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Yellow Fever Vaccine-Associated Adverse Events: Viscerotropic Disease in a Young Female

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Abstract

We report a case of a Yellow Fever Vaccine-Associated Viscerotropic Disease Adverse Event (YEL-AVD) in a young female, who presented to the emergency ward with fever, jaundice, acute kidney failure and thrombocytopenia. Diagnosis was made based upon diagnostic criteria proposed by The Brighton Collaboration Viscerotropic Disease Working Group. YEL-AVD is a very rare but potentially life-threatening acute infection of liver and other vital organs resembling naturally acquired yellow fever disease. Awareness of this rare complication is pivotal in its diagnosis.

Keywords: Yellow fever • Vaccination • Yellow fever vaccine-associated viscerotropic disease

Introduction

Yellow Fever (YF) refers to a potentially lethal acute viral hemorrhagic disease accompanied by fever, jaundice (hence the name "yellow fever"), spontaneous bleeding and renal failure. It is transmitted by day biting infected Aedes and Hemagogus mosquitoes, that breed around houses, in forests or jungles and carry an enveloped RNA flavivirus along. Vaccination is the most important means of preventing the infection. Symptoms manifest after an incubation period of 3-6 days with fever, muscle pain with prominent backache, headache, loss of appetite, and nausea or vomiting as the most common ones. In most cases, symptoms disappear after 3-4 days. A small percentage of patients however enters a second, toxic phase within 24 hours after recovering from initial symptoms. They experience high fevers, jaundice, abdominal pain and vomiting, spontaneous bleeding from the gastrointestinal tract, nose and eyes. Half of these patients die within 7-10 days due to multiple organ failure. Diagnosis can be made by PCR (blood or urine, in an early stage) or serology. Treatment is merely supportive [1].

Prevention can be obtained through mosquito control and vaccination [1]. YF vaccination is recommended by the World Health organization and made obligatory for all travelers ≥ 9 months of age in areas where there is evidence of persistent or periodic YF virus transmission. The YF vaccine is a live attenuated vaccine and generally considered to be safe. It is contraindicated in selected patients (e.g., infants aged less than 6 months, patients with thymoma/thymectomy, immunocompromised patients or solid organ recipients) [1]. Serious and possibly fatal adverse events are rare but can occur following immunization, including Vaccine-Associated Viscerotropic Disease (YEL-AVD), Vaccine-Associated Neurotropic Disease (YEL-AND) and anaphylaxis. We aim to describe a case of YEL-AVD.

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Case Report

A 32-year-old female was referred to our emergency room because of headache, vomiting, continuous right upper quadrant pain and small-stool watery diarrhea for 3 days. She had also noticed jaundice coinciding with darkly brown-coloured urine as well as spontaneously bleeding gingiva, epistaxis and some small skin petechiae since the day before admission. The patient did not take any medication, herbs or drugs. She was an active smoker and stopped drinking alcohol (5 units a day) one month before admission. Her medical history was trivial with an appendectomy and vaginal delivery. She was vaccinated for hepatitis A and B and did not travel abroad in the last 6 months. Five days prior to the onset of her symptoms, she received a YF vaccine for an upcoming journey to Africa. Upon clinical examination, we observed a normotensive sick, jaundiced patient with a fever of 38°C. She had a diffusely tender abdomen and multiple painful adenopathies cervically, axillary and inguinally as well as petechiae and small hematomas on arms and legs. The patient was conscient and adequate without any clinical signs of meningitis.

Laboratory results showed markedly elevated bilirubin and transaminases, grade 3 acute kidney failure, coagulopathy and pancytopenia, with significant thrombopenia (Table 1). Abdominal ultrasound revealed no abnormalities except for hepatic steatosis and an accentuated gallbladder without concurrent gallbladder stones (Figure 1). An extended infectious, toxic and auto-immune panel (including hepatitis E, Hantavirus, Puumala virus, Leptospirosis) came back negative. She was started on intravenous fluids and N-acetyl cysteine and transferred to the hepatology ward after a 24-hour observation at the intensive care unit. The diagnosis of YEL-AVD was made based on the clinical spectrum, the corresponding time frame to YF vaccination and the exclusion of other diagnoses. She was discharged after 11 days of admission and recovered fully. She never departed for her intended holidays to Africa afterwards.

Discussion

Yellow Fever Vaccine-Associated Viscerotropic Adverse Event (YEL-AVD) is a very rare but potentially life-threatening acute infection of liver and other vital organs resembling naturally acquired yellow fever disease. Only 56 cases have been described so-far worldwide with an overall estimated prevalence of 0.4/100.000 vaccinations [2,3]. The common denominator of all cases involves an acute onset of illness, characterized by fever, headache, myalgia, gastrointestinal symptoms, hepatic and renal dysfunction, and

Table 1. Schematic overview of the biochemical evolution of our patient from admission to discharge.

