

Case series of yellow fever in referral hospitals in Addis Ababa, Ethiopia

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Abstract

Background: Yellow fever is one of the most critical acute viral hemorrhagic diseases, which is transmitted by the bites of infected *Aedes* mosquitoes. Though adequate diagnosis of yellow fever constitutes the first line of defense, it is not easily diagnosed. These case series aim to show the significance of adequate knowledge on the disease while practicing in referral hospitals of Ethiopia.

Study setting: This case series of yellow fever case was identified from Black Lion Specialized Hospital and St. Paul's Referral Hospital. The case was first notified to Ethiopian public health institute from the community through rumor notification. Then a team of experts visited the hospital and conducted necessary investigation and serum sample collection. The serum samples were tested in national influenza and arboviral laboratory of Ethiopian public health institute.

Case presentation: *Case 1:* A 14 years old male patient experienced nausea and vomiting of ingested matter, intermittent fever, generalized headache, bleeding from his nose and mouth, coffee-colored vomiting 07/02/2020. Bilirubin total-6.9 mg/dl, Bilirubin direct- 5.1 mg/dl with elevated liver enzymes, creatinine-7.7mg/dl, blood urea nitrogen-36.6 mg/dl, prothrombin time-14.7 Sec and white blood cells- 8000/microliter. *Case 2:* A 48-years-old male patient experienced frequent vomiting of ingested matter, intermittent fever, yellowish discoloration of his eyes, bleeding from his nose and mouth, change in mental status and decreased urine output, severe tenderness over the right upper quadrant of his abdomen, diffuse edema on the left proximal lower extremity. Bilirubin total-13.9 mg/dl, Bilirubin direct- 9.6 mg/dl with elevated liver enzymes, creatinine-11.7mg/dl, blood urea nitrogen-209 mg/dl, Prothrombin time -15.2 Sec and white blood cells- 18,600/microliter. *Case 3:* A 55 years old female patient experienced headache, high-grade fever, vomiting of ingested matter, loss of appetite and fatigue associated with flank pain. The patient expired at the emergency department on 15/02/2020.

Conclusion: The case series shows yellow fever case misdiagnosis. One has to weigh all the possible conditions that can manifest with the patient's symptoms and signs. It is recommended to build the skill and knowledge of health professionals on high impact epidemic diseases like yellow fever through regular capacity building activities.

Key Words: Yellow Fever, case report, Ethiopia, misdiagnosis

Introduction

Yellow fever (YF) is one of the most critical acute viral hemorrhagic diseases caused by a *Flavivirus* which is transmitted to humans by the bites of infected *Aedes* and *Haemogogus* mosquitoes (WHO 2016). The virus is endemic in tropical areas of Africa, Central and South America. Globally, about 200,000 cases and 30,000 deaths could be recorded in a year (Beasley et al. 2015). Humans develop symptoms at a median of 4 days after yellow fever virus (YFV) inoculation (Johansson et al. 2010). The clinical course of YF has been classically described in three phases; infection, remission, and intoxication (Monath and Vasconcelos 2015). In humans, the wild-type YFV infection is mainly viscerotropic and affects firstly the liver, before damaging other tissues, including the kidneys, spleen, lymph nodes and heart (WHO 2013). After the incubation period, the first infection phase is characterized by a flu-like disease, during which fever is accompanied by chills, headache, nausea and myalgia. Then, a period of remission ensues, and most infected individuals recover. However, in the severe forms of YF, after a

brief remission period of no more than 48 hours, some patients progress to the intoxication phase (Klitting et al. 2018). It begins 3 to 6 days after the onset of initial symptoms and is marked by the return of fever, abdominal pain, nausea and vomiting, oliguria, and jaundice (Monath and Vasconcelos 2015). Hepatic dysfunction results from apoptosis with limited inflammation and manifests with elevated transaminases, bilirubin and decreased synthesis of clotting factors synthesized by the liver (Quaresma et al. 2007). Renal failure is likely multifactorial, with elements of hepatorenal syndrome, prerenal azotemia, and possibly direct viral injury. During the phase of intoxication, these symptoms are expected bleeding from mucosal sites, oozing from needle puncture sites and lines, petechial, ecchymosis, oliguria and jaundice. Encephalopathy can occur at later stages of disease (Gardner and Ryman 2010). There is no cure for YF, treatment involves symptomatic treatment. Vaccination (WHO 2016).

