemorrhagic fever. Regarding the hemorrhagic fever etiology, the hypotheses of dengue, leptospirosis and yellow fever were raised. A liver histopathological study and immunohistochemistry for the YFV were requested, which showed, respectively, intense areas of necrosis (Figure 2 and 3) and a positive result.

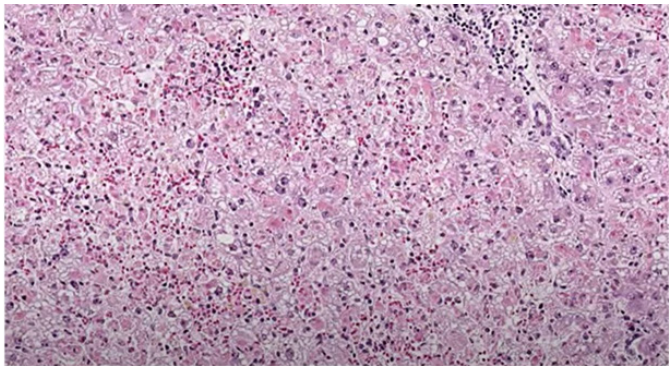

Figure 2 Liver microscopy showing inflammation, necrosis and steatosis (10X).

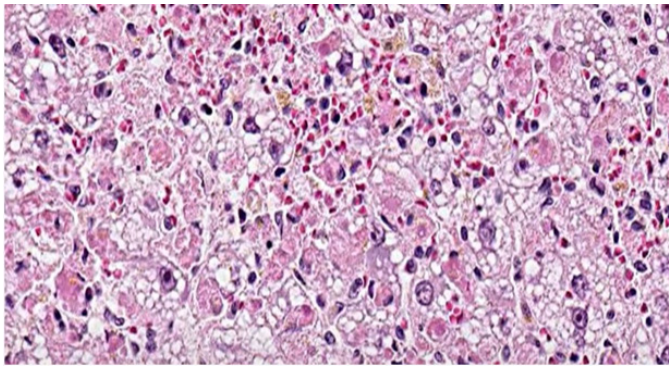

Figure 3 Liver microscopy showing inflammation, necrosis and steatosis (40X).

A molecular test was performed on fragments of the liver, spleen, kidney, central nervous system, in addition to blood sample, using the reverse transcription polymerase chain reaction (RT-PCR) method. The result in all samples was positive for YFV of vaccine origin. Tests with the same methodology for dengue, zika and chikungunya showed undetectable results for each agent. The result for IgM against YFV in a cerebrospinal fluid (CSF) sample using the IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) method was also positive. However, serologies for leptospirosis, dengue, HIV and chikungunya were non-reactive. Furthermore, cultures performed with lung, liver, CSF and blood samples showed no bacterial growth, including *Burkholderia pseudomallei*.

Discussion

The yellow fever vaccine is highly immunogenic, conferring immunity in up to 99% of those vaccinated within 30 days post-vaccination.[3] It is produced from the live attenuated 17D virus strain and is currently available in two sub-strains, 17D-204 and 17DD, which have 99.9% homology. Both sub-strains are cultured in embryonated eggs.[5]

The global recommendation of the World Health Organization (WHO) for yellow fever vaccine use aims to protect populations living in endemic areas, as well as people who will travel to these regions, in order to prevent the worldwide spread of the pathogen through these travelers. Studies have shown that a single dose of the vaccine is capable of maintaining a permanent immune response against YFV, with no need for booster doses.[6]

The general recommendation is to vaccinate individuals from 9 months of age who live in areas at risk for the disease. Exceptions to this rule include pregnant and lactating women, groups in which the vaccine use is generally not recommended, although they can receive it when the benefits outweigh the risks, such as during outbreaks of yellow fever. The same applies to children between 6 and 8 months, adults over 60 years of age, people living with HIV and other types of immunosuppression.[7] In all these groups the risk-benefit ratio of applying the vaccine must be evaluated. Another important contraindication is severe egg hypersensitivity.[6] Therefore, the patient described in this report was not included in any risk group for the yellow fever vaccine.

Several authors have reported the multicausal origin of adverse events following immunization (AEFIs), although it remains unclear. In this context, the role of genetic susceptibility and host immune response in the genesis of events have been researched over the last few years. It is not uncommon that genetic alterations involving innate immune mechanisms are responsible for an increased vulnerability to various infectious diseases.[8] Likewise, the possibility that a single variation or a combination of different genetic alterations may increase the risk of developing YEL-AVD has been studied,[9] since changes in the expression of genes encoding cytokines, toll-like receptors, cytokine receptors, or other immune response elements can, alone or along with other genetic variations, alter the immune response to vaccination, resulting in YEL-AVD.[10] There are probably errors in the host's innate response, in line with the early onset of symptoms, as observed in most patients.[11]

Significant and lasting viremias were observed in several cases of YEL-AVD, and it is possible that there may be a relationship with changes in the innate immune response to the vaccine, enabling the disease's characteristic systemic inflammatory response.[10,12] In this regard, the role of cytokines and chemokines as active immunomodulators in the regulation of YF is highlighted, as well

as some of the genes that express them, although both have not yet been fully understood.[13] Belsher *et al.*[14] assert that small genetic variations in genes that mediate innate antiviral immunity, such as *OAS1* and *OAS2*, are possibly associated with the high viral serum titers observed. In humans, *OAS1* and *OAS2* genes have been shown to mediate innate antiviral immunity through their products, the enzyme 2'-5'-oligoadenylate synthetase (OAS), which catalyzes the production of 2'-5'-oligoadenylates. These oligoadenylates activate latent RNase which has the function of degrading viral mRNA, therefore inhibiting protein synthesis. Furthermore, the interferon-induced peripheral lymphocytes response to the 17D vaccine may be partially mediated by the action of 2'-5'-oligoadenylate synthetase. Hence, alterations in the genetic coding for OAS expression may have a strong influence on the immune response to YFV.[10]

