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Acute Kidney Injury (AKI) in the Setting of Multi-Organ Dysfunction Syndrome (MODS) Secondary to Yellow Fever Infection (YFI) in a 19-Year-Old Woman

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Abstract

Background: Outbreak of yellow fever infection (YFI), a mosquito-borne disease, occurs sporadically worldwide especially in tropical nations. Acute kidney injury (AKI) commonly results from YFI and could be associated with a poor prognosis for victims even under intensive care unit (ICU). Pathophysiologic mechanisms for AKI include hypovolemic shut down, cytotoxicity, acute tubular necrosis (ATN), hemolysis, or coagulopathy. Early diagnosis, prompt and effective treatment modalities including dialysis improve treatment outcome. **Aim:** We report the case management of a 19-year-old woman who had yellow fever infection complicated by acute kidney injury in the setting of multi-organ dysfunction syndrome (MODS). **Case Presentation:** A 19-year-old woman who presented with fever, headache and vomiting for 2 weeks. In the course of the illness, urine volume became reduced and coke colored, followed by body swelling, yellowness of the eyes bleeding from the orifices. Examination revealed an acutely ill looking woman, icteric, and with pedal edema. Her pulse was 100/min and blood pressure was 120/80 mmHg. Liver was enlarged, soft and tender. She had proteinuria 3+ and polymerase chain reaction (PCR) confirmed yellow fever infection. She had markedly deranged serum biochemical parameters for which she had a three-hour session of hemodialysis with Heparin anticoagulation. The urea reduction ratio (URR) was 46.9%. Barrier nursing was commenced. She had 7 units of whole blood and a pint of fresh frozen plasma (FFP) with antibiotics, Rabeprazole, Tranexamic acid, Vitamin K and Frusemide. She had the second dialysis ses-

sion of HD and entered into the recovering phase of AKI and was subsequently discharged after 18th days on admission. **Conclusion:** Yellow fever infection occurs sporadically and could lead to MODS involving the kidneys, liver and hematologic system. Prompt initiation of dialysis, correction of coagulopathy, and antibiotics use are measures needed to arrest progression and death. Vaccination, destruction of the natural habitat of the carrier and infective organisms are necessary particularly in endemic regions of the world.

Keywords

Acute Kidney Injury, Acute Tubular Necrosis, Dialysis, Yellow Fever Virus, Fresh Frozen Plasma

1. Introduction

Yellow fever is a viral hemorrhagic fever (VHF) caused by yellow fever virus (YFV), of the *Flavivirus* genius and *Flaviridale* family that include other mosquito-borne infections caused by Dengue and Zika viruses [1]. *Flaviviruses* are enveloped, single-stranded RNA viruses transmitted by *hematophagus arthropods* and hosted by vertebrates mostly man and primates. Transmission is by urban, enzootic (sylvatic) cycle. First outbreak was in Cuba in 1646, in Nigeria, 1864 and has been reported in many countries particularly Angola and Brazil. Outbreaks in Nigeria are common between August and November due to surface waters, greater forests growth and less bush burning. Annually, about 20,000 individuals are affected worldwide with mortality up to 20% - 50% in severe cases [2].

Organ system most commonly affected by YFV infection included the liver, kidneys, hematological, and gastrointestinal. It also commonly presents with multi-organ dysfunction syndrome (MODS) as in the index case. Mortality could be up to 20% - 50% [2]. Prevention and vaccination remain the only means of curtailing disease at present [3].

Yellow fever virus infection has resulted in many fatalities in Nigeria usually from comorbidities and complications particularly those affecting the kidneys, liver and coagulopathy. Most deaths could have been averted (particularly those with AKI) with dialysis treatment. Studies on AKI from yellow fever infections are rare in our clime hence the need for this case report to highlight the need for prompt and effective treatment to reduce fatalities. A written informed consent was obtained from the patient for this publication.

2. Case Report

A 19-year-old female, presented with persistent fever, headache and vomiting for 2 weeks. Seven days into illness, she noticed coke colored urine, reduced urine volume, body swelling and yellowness of the eyes.

Examination: A young woman, acutely ill looking, icteric, with pedal edema.

