Cerebral Vasospasm, Intracardiac Clot, Wellens Syndrome, and Popliteal Vein Aneurysm in a Hypercoagulable State in Lassa Fever

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Abstract

Background: Lassa fever could precipitate a condition of hypercoagulable state with multiple organ involvement. We report an unusual presentation of cerebral vasospasm, intracardiac clot, Wellens syndrome, and popliteal vein aneurysm in a case of Lassa fever. We demonstrate the use of noninvasive imaging in the diagnosis and management of hypercoagulable state in a first case presentation in Lassa fever. **Methods:** We present a 53-year-old Nigerian woman, with a high-grade fever (39°C) that was associated with chills, headaches, insomnia, anxiety, chest pain, diaphoresis, palpitation, general weakness, muscle aches in all extremities, muscle cramps, dizziness spells, hyperacusis, nausea, vomiting, diarrhea, hematochezia, and abdominal pain. She admitted that her home is infested with rodents. Physical examination revealed severe anemia. Laboratory tests including blood sample analysis and biochemistry were conducted. Lassa fever was confirmed using Lassa virus-reverse transcription-polymerase chain reaction tests. Electrocardiography (ECG), two-dimensional echocardiography, venous duplex ultrasound of the leg veins, and transcranial Doppler ultrasound were performed. **Results:** Blood tests showed electrolyte imbalance and hypertriglyceridemia. Ultrasound tests revealed intracardiac clots with dyskinetic apical septal wall motion abnormality, saccular aneurysm with popliteal venous thrombosis of the right leg popliteal vein, and cerebral vasospasm of the right internal carotid artery due to cardiogenic microemboli. ECG demonstrated Wellens syndrome. The patient was successfully treated with intravenous ribavirin, whole blood transfusion, broad-spectrum antibiotics, isosorbide dinitrate, pentoxifylline, metronidazole, antimalarial, dexamethasone, erythropoietin, anticoagulants (low-molecular-weight heparin and warfarin), and supportive care. **Conclusion:** Noninvasive ultrasound modalities were useful for early detection and treatment of hypercoagulable state in Lassa fever.

Keywords: Blood clots, diarrhea, gastrointestinal bleeding, Lassa fever, Nigeria, stroke

Introduction

Lassa fever is an acute viral hemorrhagic illness that is known to be endemic in various West African countries including Nigeria. Outbreaks of Lassa fever occur annually in the West African region, with a peak period observed between December and June.[1] Lassa fever is caused by the single-stranded RNA Lassa virus (LASV) hosted primarily by Natal multimammate mouse (*Mastomys natalensis*) rats, endemic in West Africa. The transmission of LASV to humans occurs via contact with food or household items contaminated with rodent urine or feces. Person-to-person infections and nosocomial and laboratory transmission can also occur. LASV infects immune cells in the nasopharynx, with subsequent spread to regional lymph nodes followed by multi-organ dissemination. After an incubation period of 1–3 weeks, its clinical course is heterogeneous. The majority of patients experience mild symptoms of malaise, headache, and low-grade fever, but more severe cases can include such diverse manifestations as diarrhea, hematochezia,

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hypotension, and pulmonary edema. Bleeding from the oropharynx or, less commonly, the rectum or genitals is seen in fewer than 20% of patients.[2] The most common neurologic complication of Lassa fever is sensorineural deafness, which has been reported in up to 25% to one-third of patients who survive the illness, although others have suggested that the complications have been overestimated.[2,3] The occurrence of the hearing loss during the convalescent phase of the illness has led some to suggest that it is a result of immune complex reactions to the viral infection.[4] The hearing loss could appear unilateral or bilateral, and resolves spontaneously in about half of cases regardless of the severity of the disease.