Moreover, Pulendran et al.,[15] highlight the expression of another genetic element related to the immune response in the YEL-AVD: the *RANTES* gene, which encodes a homonymous chemokine. In addition to regulating both expression activation and secretion of normal T cells, this chemokine may affect platelet function by triggering the release of arachidonic acid by T lymphocytes, selectively attracting Th1 lineage cells to the infection site. It may also non-competitively inhibit platelet activation, thus, likely playing a regulatory role in the platelet response to inflammation.[13] RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted) signaling occurs through the CCR5 receptor, which is expressed by CD14 and $CD16^{bright}$ monocytes and mediates the chemotaxis of these cells in tissues. Defects in the migration of monocytes to infection sites due to *CCR5* polymorphisms can also promote an ineffective immune response to viral replication, despite an immune response proper assembly.[15]

It is worth noting that, although these genetic polymorphisms and specific immune components have been mentioned in more detail, other host defects may be responsible for the development of adverse events in other patients after vaccination. Other cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), growth-related oncogene (GRO), monokine induced by IFN-γ (MIG), monocyte chemotactic protein–1 (MCP-1), transforming growth factor (TGF-β1), tumor necrosis factor (TNF-β) may also play important roles in the development and severity of YEL-AEs, especially IL-6, which can be related to a coagulation cascade dysfunction, favoring the hemorrhagic syndrome observed in fatal cases of YEL-AVD.[13]

Considering epidemiological aspects, there are studies relating the occurrence of AEFIs with factors such as gender, age group, clinical and surgical occurrences, although this association may differ or coincide depending on the authors. Bae *et al.*[13], Hayes[10], Barrett and Teuwen[12] seem to agree on the two main risk factors, *i.e.* age (60 years or older) and history of thymic disease. Lindsey *et al.*[4] and Bae *et al.*[13] proposed male gender as a risk factor. Furthermore, Bae *et al.*[13] assumed that a higher humoral immune response in men may be due to a higher viremia followed by a higher rate of AEs in men than in women. However, the authors admit that it is unclear whether the increased viremia in men is caused by a delayed immune response, which may put this group at greater risk for YEL-AEs.

On the other hand, Whittembury et al.,[9] reported 5 cases of YEL-AVD in young women aged 19 to 26 years, of which 3 were fatal, in line with the case profile reported in the present article. The authors proposed a likely correlation with a genetic predisposition to YEL-AVD, although no common genetic risk factor has yet been discovered. In a systematic review, the association with the female gender was also addressed, highlighting the increased incidence of YEL-AVD and fatal cases in women aged 19 to 34 years.[16] However, the authors assert that the data are still preliminary and require evaluation of cofactors and causalities. Finally, Seligman,[8,17] in addition to considering individuals with autoimmune diseases and thymectomy for thymoma as factors, reported that men over 56 years old and women aged 19 to 34 years have a higher risk of developing a severe post-vaccination adverse effect, with fatality rates of 50% and 80%, respectively.

The yellow fever vaccine adverse events reported most frequently in the study by Lindsey et al.,[18] were pain, pruritus and erythema at the site of application, in addition to fever, headache, urticaria, rash, nausea, dizziness, dyspnea and fatigue. In most cases, symptoms started two days after vaccination. It was also observed that 71% of AEFIs occurred in those patients who received the vaccine against YFV associated with other vaccines, consistent with the case reported here. Nevertheless, 11% of cases were classified as serious adverse events.

Among the serious adverse effects, YEL-AVD initially has nonspecific clinical manifestations similar to those of YF, namely: fever, headache, myalgia, arthralgia, nausea, vomiting and diarrhea. The condition can then evolve with liver and kidney damage, hyperbilirubinemia, rhabdomyolysis, respiratory failure, thrombocytopenia and coagulopathy.[19] YEL-AVD should be considered in the presence of a clinical picture compatible with that described above, having a report of recent YFV vaccination, usually within a period of up to 8 days. Thus, it is observed that the clinical picture presented by the patient described in this case report is a YEL-AVD. Confirmation of YEL-AVD is done through the YF virus 17DD strain detection in the patient's blood or tissues, as well as through compatible histopathological findings.[20,2]

To date, the only reports of YEL-AVD have been in people who received the first dose of yellow fever vaccine. There are no reports of cases in people who received some kind of booster. Nevertheless, Hayes[10] showed that the frequency of YEL-AVD in the United States is 0.3 per 100,000 doses. In Brazil, the estimated risk of a fatal event due to YEL-AVD ranged from 0.004 to 0.21 fatalities per 100,000 doses.[10]

The treatment of YEL-AVD is based on clinical support for the patient, with no specific treatment for the condition so far. Most cases reported until this point have been fatal (60%), with deaths occurring within an average period of 10 days (range between 7 and 30 days) from the onset of symptoms.[19]

Conclusion

This article addresses a case report of death resulting from viscerotropic disease associated with the yellow fever vaccine in Brazil. It is important to consider the possibility of YEL-AVD in face of a clinical picture such as the case reported here, especially when there is a strong temporal relationship between the vaccination against yellow fever and the symptoms, as well as the presence of relevant risk factors, in order to promote early intervention and increase the patient's chances of recovery. However, vaccination should not be discouraged in populations for which it is indicated, given rarity of these serious adverse effects. Finally, we emphasize the importance of further studies aimed at better understanding of the related risk factors, mainly the genetic characteristics that favor the development of severe post-vaccination adverse reactions.

Acknowledgments

None.

Conflicts of interest

The authors declare that there is no conflict of interest.

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