Days from admission	0	1	2	3	4	5	6	9	11
Bilirubin (mg/dl)	8.81	6.61	3.62	2.94	2.44	2.03	1.76	1.46	1.27
AST (U/L)	1330	471	183	118	98	82	72	48	38
ALT (U/L)	1823	1112	658	430	319	250	194	86	44
Gamma GT (U/L)	655	512	373	348	336	309	288	190	136
APH (U/L)	136	116	93	92	93	88	86	72	61
Creatinine (mg/dl)	6.35	6.96	6.99	5.96	4.97	3.92	2.93	1.47	1.12
CPK (U/L)	103								
Platelets (10^{-9}/L)	52	32	36	34	34	33	32	36	46
INR	1.5	1.6	1.5	/	1.3	/	1.1	/	/
aPTT (s)	27.4	/	/	/	33.9	/	37.6	/	/
PT (s)	17.0	18.6	17.6	/	14.5	/	12.8	/	/
Firbinogeen (g/L)	1.96	2.08	/	/	/	/	/	/	/
LDH (U/L)	706	/	/	321	337	335	314	270	228
CRP (mg/l)	19.5	17.8	13.1	11.0	10.3	9.2	7.5	13.8	3.7
WBC (10^{-9}/L)	2.74	3.07	2.99	2.54	2.30	2.68	3.02	4.81	4.55

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; APH: alkaline phosphatase; CPK: creatinine phosphokinase; INR: International Normalized Ratio; aPTT: Activated Partial Thromboplastin Time; PT: prothrombin time; LDH: Lactate Dehydrogenase; CRP: C-Reactive Protein; WBC: White Blood Cell Count