Ethiopian public health institute experts hear the rumor that three clinically similar hemorrhagic fever cases were reported from the same vicinity and blood

samples were taken from both patients and examined with RT-PCR for yellow fever and were confirmed that the second patient was positive for yellow fever Virus. It is not easily diagnosed, Laboratory confirmation of suspected cases of YF is imperative for the effective control and prevention of outbreaks (Domingo et al. 2018). There are several reasons for a misdiagnosis to occur. People who have suffered as a result of a misdiagnosis are often tempted to blame inefficient doctors or medical personnel. However, different factors including but not limited to malfunctioning of medical equipment (Sheela et al. 2012). These case series aim to show the significance of adequate knowledge on diagnosing the diseases while practicing in referral hospitals of Ethiopia.

Study setting

This case series of yellow fever case was identified from Black Lion Specialized Hospital and St. Paul's Referral Hospital. The case was first notified to Ethiopian public health institute from the community through rumor notification. Then a team of experts visited the hospital and conducted necessary investigation and serum sample collection. The serum samples were tested in influenza and arboviral laboratory of Ethiopian public health institute.

Case Presentation

Case 1

Clinical presentation: A 14 years old male patient started to experience nausea and vomiting of ingested matter of three episodes on 07/02/2020. Associated with this, he started to experience a high-grade intermittent fever and headache. He visited a health center and was given an unspecified tablet after he was diagnosed with Typhoid fever. On 12/02/2020, he started to have bleeding from his nose and mouth. He also had coffee ground appearance vomiting of three episodes then he was referred to Black lion Hospital on 15/02/2020. He was admitted to the medical intensive care unit (ICU). He has no history of Diabetic Mellitus, Hypertension, Malaria attack and urine color change. Laboratory investigations conducted (Table 1).

Physical examination finding: Acutely sick looking; blood Pressure (B/P)-100/70 mmHg, Pulse Rate (PR)-130 Beats/min, Respiratory Rate (RR)- 28 Breath/min, Temperature (T)-37.1°C ; decreased air entry over the right lower 1/3 of the posterior lung field; ejection systolic murmur at the apex; liver is 4 cm below the right costal margin; Lethargic.

Case 2

Clinical presentation: A 48-years-old male farmer had frequent vomiting of ingested matter which persisted for a week, concomitant high-grade

intermittent fever. After one week of his initial symptoms, he developed yellowish discoloration of his eyes associated with bleeding from his nose and mouth, change in mental status and a decreased in urine output. He was then referred to St. Paul Hospital on 14/02/2020. At the time of admission, the patient was unconscious. He had no history of abnormal body movement, recent drug intake, and travel to YF endemic area, malaria attack, hypertension and diabetics. Lab investigations conducted (Table 1).

Physical examination: Acutely sick looking; BP-130/80 mmHg, PR-89 Beats/min, RR-12 Breath/min T-37.5°C; pink conjunctiva and icteric sclera; severe tenderness over the right upper quadrant; diffuse edema on the left proximal lower extremity; jaundiced skin color; GCS 12/15, pupil- pinpointed bilaterally and grossly moves his extremities.

Case 3

Clinical presentation: A 55 years old female patient who was relatively healthy three days back until she started to experience headache, high-grade fever, vomiting of ingested matter, loss of appetite and fatigue. She also had flank pain. During her visit to Ras Desta Hospital, she was evaluated and diagnosed with Acute Kidney Injury and referred to St Paul's Hospital. While evaluation and workup the patient expired at the emergency OPD on 15/02/2020. Laboratory investigations conducted (Table 1).

Physical examination finding: Acutely sick looking BP-75/50 mmHg, PR-102 Beats/min, RR-24Breath/min T- 35.5-degree centigrade; GCS-5/15.