Other less common central nervous system (CNS) complications of Lassa fever include ataxia, meningitis, seizures, and coma.[5,6] The most common neuropsychiatric manifestation is depression, but mania and psychosis are described.[7] In severe cases, Lassa fever may present with CNS manifestations, in early[8] and late stages of the disease,[9-12] and is usually associated with bleeding and poor prognosis.[12] LASV has been demonstrated in the cerebrospinal fluid even when it is absent in the serum in patients with CNS involvement.[13]

Thromboembolic complications of Lassa fever are rarely reported. Popliteal vein aneurysms (PVAs) represent a rare form of venous aneurysms and require prompt diagnosis and management because of their well-established risk of pulmonary embolism.[14] Once a massive pulmonary embolism occurs, the outcome can be fatal.[15] Early diagnosis of PVA could be achieved with venous duplex ultrasound, in which intraluminal thrombus could be detected in saccular or fusiform aneurysms, and prompt management must be initiated.[16] Clots could be detected in the cardiac cavities using two-dimensional echocardiography with a sensitivity of 95%, a specificity of 86%, and a predictive value of 72%; the predictive value of a negative study was 98%.[17] The thrombus mass has a homogeneous, grainy consistency similar to the normal myocardium.

To the best of our knowledge, there has not been a report of stroke resulting from cerebral vasospasm due to cardiogenic microembolization in Lassa fever. We present the first case management of Lassa fever that implemented diagnostic imaging tools for early detection of blood clots in the left ventricle, Wellens syndrome, cerebral vasospasm of brain arteries, as well as deep venous thrombosis with PVA but without pulmonary embolism. The patient was successfully treated with ribavirin to seroconversion from positive to negative on reverse transcription-polymerase chain reaction (RT-PCR) tests.

Methods

Case presentation

We demonstrate an approach to diagnosis and management of hypercoagulable state in Lassa fever. We examined a 53-year-old Nigerian woman, resident in Owerri Municipal Local Government Area, Imo State, Nigeria, who presented to our outpatient department on September 28, 2021, with a 5-day history of high-grade fever (39°C) that was associated with chills, headaches, insomnia, anxiety, chest pain, diaphoresis, palpitation, general weakness, muscle aches in all extremities, muscle cramps, dizziness spells, hyperacusis, nausea, vomiting, diarrhea, hematochezia, and abdominal pain. There was no history of sore throat or mucosal bleeding. She had been previously treated with antimalarial and pain-relieving drugs but did not get better. She denied any recent contact with a confirmed case of Lassa fever but admitted that her home is infested with rodents. Physical examination revealed paleness of palm and scleral icterus. There was no lymphadenopathy or meningeal irritation. During the physical examination, a soft mobile mass was palpated in the right popliteal fossa in the right leg. Her axillary temperature was 39°C. The blood pressure was 105/69 mmHg and the heart rate was 89 bpm. The respiratory rate was 24 cycles/min. The body mass index was 36.262. Laboratory tests including blood sample analysis and biochemistry were conducted. Twelve-lead electrocardiography (ECG) was performed. Two-dimensional echocardiography was performed using a wide-angle, phased array sector scanner Philips Agilent HP M2424A Sonos 5500 (Hewlett-Packard, Andover, Massachusetts), with multifrequency S4 transducer. Ultrasonographic examination of the leg veins was performed using the same ultrasound equipment. The common femoral vein was identified by lack of pulsatility, compressibility with minimal pressure, and an increase in vein lumen size induced by the Valsalva maneuver. Color flow Doppler examination was performed with the 3.5 MHz Doppler mode of the multifrequency S4 transducer to identify each deep vein of the leg including the common femoral, superficial femoral, deep femoral, popliteal, and anterior and posterior tibial veins. Transcranial Doppler (TCD) ultrasound was performed with the 1.8 MHz Doppler mode of the multifrequency S4 transducer of the same ultrasound equipment. The cerebral blood flow velocities in the major basal cerebral arteries of the circle of Willis were measured in supine horizontal position.

TCD provides a rapid, noninvasive, real-time measurement of cerebral blood flow velocities in the major intracranial arteries.[18,19] The temporal acoustic windows on the left and right temporal bones were used for ipsilateral insonation of the arteries of the circle of Willis on the left and right sides, respectively. The extracranial arteries were examined using the 7.5 MHz mode of the same S4 probe to demonstrate B-mode and Doppler flow velocities in the common carotid artery, internal carotid artery (ICA), and external carotid artery on the right and left sides, respectively.

