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Case Report

Invasive aspergillosis complication in yellow fever vaccine induced viscerotropic disease

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ABSTRACT

Invasive aspergillosis (IA) usually occurs in immunocompromised hosts, but in the last decade IA has emerged in critically ill non-neutropenic patients, as those with severe Influenza and Chronic Obstructive Pulmonary Disease (COPD). We report an unusual fatal case of disseminated IA in a non-immunocompromised patient following yellow fever vaccine-associated viscerotropic disease.

1. Introduction

Yellow fever (YF) is a mosquito-borne systemic illness caused by single-stranded RNA flavivirus. Clinical presentation may range from oligosymptomatic cases with nonspecific symptoms to cases in which the patient presents hemorrhages followed by renal, hepatic, and myocardial failure [1,2]. Since 2014, YF has re-emerged in Brazil as outbreaks, with a pattern of spreading towards southeast and southern regions of the country. Differing to previous outbreaks, most infections have been reported close to peri-urban areas with high population density, though all cases were characterized as sylvatic cycle of the disease transmission [3].

The live-attenuated 17D virus YF vaccine has been available since 1936. It has been used worldwide and is known to be highly immunogenic in 99% of vaccinated and safe, with few adverse events [1,4,5]. Nevertheless, since 2001 cases of a rare and severe syndrome following YF vaccination has been described, which is characterized by acute, hepatic and renal failure follow by multiple organ dysfunction and death. The first two countries to describe the syndrome were Brazil and USA, and since then an increased surveillance has identified a few more cases, but not enough to establish statistically significant risk factors [6].

With the rapid YF virus spread to a vast Brazilian region, a large number of people are being immunized. Thus, an increased reporting of adverse events related to this vaccine, as well as cases of vaccine induced severe YF are expected. Here, we report a fatal case of disseminated IA following YF vaccine-associated viscerotropic disease in an immunocompetent patient.

2. Case presentation

A previously healthy 45-year-old man from Southern Brazil, received a single YF vaccine dose (day zero) and on day seven developed fever, myalgia, headache, and vomiting. He had no history of recent travel and had not visited any area with confirmed circulation of sylvatic YF in the previous weeks. On the occasion, he was treated at emergency department and discharged home with antiemetics, analgesics and antibiotics (ciprofloxacin and metronidazole). No further investigation was done in that moment. On day nine, he reported worsening of symptoms, adding jaundice, abdominal pain and conjunctival suffusion, progressing to altered mental status, respiratory failure needing mechanical ventilation and hemodynamic instability needing vasopressors. On the same day he was transferred to an Intensive Care Unit (ICU), at Complexo Hospital de Clínicas da Universidade Federal do Paraná (CHC/UFPR).

Blood tests revealed leukocytosis ($18.7x10^3$/μL, normal range $3.8–11x10^3$/μL), thrombocytopenia ($67x10^3$/μL, normal range $140–400x10^3$/μL), high levels of alanine aminotransferase (5046U/L, normal range 0–55U/L), aspartate aminotransferase (7975U/L, normal range 5–34U/L), total bilirubin (7.14mg/dL, normal range 0.1–1.2mg/dL), creatinine (12.6mg/dL, normal range 0.6–1.1mg/dL), creatine phosphokinase (1,180U/L, normal range 26–155U/L) and prothrombin-

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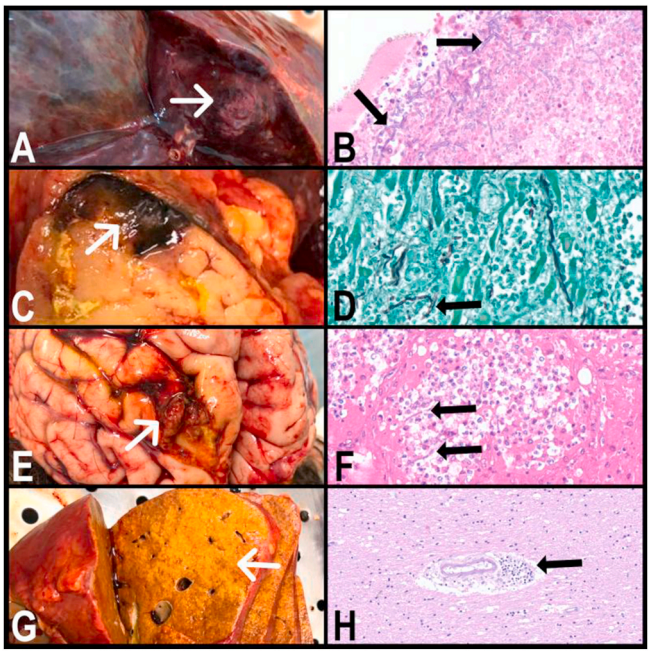