Discussion

Accurate clinical diagnosis of yellow fever is inherently challenging, as early symptoms of infection are easily confused with other hemorrhagic viral diseases, such as Sever malaria, Dengue, Zika, Ebola etc. The diagnosis of YF is made by detection of the virus, or of its genetic material in serum or tissue using virus isolation or reverse transcription-polymerase chain reaction (RT-PCR) and serological testing (WHO 2016). The diagnosis of the first case while admitted at Black Lion Hospital was leptospirosis. Leptospirosis is a zoonosis caused by the spirochete *Leptospira interrogans* (Togal et al. 2010). Leptospirosis is a disease with a variable grade of severity and organ involvement. During the septicemic phase, patients will present with a flu-like illness with fever, headache, myalgia, conjunctival suffusion, and various non-specific findings such as mild cough, rash, lymphadenopathy, nausea, and vomiting (Bal 2005). Weil's disease, the most severe form of illness, is characterized by jaundice, renal failure, and hemorrhage with a variable clinical course (Bharti et al. 2003)

Table 1: List of laboratory tests and results performed for the patients, referral hospitals in Addis Ababa, March 2020

Laboratory tests	Laboratory result		
	Black Lion Hospital Case-1	St. Paul's Hospital Case-2	St. Paul's Hospital Case-3
Alanine transaminase(ALT)	4853 U/L	3,661U/L	
Aspartate aminotransferase(AST)	2144 U	5,219 U/L	
Alkaline phosphates	313 U/L	174U/L	
Bilirubin total	0.38 mmol/L	0.76mmol/L	
Bilirubin direct	0.28 mmol/L	0.52mmol/L	
Blood urea nitrogen (BUN)	2.01 mmol/L	11.5mmol/L	
Creatinine	0.42 mmol/L	0.64mmol/L	
Uric Acid	0.99 mmol/L	0.66mmol/L	
Potassium	0.31 mmol/L	0.19mmol/L	
Sodium	8.06mmol/L	7.8mmol/L	
Chlorine	5.5 mmol/L	5.65mmol/L	
Prothrombin time (PT)	14.7 Sec	15.2 Sec	
Partial thromboplastin time (PTT)	81.2 Sec	120 Sec	
International normalized ratio (INR)	1.24	1.13	
Hepatitis A virus	Non-reactive	Non-reactive	
RDT malaria	Negative	Negative	
White blood cell	8000/micro liter	18,600/micro liter	5,700/micro liter
Neutrophil	78%	90%	88%
Lymphocyte	22%	3%	7%
Hemoglobin	4gm/dl	5.2gm/dl	13gm/dl
Red blood cell	2,180,000/micro liter	1,900,000/micro liter	4,670,000/micro liter
Platelet	124,000/micro liter	67,000/micro liter	177,000/micro liter
HBsAg		Negative	
HCV Ab		Negative	
Other Investigations			
Abdominal U/S		Minimal Intra peritoneal collection	Mild hepatomegaly with thickening gallbladder well and early appendicitis
Doppler U/S		Acute left Proximal Deep Venous Thrombosis	
Yellow fever RT-PCR	Negative	Positive	

The first case had abnormal liver, and renal function test results which indicate abnormal liver and kidney function. However, he had no conjunctival suffusion, cough, rash and lymphadenopathy. Rather, the initial symptom was nausea and vomiting, and headache followed by spontaneous bleeding from his nose and mouth which is not a typical presentation of leptospirosis. In addition, the patient had no signs of pancreatitis, rather, he had elevated CBC with neutrophil predominance, PT, PTT, INR, AST, ALT, Bilirubin (direct and total) Creatinine and BUN. After two days of stay in the wards subsequently, he was diagnosed with hepatic encephalopathy and acute kidney injury then admitted to ICU for dialysis. This case was epidemiologically linked with yellow fever confirmed case. The second case was admitted with

the diagnosis to rule out pesticide poisoning with liver failure and deep venous thrombosis. Acute organophosphate poisoning diagnosis is based on the history of exposure and clinical manifestations. As it is understood from the history, the patient is a farmer but had no history of pesticide use for his farm. The clinical manifestation of the patient rather suggests a possible infectious diseases origin because the patient had high-grade intermittent fever with other gastrointestinal symptoms which worsen gradually. The laboratory finding shows that the patient had liver and renal failure with deranged coagulation profiles. In addition, the third patient was his wife with similar clinical manifestation. She died after five days of manifesting the symptoms.

