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Case Report

Diagnosis with Hemoglobin SC Disease at Age 52 After Acute Stroke and Cardiac Arrest

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Abstract

A 52-year-old male, with no prior medical history developed status epilepticus followed by cardiac arrest with pulseless electrical activity (PEA) while at the airport returning to his home country in West Africa. He received cardiopulmonary resuscitation (CPR) and was intubated at the airport. He was found to have had a stroke and pneumonia. The peripheral blood smear demonstrated no schistocytes, but rather a few sickle cells, hemoglobin C crystals, and abundant target cells consistent with hemoglobin SC (HbSC) disease. Hemoglobin electrophoresis (HbEP) confirmed HbSC disease. Urgent red blood cell (RBC) exchange was initiated for a goal Hb S+C of <30 %. With complete neurologic recovery, he was extubated two days after the exchange transfusion and was discharged from the hospital five days after extubation. Our case is among the few reported cases of HbSC disease diagnosed as late in life as 52-years.

ABBREVIATIONS

PEA: Pulseless Electrical Activity; **CPR**: Cardiopulmonary Resuscitation; **HbSC**: Hemoglobin SC; **HbEP**: Hemoglobin electrophoresis; **RBC**: Red Blood Cell; **ICU**: Intensive Care Unit; **CXR**: Chest X-ray; **CT**: Computed Tomography; **WBC**: White Blood Cell Count; **LDH**: Lactate Dehydrogenase; **Tpn I**: troponin I; **MRI**: Magnetic Resonance Imaging; **EEG**: Electroencephalogram; **CVA**: Cerebro Vascular Accident; **TTE**: Transthoracic echocardiogram; **TTP**: Thrombotic Thrombocytopenic Purpura; **TPE**: Total Plasma Exchange; **MRA**: Magnetic Resonance Angiography; **MCA**: Middle Cerebral Artery; **HbSS**: Hemoglobin SS disease; **HbS**: Hemoglobin S; **HbC**: Hemoglobin C

CASE PRESENTATION

A 52-year-old male, with no prior medical history developed status epilepticus followed by cardiac arrest with pulseless electrical activity (PEA) while at the airport returning to his home country in West Africa. His connection flight had just landed and he was scheduled to board the next flight prior to the event. He received cardiopulmonary resuscitation (CPR), one round of epinephrine, and was intubated at the airport. He was transferred to an intensive care unit (ICU) of a nearby hospital (hospital day 1), and his chest X-ray (CXR) showed airspace opacity of the left lung base consistent with pneumonia. Subtle, diffusely increased density of the skeleton was noted consistent with generalized osteosclerosis (Figure 1A). Coronal enhanced chest computed tomography (CT) confirmed the consolidation in the left lower lobe and revealed a small, calcified spleen (Figure 1B). Leukocytosis was noted with white blood cell count (WBC) 23.6 K/UL. Anemia (hemoglobin 11.3 g/dL) was noted; platelets were 143,000 per cubic mm (range 133-450k). Lactate dehydrogenase (LDH) was elevated at 497 IU/L (range 98-192). Sepsis was suspected and broad-spectrum intravenous antibiotics, Vancomycin and Piperacillin/tazobactam, were initiated. He remained intubated and unresponsive. Acute renal insufficiency with a creatinine of 1.8 mg/dl was noted. The troponin I (Tpn I) was elevated at 5.81 µg/L. Non-contrast CT of the brain was negative for stroke (Figure. 2). However, the patient was too unstable to be sent for magnetic resonance imaging (MRI). His electroencephalogram (EEG) was negative for any ongoing seizure activity. There was also transaminitis (AST 80 IU/L and ALT 108 IU/L) with coagulopathy (INR 4.59, PT 42.9) but no bleeding or bruising. Metabolic acidosis with a pH of 7.21 and bicarbonate of 20 were noted. The morning following admission platelets declined to 113,000 per cubic mm.

Due to the seizures and unresponsiveness, neurology was consulted. CVA was not suspected based on a negative CT brain. It was questioned whether the initial seizures were triggered

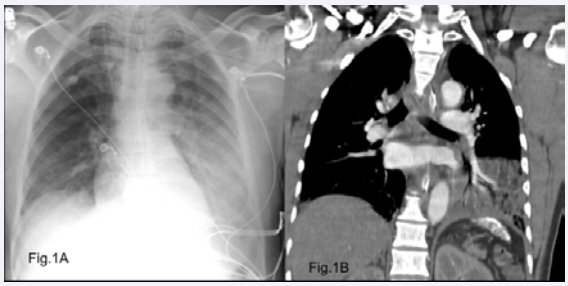

Figure 1 (A) Chest X-Ray shows airspace opacity of the left lung base obscuring the left hemi-diaphragm without volume loss compatible with pneumonia. Subtle diffusely increased density of the skeleton is consistent with generalized osteosclerosis.