Chidicon Medical Center team comprising Medical, Nursing care, Laboratory services, Epidemiology Unit of the Imo State Ministry of Health, National Reference Laboratory GADUWA Abuja, Virology Centre Laboratory Federal Teaching Hospital Abakaliki, were all participants in the diagnosis and supervision of management of the patient. The patient was placed in the isolation unit from the time of admission to discharge. Barrier

nursing was instituted throughout the course of treatment. Contact tracing of all relatives and persons living with the patient was initiated by the Epidemiology Unit of the Imo State Ministry of Health, Owerri. Epidemiologic control of rodents around the home of the patient and hospital environment was instituted according to the usual protocol under the supervision of the Epidemiology Unit of the Imo State Ministry of Health, Owerri. Blood samples collected from all medical and nursing staff, as well as all close contacts of the patient, were tested for LASV-RT-PCR. The Institutional Review Board approved the protocol.

Results

Blood sample analysis revealed hematocrit (HCT) of 23.7%, hemoglobin (Hb) of 7.9 g/dL, white blood cell count (WBC) of 10,000/mm^3, erythrocyte sedimentation rate (ESR) of 45 mm/h, clotting time (CT) of 7 min, platelet count of 230,000/mm^3, prothrombin time (PTT) of 21 s. Malaria parasites were seen in blood. There was electrolyte imbalance showing hypernatremia (sodium = 190 meq/L); potassium level was normal (4.7 meq/L). There was raised level of chloride (110 meq/L). There was hypercalcemia (calcium = 11 mg/dL). Similarly, there was hypermagnesemia (magnesium level = 2.7 mg/dL). The uric acid level was normal (6.2 mg/dL). The urea level was normal (35 mg/dL). Serology tests including hepatitis B antigen, hepatitis C antigen, and HIV test were negative. The carcinoembryonic antigen test was normal (1.82 ng/mL). The liver function enzymes: aspartate aminotransferase (7 IU/L) and alanine aminotransferase (9 IU/L) were within normal range. There was hyperbilirubinemia, the total bilirubin was raised to 1.5 mg/dL, and conjugated bilirubin was raised to 0.9 mg/dL. Lipid profile: total cholesterol (150 mg/dL), and low-density lipoprotein (LDL) (68 mg/dL) were within normal range. The high-density lipoprotein was low (31 mg/dL). The triglycerides were raised (255 mg/dL), along with raised very LDL (51 mg/dL). Urinalysis revealed urinary tract infection showing WBCs at 2–3/HPF, bacteria (cocci) present, and epithelial cells were numerous. ECG revealed a ventricular heart rate of 88 bpm, but an atrial rate at 500 bpm in lead V4, indicating paroxysmal atrial fibrillation (PAF) [Figure 1, top panel shows P-waves with three small arrowheads in lead V4]. There was deep symmetrical T-wave inversion in leads V1, V2, and V3, respectively, suggestive of Wellens syndrome Type B on admission [Figure 1, top panel shows inverted T-waves in leads V1, V2, and V3]. In the posttreatment period after 7 weeks, the ECG showed an evolution with reversal to upright T-wave in lead V3 [Figure 1, bottom panel arrow, upright T-wave in lead V3]. However, T-wave remained inverted in leads V1 and V2 [Figure 1, bottom panel arrowheads on inverted T-waves in leads V1 and V2], which were considered as normal variants in the absence of T-wave inversion in V3.