Fig. 1. **A** - Extremely congested and very poorly ventilated lungs with signs of consolidation; there are signs of alveolar hemorrhage and several firm and solid nodules - white arrow; **B** - Histological slide of lung nodule shown in panel A; lung necrosis and an angioinvasive hyaline hyphae disease (black arrows) (H&E – 20 × objective) can be seen; **C** - Pancreas and peripancreatic region that presents many areas of pancreatic necrosis and necrohemorrhagic pancreatitis (white arrow) are shown; **D** - Histological slide showing fungal myocarditis and necrosis of cardiomyocytes; hyaline hyphae (black arrow) can be seen in the myocardium (Groccott - 20 × objective); **E** - Brain abscess in the right fronto-parietal region (white arrow); **F** - Spleen with areas of necrosis and hemorrhage containing septate hyaline hyphae (black arrow) is shown, (H&E – 20 × objective); **G** - Left lobe of the liver with severe steatosis and moderate congestion; **H** - Brain tissue with signs of cerebritis represented by perivascular lymphocyte cuffing (black arrow), (H&E – 10 × objective).

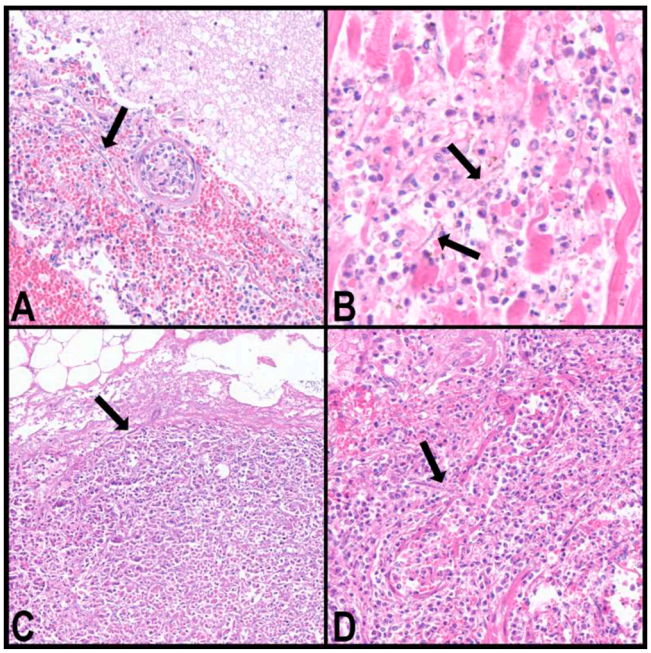

Fig. 2. **A** - Histopathological of brain slide with acute abscess inflammatory pattern with fungal (black arrow) micro thrombosis, (H&E – 10 × objective); **B** - Histological slide with fungal myocarditis and necrosis of cardiomyocytes; hyalo-hyphae (black arrow) in the myocardium can be seen (H&E – 20 × objective); **C** - Histological slide demonstrating necrosis of the pancreas (black arrow) and the adjacent adipocytes due to a fungal thrombosis, (H&E – 5 × objective); **D** - Histological kidney slide with hematogenic acute pyelonephritis due to angioinvasive hyaline hyphae disease (black arrow), (HE - 10 × objective).

time international normalized ratio (2.99, normal range 0.8–1.2). Antibiotic therapy was started, initially with ceftriaxone (2g once daily) for suspected bacterial sepsis or leptospirosis and later changed to piperacillin-tazobactam (2.25g every 6 hours adjusted for renal impairment) in order to expand antimicrobial spectrum. Further management combined steroids (methylprednisolone 60mg/day), hemoderivatives transfusion and hemodialysis.