(B) Coronal enhanced chest CT confirms the consolidation in the left lower lobe as well as a small, calcified spleen.

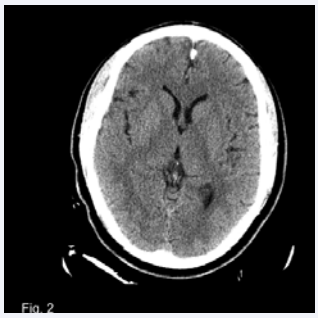

Figure 2 Axial unenhanced CT image of the brain shows no evidence of stroke.

by a cardiac event or whether the PEA arrest was triggered by seizures; EEG was negative for ongoing seizure activity. Brain MRI was recommended once the patient was stabilized. Because of the cardiac event and a Tpn I elevation of 5.81 µg/L, cardiology was consulted. EKG revealed sinus rhythm, incomplete right bundle branch block without acute ST elevation. Transthoracic echocardiogram (TTE) was normal with an ejection fraction of 65%. The Tpn I elevation was assessed to be related to CPR. A nuclear stress test was recommended once the patient was stable. Fasting lipids were: total cholesterol 135, triglycerides 191, high-density lipoprotein 21, low- density lipoprotein, 76. Statins and angiotensin-converting-enzyme inhibitors were avoided due to hepatic and renal impairment. Notably, the INR normalized without treatment.

Given seizures at initial presentation, persistent unresponsiveness, thrombocytopenia, and 1-3 schistocytes/hpf reported by automated analyzer, hematology was consulted on hospital day 4, at which point platelets had declined to 98 K. Out of concern for possible thrombotic thrombocytopenic purpura (TTP), an urgent transfer to our institution for total plasma exchange (TPE) was recommended. Upon arrival to our institution, his platelets were noted to be 119K, and his peripheral blood smear was reviewed demonstrating no schistocytes, but rather a few sickle cells, hemoglobin C crystals, and abundant target cells consistent with HbSC disease (Figure. 3). Hemoglobin electrophoresis (HbEP) confirmed HbSC disease, with hemoglobin C level 44.6% and hemoglobin S of 51.5%. Brain MRI (Figure. 4A-4C) was then performed revealing late acute or early sub-acute infarct within the genu of the right internal capsule of the basal ganglia. In light of these findings -- recent stroke, chest consolidation signifying acute chest syndrome and multi-organ failure -- urgent RBC exchange was initiated for a goal Hb S+C of < 30 %. Thirteen Rh and Kell phenomatched RBC units were used as replacement fluid. Twelve hours after completing the RBC exchange procedure, hemoglobin electrophoresis revealed the presence of 11.2% of hemoglobin S, 9.6% of hemoglobin C, and 75.8% of hemoglobin A. Of note, the family was later interviewed and reported that the patient was previously healthy with no personal or family history of hemoglobinopathy.

After completing the RBC exchange transfusion, the patient underwent bronchoscopy with bronchioalveolar lavage confirming pan-sensitive pseudomonal pneumonia and appropriate IV antibiotics were administered. He was extubated two days after the RBC exchange transfusion. Once extubated, the patient reported recalling the moments leading up to his seizure and cardiac arrest event as “feeling dizzy” and then “falling”, but there was no recollection of any antecedent chest pain, shortness of breath, diaphoresis, palpitations, or nausea. Although the patient appeared to be neurologically recovered without any focal weakness, he reported a new hearing loss in the right ear.

Neurology was reconsulted regarding the hearing loss with right internal capsular stroke, which appeared sub-acute on MRI. Magnetic resonance angiography (MRA) revealed left middle cerebral artery (MCA) M1 moderate stenosis; however, because the stroke was on the right, the neurology team considered this stenosis as asymptomatic. The etiology of the stroke was assessed to be secondary to sickle cell disease, small vessel disease or possibly a complication of CPR. The recommendations were continuation of leveteracetam, aspirin, statin, and referral to otolaryngology for audiology assessment.

Because of persistent mild elevation of troponin I (declined to 0.18) cardiology was again consulted. The cardiac enzyme elevation was assessed to be secondary to the CPR. To further assess the PEA arrest, a nuclear (Tc-99m) adenosine stress test and myocardial perfusion study was performed, demonstrating normal hemodynamics and normal electrocardiogram.