Nearly half a century following the historic YF outbreak in Ethiopia, there was another confirmed YF outbreak in South Omo, Wolayta, Gurage Zones of Southern Nations, Nationalities and Peoples Regional State (SNNPR) in 2013, 2018 and 2020, respectively (Abate et al. 2020). Despite the frequent occurrence of YF, awareness among the clinicians is not adequate. Especially, diseases with epidemic potential like yellow fever need to be diagnosed as soon as possible because of their higher case fatality rate among the people who acquire the virus. It is important to reach on the correct diagnosis of the disease since it also affects the social and mental well-being of the patient and the community in general.

Conclusion and recommendation

The case series shows yellow fever case misdiagnosis. A clinician has to be careful in eliciting the patient's signs and symptoms before reaching on diagnosis. An accurate interpretation of these is even more important. Theoretical knowledge and clinical experience too matter in preventing a wrong diagnosis. Most importantly, one has to weigh all the possible conditions that can manifest with the patient's symptoms and signs which in turn guides the clinicians to provide the necessary medical care for their patients and it prevents further health danger in the community in the case of epidemic-prone diseases like yellow fever. It is recommended to build the skill and knowledge of health professionals on high impact epidemic diseases like yellow fever through regular capacity building activities.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

- Abate W, Chalachew S, Yosef A, Mesay G, Desalegn B, Geremew T, et al. (2020). Aedes Mosquitos' distribution and risk of Yellow Fever Transmission in Gurage Zone, Ethiopia. *Ethiopian Journal of Public Health and Nutrition* 04(01):1-87.
- Bal AM (2005). Unusual clinical manifestations of leptospirosis. *Journal of Postgraduate Medicine*, 51(3):179-183.
- Beasley DW, McAuley AJ & Bente DA (2015). Yellow fever virus: genetic and phenotypic diversity and implications for detection, prevention and therapy. *Antiviral Research Journal*, 115:48-70.
- Bharti AR, Nally JE, Ricaldi JN, Matthias MA, Diaz MM, Lovett MA, et al. (2003): Leptospirosis: a zoonotic disease of global importance. *Lancet Infectious Disease*; 3(12):757-771.
- Domingo C, Charrel RN, Schmidt-Chanasit J, Zeller H & Reusken C (2018): Yellow fever in the diagnostics laboratory. *Emerging Microbes Infections*, 7:129.
- Gardner CL & Ryman KD (2010): Yellow fever: a reemerging threat. *Clinical Laboratory Medicine*, 30:237-260.
- Johansson MA, Arana-Vizcarrondo N, Biggerstaff BJ & Staples JE (2010): Incubation periods of yellow fever virus. *American Journal of Tropical Medicine and Hygiene*, 83:183-188.
- Johansson MA, Vasconcelos PF & Staples JE (2014): The whole iceberg: estimating the incidence of yellow fever virus infection from the number of severe cases. *Transaction of the Royal Society Tropical Medicine and Hygiene*, 108:482- 487.
- Klitting R, Roth L, Rey FA & de Lamballerie X (2018): Molecular determinants of yellow fever virus pathogenicity in Syrian golden hamsters: one mutation away from virulence. *Emerging Microbes and Infections*, 7:51.
- Monath TP & Vasconcelos PF (2015): Yellow fever. *Journal of Clinical Virology*, 64:160 -173.
- Quaresma JAS, Barros VL, Pagliari C, Fernandes ER, Andrade HFJ, Vasconcelos PF, et al. (2007): Hepatocyte lesions and cellular immune response in yellow fever infection. *Transaction of the Royal Society Tropical Medicine and Hygiene* 101:161-168.
- Sheela S, Bhat SG, Iyer SK & Kumar KK (2012): *Hindawi Publishing Corporation Case Reports in Dentistry Volume*, Article ID 946327 doi:10.1155/2012/946327
- Togal T, Sener A, Yucel N, Demirbilek S, Akgun FS, Aydogan M, et al. (2010): Intensive care of a Weil's disease with multiorgan failure. *Journal of Clinical Medicine Research*, 2(3):145-149.
- World Health Organization (2016). *Yellow Fever Fact Sheet*; 2016.
- World Health Organization (2013). Vaccines and vaccination against yellow fever. WHO Position Paper – June 2013. *The Weekly Epidemiological Record*; 88:269-83.