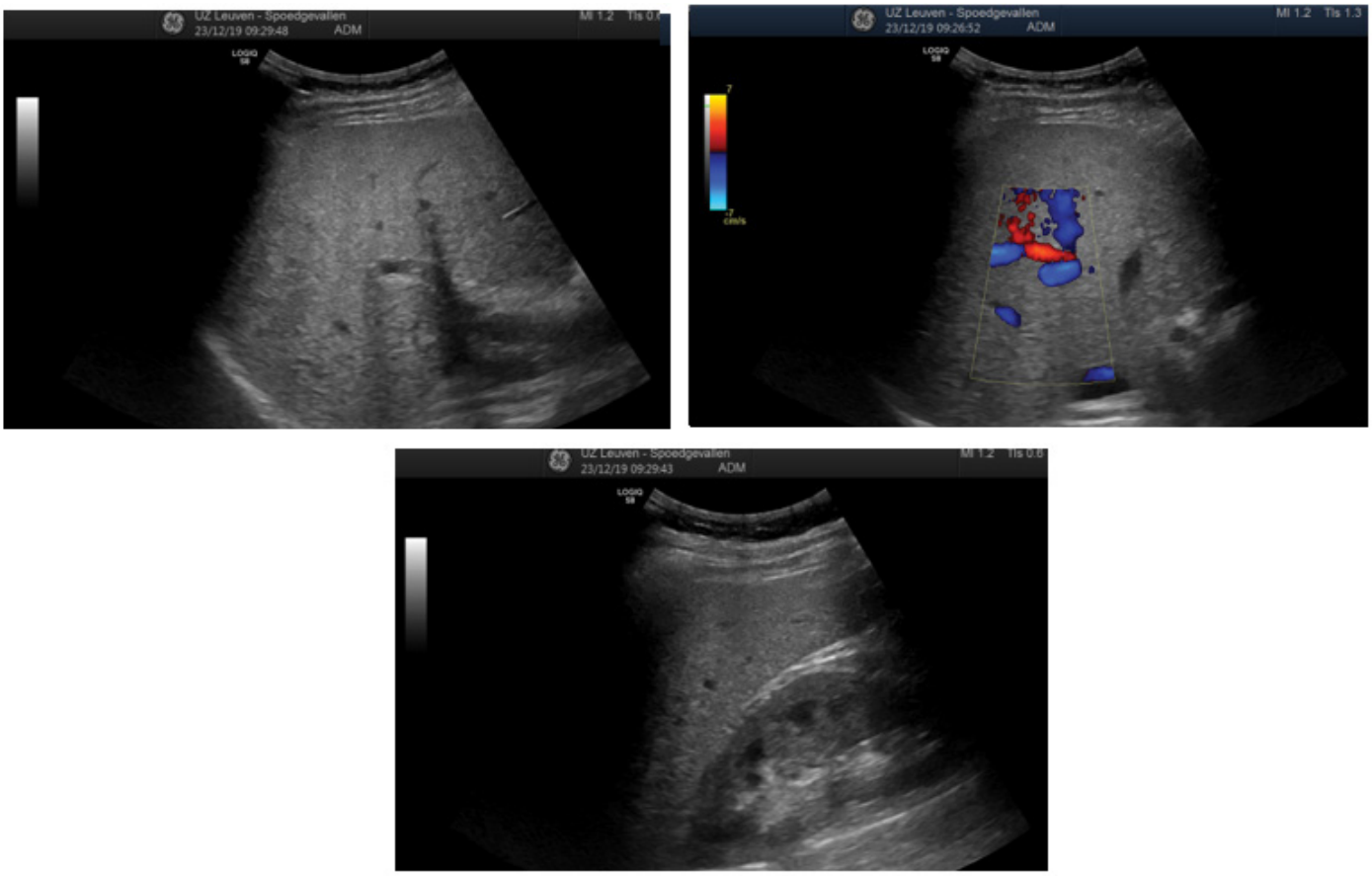

Figure 1. Ultrasound images of the liver and kidney of our patient showing a steatotic liver (upper left panel), patent vascularity (upper right panel) and a normal right kidney (excluding chronic liver injury) (lower left panel).

in extreme cases, shock and coagulopathy, 3-6 days after yellow fever vaccination. The pathogenesis of this adverse event involves an uncontrolled replication of the vaccine (live) virus in visceral organs. The predisposing factors to develop YEL-AVD remain unclear but advanced age and immune dysregulation (such as seen with autoimmune diseases like systemic lupus erythematosus and Addison's disease) have been proposed as potential risk factors [3,4]. A conceivable role herein has been ascribed to polymorphisms in genes controlling innate immunity leading to impaired control of YF 17D virus infection [4,5]. Genetic testing was not performed in our patient.

The diagnosis of YEL-AVD is usually made based on clinical suspicion and association in temporal relation to YF-vaccination. In 2012, The Brighton Collaboration Viscerotropic Disease Working Group defined three diagnostic certainty levels for YEL-AVD, based on (a combination of) major and/or minor criteria. Our patient met 4 major criteria (hepatic, renal, platelet disorder and coagulopathy), resulting in a level 1 of diagnostic certainty for YEL-AVD (highest degree of specificity and the lowest degree of sensitivity) [2] (Table 2). The Brighton Collaborative Working Group mainly underscored the severity and type of organ failure. The time interval between immunization and onset of the Viscerotropic Disease (VTD) was not considered a diagnostic feature in this classification as signs of YEL-AVD can extend up to 30 days following

Table 2. Major and minor criteria for the case definition of viscerotropic disease.

Major criteria	Laboratory or clinical data
Hepatic	Total bilirubin ≥ 1.5 ULN or 1.5x patient's BV or ALT or AST ≥3xULN or ≥3x patient's BV
Renal	Creatinine ≥1.5x ULN or 1.5 patient's BV
Musculoskeletal	CPK ≥5x ULN
Respiratory	Oxygen saturation ≤88% on room air or requirement for mechanical ventilation
Platelet disorder	Platelets <100,000/ µL
Hypotension	Requirement for vasopressor drugs to maintain systolic BP
Coagulopathy	INR≥1.5 or prothrombin time ≥1.5x ULN or activated partial thromboplastin time ≥1.5 ULN or elevated fibrin degradation products or hemorrhage from more than one site
Minor criteria	
Hepatic	Jaundice
Renal	Urine output <500 mL urine/24 hours for adults; <0.5 mL/kg/h for children
Musculoskeletal	Positive urine dipstick test for blood with a negative urine microscopy examination for red blood cells
Respiratory	Increased respiratory rate for age
Platelet disorder	Petechiae or purpura present
Hypotension	Systolic BP<90 mmHg for adults; <fifth percentile for age in children <16 years
Coagulopathy	Clinically evident hemorrhage (one of): epistaxis, hematemesis, melena, hematochezia, hemoptysis, metrorrhagia or menorrhagia, gingival hemorrhage, persistent bleeding from needle puncture sites

Notes: Symptoms and physical signs are indicated in bold. Adapted from Vaccine, 30(33), Gershman MD, Staples JE, Bentsi-Enchill AD, et al., Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data, 5038-5058, Copyright 2012, with permission from Elsevier. ULN: Upper Limit of Normal; BV: Baseline Value; h: Hour; BP: Blood Pressure; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; INR: International Normalized Ratio; CPK: Creatinine Phosphokinase

vaccination and to facilitate detection of cases in resource-poor settings, where a post-mortem diagnosis more likely is the case [2]. A further classification with causality criteria was made, since the symptoms in VTD are not disease specific. Liver biopsy is not considered helpful as there are only aspecific features such as hepatocellular degeneration with eosinophilic Councilman bodies (that can also be seen in the kidneys and myocardium) [6]. In some reference centers, a recombinase polymerase amplification assay can be performed to aid in diagnosis.

Conclusion

In conclusion, this case represents a rare cause of jaundice and should raise awareness for this rare adverse event, particularly in potentially susceptible patients recently vaccinated for YF.

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