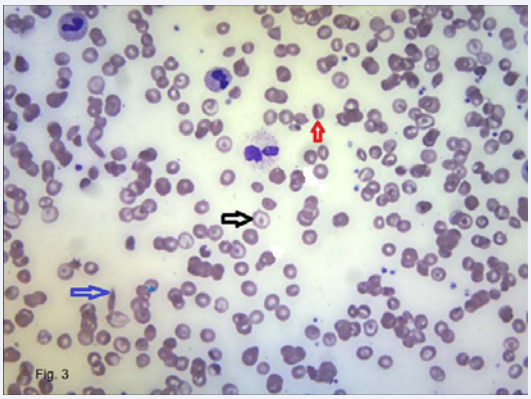

Figure 3 Blood smear showing changes associated with hemoglobin SC disease including numerous target cells, folded RBCs (so called taco cells), and crystal formation resembling the Washington monument (*Wright stain*). Target cell: Black arrow. Taco cell: Red arrow. Washington monument: Blue arrow.

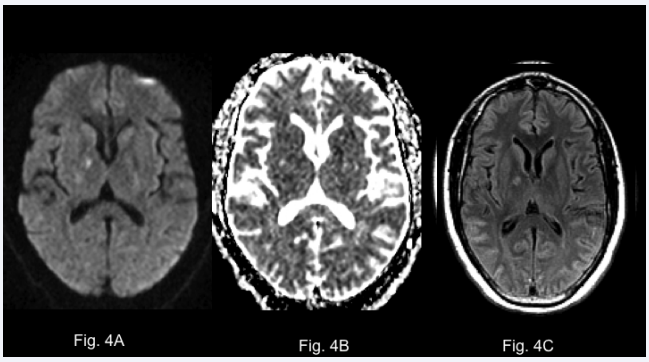

Figure 4 (A) Axial diffusion weighted MR image shows an ill-defined region of high signal in the right posterior limb of the internal capsule.

(B) The corresponding apparent diffusion coefficients (ADC) map shows subtle decreased signal in the same distribution, confirming the presence of restricted diffusion, compatible with acute infarct.

(C) Axial FLAIR MR Image shows associated abnormal T2 signal.

The patient was discharged from the hospital five days after extubation. His creatinine had normalized and the LFT's were nearly normal (aspartate aminotransferase 41/ IU/L, alanine transaminase 49 IU/L) before discharge. He was discharged home with prescriptions for beta blocker, statin, folic acid, and aspirin.

Occurring only two days after the RBC exchange transfusion procedure, this patient's neurologic recovery was remarkable. The rapid resolution of neurologic symptoms was a consequence of timely recognition and treatment of complications of HbSC disease, demonstrating the importance of prompt and accurate diagnosis.

DISCUSSION

After getting off of a plane, the patient suffered cardiac arrest and seizures in the context of sepsis: pneumonia, leukocytosis, metabolic acidosis, and multiorgan failure. Such events in a 52-year-old male should raise concern for underlying coronary artery disease leading to cardiac arrest, possibly secondary to seizures versus seizures as a consequence of a cerebrovascular accident (CVA) subsequent to the cardiac event. A complete cardiac and neurologic workup, including fasting lipids, serial troponins, and EEG is mandatory. MRI is needed when feasible to assess the etiology of seizures and to detect other cerebral perfusion abnormalities not seen on non-contrast CT, such as the subacute phase of stroke. Sepsis and pneumonia should raise suspicion for an underlying immune deficit, especially given the atrophic spleen on imaging. Furthermore, given that the patient is from West Africa, a hemoglobinopathy is a reasonable concern in view of sclerotic bones noted on imaging.

A prompt hematology consultation was warranted, given that TTP is part of the differential diagnosis in the setting of renal impairment, neurologic symptoms, thrombocytopenia, elevated LDH, and possible schistocytes. However, relying on reports of schistocytes from the automated analyzer, rather than direct microscopic visualization, can lead to premature and misguided clinical decisions. This patient's onset of acute seizures, cardiac arrest, stroke, and multi-organ failure after landing from an airplane demonstrates how altitudes can increase the risk of vaso-occlusive sickle cell crisis episodes and should trigger the clinician to think of a hemoglobinopathy in a patient from West Africa, even if the family denies a prior history [1].