Her vitals were: pulse rate (PR)-100/min, blood pressure (BP)-120/80 mmHg and 26/min. Liver was enlarged, soft, tender, and she had ascites.

Urinalysis showed: protein 3+, glucose 3+.

Assessment: Acute kidney injury secondary to sepsis.

She had full systemic work up and investigation results showed markedly deranged serum electrolytes, urea, creatinine, markedly elevated liver enzymes and bilirubin and reduced albumin. She had the first hemodialysis (HD) session with Heparin 5000 IU anticoagulation, blood flow rate (BFR) of 300ml/min for 3 hours. The urea reduction ratio (URR) was 46.9%.

Bleeding from the orifices was noticed six hours post dialysis, from intravenous sites, with epistaxis, hemoptysis, hematemesis and vagina. Clotting profile was deranged (beyond expected for dialysis anticoagulation) as shown in Table 1 & Table 2. Further history revealed ingestion of "bush meat" (wild life animals like rabbit). The diagnosis was modified to:

Probable Viral Hemorrhagic Fever (VHF) complicated by acute kidney injury (AKI) and coagulopathy.

Barrier nursing was commenced. The Infection Prevention and Control (IPC) Team was called in, they instituted IPC measures that cover both standard and contact-based precautions. Blood samples were collected under strict aseptic condition, standard and VHF IPC measures. Blood sample was accorded the standard triple packaging and transported to Virology laboratory of the Lagos University Teaching Hospital, Lagos Nigeria. The result confirmed yellow fever infection.

She had 7 pints of whole blood and a pint of fresh frozen plasma (FFP) after Hematologist's review and bleeding stopped. Antibiotics, Rabeprazole, Tranexamic acid, Vitamin K and Frusemide were continued. She had the second session of HD and then entered the recovering phase of AKI with daily urine output of >4 L which normalized at the end of the 2nd week. She was discharged on

Table 1. Laboratory investigation results on admission and clinic follow up.

Variables	Admission	Day 8	Day 15	1st Clinic visit
Packed cell volume (40% - 52%)	28	18	29.5	28
Mean corpuscular volume (76 - 96)	72	60	64	62
White blood cell (4 - 11 × 10^9)	4.3	3.7	3.1	4.8
Granulocytes (2 - 7 × 10^9)	2.6	1.7	1.2	2.2
Lymphocytes (1.5 - 4 × 10^9)	1.1	1.3	1.7	2.2
Platelets (150 - 400 × 10^9)	64	88	180	163
Erythrocytes sedimentation rate (<15 mm/Hr)	102			22
Prothrombin time (12 - 14 s)	21	18		15
International normalized ratio (0.9 - 1.1)	1.6	1.2		1.0
Partial thromboplastin time (30 - 42 s)	>120	50		43

Table 2. Laboratory results on admission and clinic follow up.

Variables	Admission	Day 8	Day 15	Day 29
Sodium (135 - 145 mmol/l)	135	139	139	139
Potassium (3.5 - 5.0 mmol/l)	4.5	2.9	3.1	4.5
Chloride (97 - 107 mmol/l)	99	101	106	105
Bicarbonate (22 - 30 mmol/l)	18	21	23	28
Urea (3 - 7 mmol/l)	32	10.4	3.9	2.9
Creatinine (50 - 110 umol/l)	877	194	83	59
Uric acid (mmol/l)	631		182	235
Alanine transaminase (5 - 35 IU/l)	315		72	49
Aspatate transaminase (5 - 40 IU/l)	227		189	87
Gamma glutaryl transferase (7 - 45 IU/l)	827		783	364
Alkaline phosphatase (50 - 125 IU/l)	850		919	398
Total protein (60 - 80 g/dl)	73			58
Albumin (35 - 55 g/dl)	22		31	24
Globulin (25 - 35 g/dl)	42			34
Total bilirubin (1.7 - 20 umol/l)	191		23.3	19.7
Conjugated bilirubin (<5.1 umol/l)	21.8			8.6
Total cholesterol (<5.2 mmol/l)	7.5			5.5
High density lipoprotein (>1.3 mmol/l)	1.3			2.1
Low density lipoprotein (<2.6 mmol/l)	4.9			3.0
Triglyceride (1.7 mmol/l)	3.0			2.0

the 18th day on admission and has remained stable in follow up visits. The care giver of the index patient (mother) received vaccination in the course of patient stay in our facility.