The two-dimensional echocardiography (2D echo) in parasternal long-axis, short-axis, apical two-chamber and four-chamber views was obtained. 2D echo identified thrombus as a distinct mass of echoes in the left ventricular cavity that was contiguous

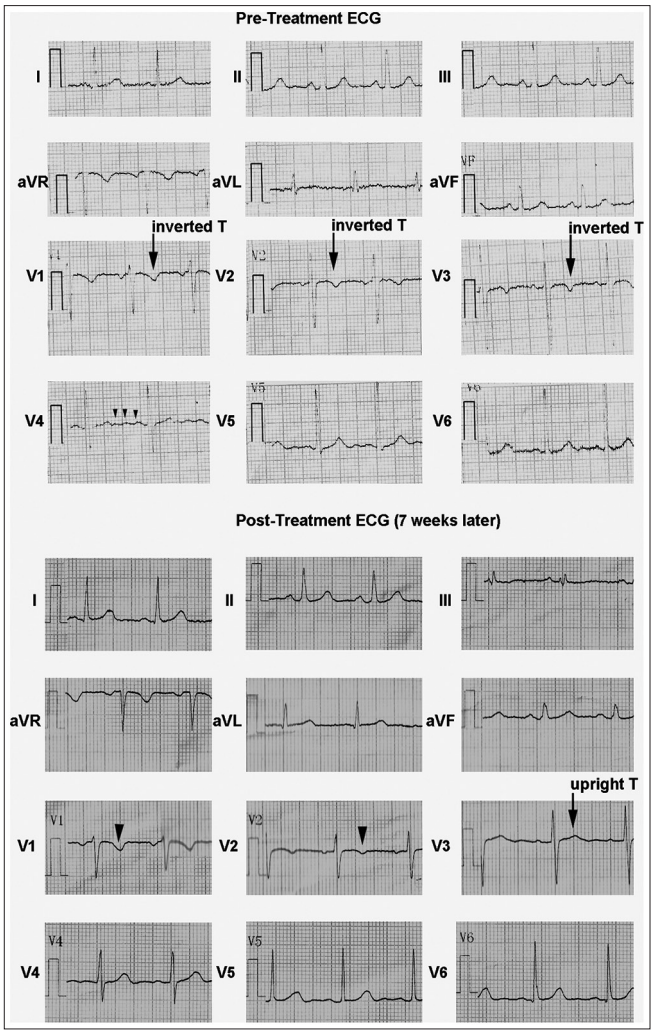

Figure 1: Electrocardiography in pre-treatment (top panel) and post-treatment (bottom panel)

with the endocardium in an area of abnormal wall motion of dyskinesia present throughout the cardiac cycle in at least two different echocardiographic views. Figure 2a-d shows the 2D echo in several views. In the pretreatment test, the long-axis view showed a clot of size 1.05 cm × 1.51 cm on the apical septal wall [Figure 2a, small arrows]. The end-diastolic volume was 38.7 mL, and the posterior wall thickness was 1.47 cm; the systolic volume was 16 mL, and the posterior wall thickness was 1.6 cm. There was dyskinetic wall motion abnormality of the apical septal wall. The ejection fraction was reduced to 58.7%. In posttreatment control 2D echo, there was no clot in the same area [Figure 2b, arrow]. The end-diastolic volume was 24.7 mL, and the posterior wall thickness was 1.29 cm; the systolic volume was 9.22 mL, and the systolic posterior wall thickness was 1.47 cm. There was normal wall motion, and the ejection fraction was raised to 62.7%. In pretreatment test, in apical cross-sectional view [Figure 2c, arrow], the same clot measured 1.11 cm × 1.17 cm. However, in the posttreatment control 2D echo, in the apical cross-sectional view [Figure 2d, arrow], there was no clot in the same area.