HbSC disease is the second most prevalent hemoglobinopathy after hemoglobin SS disease (HbSS) [2]. While in West Africa it affects up to 25% of populations in some areas, in the US, its frequency is estimated at 1:833 births [3]. It is a distinct entity from HbSS disease, with frequent viscosity-associated complications including otological and ophthalmological disorders, as well as potentially catastrophic vaso-occlusive events including strokes, cardiopulmonary, and renal complications[4,5]. Ocular lesions, thromboembolic events, and renal papillary necrosis have been reported more frequently in HbSC than HbSS disease, and it has been speculated that this is due to the higher Hb and hematocrit levels [3]. The patient described in this case report had unilateral hearing loss after the acute event. Sensorineural hearing loss and/or vestibular disorders are quite common, occurring in 56% of patients with HbSC disease who are over 40 years old, with hearing loss occurring in 39% [4]. Functional asplenia is frequent in many patients with HbSC disease and occurs in 45% of those older than 12 years of age [6]. Splenic infarction and fibrosis with HbSC disease is well described in the literature, often following splenic enlargement or rupture [7,8].

Rates of CVA have been reported to be similar to HbSS disease in a study [3]; however, in another study, it is reported as much less frequent [4]. The 2010 American Society for Apheresis outlines stroke as Category I indication for RBC exchange whereas multi-organ failure is listed as a Category III (controversial) indication for RBC exchange [9]. Maintaining HbS <30% with exchange transfusion is recommended for prevention of primary and secondary stroke. RBC exchange is being used more frequently for severe acute complications of sickle cell diseases and has been shown to be effective in a variety of clinical situations. Compared to simple transfusion, both manual and automated types of RBC exchange transfusion are more effective in preventing subsequent stroke [9].

Vaso-occlusive crisis, aplastic crisis, sepsis, acute chest syndrome, stroke, and multi-organ failure are some of the causes of morbidity and mortality in sickle cell disorders. If indicated, RBC transfusion, either simple or exchange transfusion, is critical to manage some of these acute and chronic complications of sickle cell disorders [9].

HbSC disease often has a later-onset symptomatology with less frequent illness and anemia than HbSS disease [4,10]. Patients typically have mild anemia, mild hemolysis, and 50% fewer acute pain episodes [3]. Moreover, complications such as retinopathy, acute chest syndrome, and osteonecrosis can occur at equal or higher rates in HbSC disease[11]. This paradox of mild anemia with the potential for severe complications and hypercoagulability is due to the combination of hemoglobin S (HbS) and hemoglobin C (HbC) with interplay of increased activity of K:Cl cotransport and loss of intracellular water [11]. By dehydrating the SC red blood cell, hemoglobin C enhances the pathogenic properties of hemoglobin S, allowing for lower levels to polymerize rapidly [11].

While Lionnet et al reported delayed diagnosis after age 18 in 29% of their HbSC patients [4], it is extremely rare to be diagnosed after age 50 [10,12]. Our case is among only a few diagnosed as late in life as age 52. Ballas et al described a late presentation at age 52, however, the diagnosis was made post-mortem after a fatal pulmonary embolism [10]. Lionnet et al reported diagnosis at age 68[4] while Conley et al reported diagnosis at age 75 [13,14]. As a doubly heterozygous hemoglobinopathy, resulting from inheritance of HbS from one parent and HbC the other, diagnosis of HbSC disease is straight forward with HbEP revealing 50% HbS and 50% HbC [5]. Peripheral blood findings also provide helpful hints towards the diagnosis.

Phlebotomy has been proposed as a potential treatment for preventing vaso-occlusive events in HbSC disease, warranting further investigation. Lionnet et al reported that when phlebotomy was administered to 64 patients, it effectively prevented recurrence of acute events in 71% of those patients [4]. The patients had baseline hemoglobin of approximately 11.5 g/dL [4]. Multiple other case reports in the literature have also supported the preventative role of phlebotomy in HbSC disease [4,15-17].

Such late presentations of HbSC disease may be challenging for clinicians to recognize, underscoring the need to rule out sickle cell disease in patients at risk who present with potential hemoglobinopathy-associated complications. This case also demonstrates the pitfalls of relying on reports of schistocytes from the automated analyzer, to guide clinical decisions rather than first-hand visualization under the microscope. There were signs of hemoglobinopathy present at initial presentation at the outside hospital: sclerotic bones and calcified atrophic spleen- both of which could have raised suspicion early on for a hemoglobinopathy given the acute events occurring after airplane travel. We hope this case raises awareness of late onset manifestations and life-threatening complications of HbSC disease.

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