3. Discussion

We report a case of multi-organ dysfunction syndrome (with AKI, hepatotoxicity and coagulopathy) induced by yellow fever infection which occurred in a 19-year-old woman. The high mortality recorded in the past due to late diagnosis and management prompted us to institute an aggressive treatment modality of her condition considering the likely poor prognostic effects of combined renal, hepatic and clotting profile affectation.

The transmission of YFI can be by enzootic (sylvatic), intermediate (savannah) or urban. Mortality is often associated with MODS particularly hepato-renal disease [2]. Inoculation and viral release into blood stream follows a female mosquito bite. Viruses migrate through subcutaneous layer, lymph nodes

(with replications), blood stream, to the liver, kidneys, heart, spleen [4] [5]. Cellular injury seen in severe forms of disease could be from viral toxicity, coagulopathy, vascular damage/leakage and shock. Endothelial injury with dysregulated coagulation is the primary pathologic pathway to MODS [6]. Genetic variants conferring some immunity on host is suggested though not authenticated.

Kidney damage results from vascular instability/leakage, shock and viral toxicity. ATN seen in the index patient could have resulted from bilirubin deposition, metabolism, epithelial cell obstruction or interlobular vessel thrombosis. Adrenal gland hemorrhage and necrosis could also cause AKI. Urine PH is low (increased tubular bicarbonate reabsorption) [7]. Non-fatal, progressive disease leads to interstitial fibrosis from interstitial necrosis, with edema, reperfusion injury, healing and interstitial scarring.

Diagnosis is by antigen detection (IgM) or IgG specific antibodies and confirmation by viral isolation. Molecular techniques like point of care (POC) and polymerase chain reactions (PCR) can be used. Index patient was diagnosed using a PCR-based screening test [8].

Treatment is by rehydration, blood transfusion, antibiotics, antipyretics and dialysis. Sofosbuvir, a direct antiviral inhibitor of RNA-directed RNA-polymerase-enzyme of hepatitis C virus has been used with some improvement in clinical outcome [9]. Dialysis reduces cytokine production by viral antigens, the viral load and promotes homeostasis. It is improved with high flux dialyzers and high blood flow rates (BFR) as was done for the index patient who had a BFR of 300 - 350 ml/min, even for the first session of HD. A set back of this dialysis protocol is increased risk of arrhythmias (from myocardial adrenergic over-activity, cytotoxicity, and the stress of the dialysis procedure), membrane instability, hypotension and hyperthermia which fortunately were not seen in this index case. Polyuria in AKI mostly indicates recovering of kidney function and could be associated with transient salt loosing state with marked reduction in levels of serum electrolytes. Though the index patient's polyuric phase was largely uneventful, however, when it does occur, management could be challenging as daily and at times twice daily serum electrolyte assessment could be needed and this could be difficult to meet in a low income setting. The Fresh frozen plasma (FFP) replaces plasma proteins, clotting factors and helps attenuates coagulopathy.

Prognosis is poor in MODS, coagulopathy and shock. Vaccination is with single dose, envelop-targeted YF-17D-vaccine [10]. The WHO's 10-year program "eliminate yellow fever epidemics" (EYE) in 2016 is expected to combat disease outbreak [4].

4. Conclusion

Yellow fever virus is a cause of VHF found sporadically in tropical regions of the world. It is commonly seen in the rainy season. The liver, kidney and coagulation pathways are commonly affected and usually carry worse prognosis. It also commonly presents with MODS requiring a multidisciplinary approach with

rehydration, blood transfusion, control of secondary infections and dialysis. Dialysis, particularly in kidney affectation is very vital and gives dramatic improvement in treatment outcome. YFI could be fatal in MODS and hepato-renal disease. Large scale vaccination programs and vector eradication are the only means of combating disease. The observance of standard safety measures is also needed to reduce disease transmission.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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