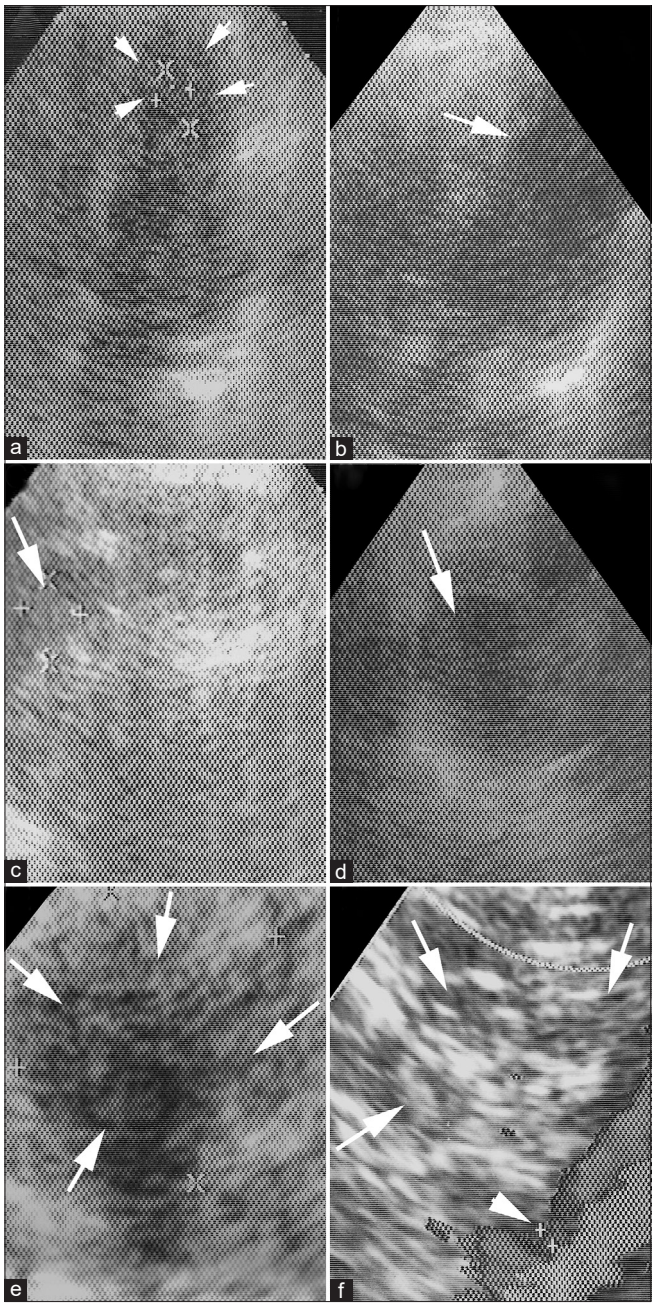

Figure 2: Echocardiography showing views in pre-treatment long-axis (a) and short-axis (c); post-treatment long-axis (b) and short-axis (d). Duplex venous ultrasound of the popliteal deep vein aneurysm (e) showing occlusive thrombus (f)

Duplex venous ultrasound of the leg veins revealed a saccular dilation in the right popliteal vein measuring 2.16 cm × 1.84 cm, with intraluminal thrombus [Figure 2e, arrows]. Despite the compression by thrombus of the underlying main trunk of the popliteal vein, there is evidence of recanalization of the vein [Figure 2f, arrowhead] on color flow Doppler mapping.

Pretreatment TCD [Figure 3] showed a raised mean flow velocity (MFV) to 118 cm/s, the pulsatility index (PI) was 0.851, and the Lindegaard ratio was 3, suggestive of probable vasospasm of the right ICA (RICA). The MFV in the right

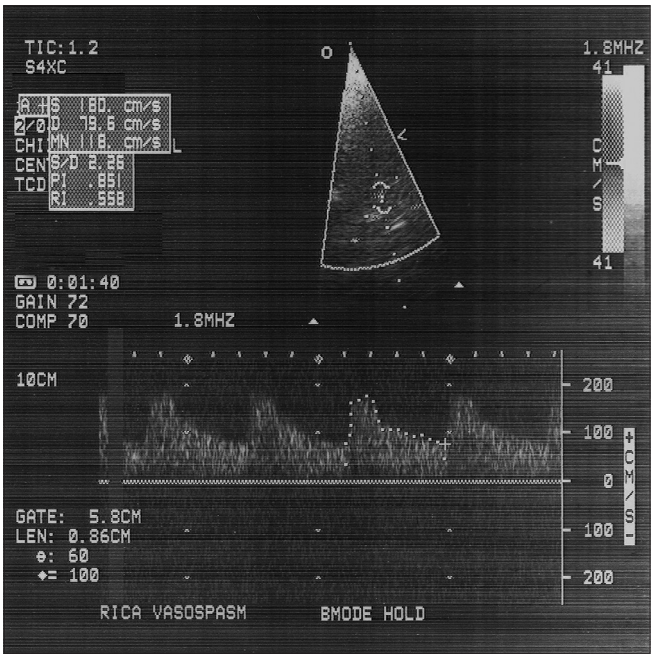

Figure 3: Transcranial Doppler flow waveform showing right internal carotid artery vasospasm