Additional investigation included negative blood cultures, negative serology for dengue fever and leptospirosis, and an abdominal computed tomography (CT) without significant findings, except for moderate free fluid in the abdominal cavity. Besides improvement in laboratorial and haemodynamic parameters, the patient did not recover conscience after suspension of sedative drugs. On day fourteen a central nervous system (CNS) CT was performed, revealing a small frontal lobe bleeding, which could not justify the neurological compromise. Electroencephalogram analysis revealed severe diffuse brain dysfunction.

Despite the critical care support received, the patient evolved to death on day twenty; the same day that a laboratory molecular test confirmed YF infection.

Necropsy revealed macro and microgoticular steatosis, hepatocytic necrosis with signs of regeneration, and multifocal lymphocyte perivascular encephalitis, thus corroborating the diagnosis of YF vaccination associated-viscerotropic disease. Further analysis revealed angioinvasive hyalohyphomycosis with fungal embolism and thrombosis of large and medium vessels, with involvement of lungs, prostate, stomach, kidney, pancreas, and spleen; fungal endomyocarditis with cardiomyocyte necrosis and fungal brain abscesses associated with necrotizing encephalitis (Fig. 1) were also observed.

Kidneys presented a rough surface with hyalinized glomeruli and tubular atrophy configuring benign nephrosclerosis and hematogenic acute pyelonephritis due to hyalohyphomycosis. Moreover, microscopic analysis of kidney showed a 4-mm renal papillary neoplasm and a 5-mm clear cell renal adenocarcinoma. Furthermore, pancreas presented areas of fat necrosis due to fungal thrombosis (Fig. 2).

PCR-based nucleic acid detection using tissue samples confirmed Aspergillus spp. infection, while RT-PCR test for YF virus using blood sample returned positive; subsequent nucleotide sequencing identified that the virus was 17D YF- vaccine virus strain.

3. Discussion

The Brighton Collaboration defines viscerotropic disease (VTD) as acute multiple organ system dysfunction following YF vaccination [2,5]. The spectrum ranges from mild to severe multisystem disease, leading to organ failure and death. Similar to wild transmission, YF vaccine associated-VTD probably is caused by multiplication of live attenuated 17D YF vaccine virus in target tissues following vaccination [5]. Earlier virologic studies have also documented presence of vaccine strain virus in a number of postmortem VTD tissues. Severe VTD cases are characterized by hypotension, hemorrhage, acute renal failure, and acute respiratory failure. Less frequent manifestations include rhabdomyolysis and disseminated intravascular coagulation [1,4,5].

IA is a well-known complication in immunocompromised patients such as those with hematological malignancies, allogeneic hematopoietic stem cell transplantation recipients, and solid organ transplantation recipients [6]. Less commonly, IA can affect other patients, like those receiving corticosteroids therapy, with AIDS, and those in the ICU [7–9]. Although being an infrequent condition, concomitant liver failure and IA was previously reported in different scenarios of acute and chronic

liver failure, including some reports in patients with dengue shock syndrome [10–12]. Acute liver failure (ALF) together with immunoparalysis, has been demonstrated to represent an acquired immunodeficiency state that increases the risk of IA in critical patients [12]. Patients present a paradox that includes secretion of pro-inflammatory cytokines with monocyte and macrophage dysfunction. At tissue level, the increase in hepatic macrophages causes local injury complicated by systemic inflammation and subsequent immunosuppression. The consequent impairment of the innate and adaptative responses lead to a high risk of secondary infections, which are the main cause of death in these patients [13]. Further, systemic viral infection induces Th1 and Th2 imbalance along with CD4/CD8 inversion, affecting the cytokine inflammatory cascade leading to a transient immunosuppression state in these patients [14,15].

ICU patients usually do not have the classic risk factors for IA, such as leukopenia and use of immunosuppressive drugs. Although most ICU patients do not exhibit these classic risk factors, they have other evidence that should be considered as risk factors, such as high severity score, concomitant pulmonary infection and corticosteroid use.

In conclusion, it is necessary to raise awareness about occurrence of IA in critically ill patients presenting with hepatic failure to ensure early recognition and treatment.

Declaration of competing interest

The authors have no conflict of interests to disclose.

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