middle cerebral artery was raised at 90 cm/s, the PI was normal at 0.946, and the Lindegaard ratio was <3, suggestive of hyperemia. The MFV in other intracranial arteries was within the normal range. In the posttreatment test, MFV was within the normal range in all major intracranial arteries. However, in the posttreatment period, there was increased difficulty to use the left temporal window on the temporal bone for insonation, rather flow velocities in the left intracranial arteries were measured through the right temporal window, and showed normalized levels. The difficulty with left temporal bone insonation was due to ossification of the temporal bone as a result of treatment with ribavirin which changes bone mineral density.[20] The extracranial arteries were examined using carotid duplex ultrasound and demonstrated mild-to-moderate carotid wall intimal thickening on both sides.

The patient in the course of treatment developed rapidly evolving DIC with massive bleeding, HCT was 26.4%, Hb was 8.8 g/dL, WBC was 6000, ESR was 42 mm/h, CT was 9 min, platelet count was 30,000/mm^3, and PTT was 31 s. The diagnosis of Lassa fever was confirmed using LASV-RT-PCR tests. The treatment included intravenous fluids at maintenance rate, intravenous ribavirin given by the McCormick regimen,[21] whole blood transfusion, broad-spectrum antibiotics, isosorbide dinitrate, pentoxifylline, metronidazole, antimalarial, dexamethasone, erythropoietin, anticoagulants (low-molecular-weight heparin and warfarin), and supportive care. The latter include monitoring of vital signs, correction for fluid and electrolyte imbalance, cardiovascular support with bolus doses of intravenous fluids, and maintenance of fluid balance. The patient had seroconversion to a negative test result for LASV-RT-PCR after 2 weeks of treatment. All medical and nursing staff,

as well as close contacts of the patient, tested negative on LASV-RT-PCR tests.

Discussion

The main unusual observations of hypercoagulable state in this case of Lassa fever include (1) intracardiac clots with dyskinetic apical septal wall motion abnormality; (2) Wellens syndrome diagnosed by standard criteria including history of anginal chest pain, no significant ST-segment elevation (<1 mm), no pathological precordial Q-waves, no loss of precordial R-wave progression, and deep (Type B) inverted T-waves mainly in leads V2 and V3. Wellens syndrome has been associated with critical proximal left anterior descending coronary artery stenosis; (3) saccular aneurysm of popliteal venous thrombosis of the right leg popliteal vein; and (4) cerebral vasospasm of the RICA due to cardiogenic microemboli predisposing the patient to a stroke.[22-24] The clinical presentations of the patient were indicative of a hypercoagulable state with multiple organ involvement.

The presentation of bleeding suggested that the LASV affected homeostasis and led to thrombohemorrhagic complications such as DIC. DIC is an acquired consumptive coagulopathy in which the hemostatic system is activated, resulting in the activation of platelets and the conversion of fibrinogen to fibrin.[25] Complications may develop from generalized microvascular thrombosis, multi-organ failure, and life-threatening hemorrhage due to consumption of coagulation factors and activation of the fibrinolytic system. There was evidence of activation of coagulation caused by the presence of LASV and probably the release of cytokines that mediate the process. It has been suggested that hemorrhagic fevers caused by dengue, Marburg, Ebola, Hantaan, and LASV have the ability to infect endothelial cells by inducing tissue factor (TF) expression.[26] The endothelial injury by LASV may lead to increased adherence and consumption of platelets.[27]

The chest pain could be indicative of cardiac ischemia caused by microemboli entering into the coronary circulation. Patients with chronic AF in hypercoagulable state are at high risk of stroke and heart attacks. Furthermore, the patient showed ECG signs of Wellens syndrome which is a preinfarction stage of coronary artery disease and heralds an impending extensive myocardial infarction of the anterior wall.[28,29] It presents the typical anginal chest pain, characteristic ECG changes that usually occur after chest pain has resolved, and negative cardiac biomarkers.[30] Wellens' syndrome is relatively rare, and if left untreated, the patient could be at a significant risk of severe myocardial infarction and death.[29-31] The ECG showed the presence of PAF which may suggest enhanced platelet aggregation and coagulation, depending on the duration of atrial fibrillation.[32] The patient was treated with isosorbide dinitrate and anticoagulants which relieved the clinical symptoms. In the posttreatment phase, when the symptoms were relieved, there was evolution of the ECG signs to upright T-wave in lead V3. However, 7 weeks after treatment, inverted T-waves remained in leads V1 and V2 without symptoms, and hence may suggest a normal variant.[28-31] The symptoms of pains in both legs have not fully resolved, especially in the right leg with PVA. The patient chose to continue treatment with medications and declined the option of surgery for PVA.

Cerebral vasospasm of the RICA indexed by TCD ultrasound measurements was demonstrated in the patient. Vasospasm is the narrowing of intracranial arteries, which can lead to hypoperfusion, delayed ischemic deficits, and stroke. TCD ultrasound could monitor microembolic signals and provide prognostic value for monitoring symptomatic cerebrovascular disease. The observation of cerebral vasospasm in the patient was associated with microemboli from the cardiogenic thrombus. Other sources of microemboli include deep venous thrombosis with the PVA in the right leg. Microembolic signals within the intracranial arteries could predict recurrent strokes caused by intracranial artery-to-artery embolization.[22,23] The difficulty with insonation through the left temporal acoustic window in the posttreatment period may be associated with increased bone mass and normalized bone turnover of the temporal bone, as has been observed in patients who respond to antiviral therapy with ribavirin.[20] The latter process appears to affect some bone sites more than the others.

Cerebral vasospasm and stroke are not frequently reported sequelae of Lassa fever. However, there is growing attention of the disruption of homeostasis in Lassa fever. LASV has a direct effect on vascular permeability, but the pathophysiology is poorly understood. The present case demonstrated obvious gross signs of endotheliopathy and vascular leakage pointing to changes in homeostasis. Although we did not measure the markers of endothelial activation and injury, others have shown that there is disruption of the protein C pathway and endothelial stress in severe cases of Lassa fever.[33] The investigators demonstrated that P-selectin, soluble endothelial protein C receptor, soluble thrombomodulin, plasminogen activator inhibitor 1, ADAMTS-13, von Willebrand factor, TF, soluble intercellular adhesion molecule 1, and vascular cell adhesion molecule 1 were more elevated in Lassa fever than in controls.[33] Similarly, endothelial protein C receptor, thrombomodulin, intercellular adhesion molecule 1, plasminogen activator inhibitor 1, D-dimer, and hepatocyte growth factor were higher in severe cases of Lassa fever. The impaired homeostasis and platelet dysfunction implicate alterations in the protein C pathway, which might contribute to the loss of endothelial barrier function in fatal Lassa fever infections.[33]

Conclusion

In the light of the present COVID-19 pandemic, hypercoagulable states have become an important hallmark of viral infections including Lassa fever. This calls for new approaches to diagnosis and treatment by family practice physicians. The present case demonstrated that the use of noninvasive ultrasound imaging modalities was crucial to early diagnosis of potentially fatal

complications resulting from hypercoagulable state in Lassa fever. The management protocol for hypercoagulable state associated with multi-organ involvement including cerebral vasospasm, coronary ischemia, and deep vein thrombosis reported here for the first time in literature would require further multicenter study in a cohort of patients with Lassa fever. Clinicians and investigators should deploy imaging modalities in early management of Lassa fever for proper diagnosis and treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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