Postmortem Diagnosis of Hemoglobin SC Disease Complicated by Fat Embolism*

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ABSTRACT

A case is reported of a previously healthy 52-year-old African American male who presented with acute onset of abdominal pain. Progressive increase in his abdominal symptoms led to an exploratory laparotomy; however, no pathology was discovered. Postoperatively, the patient became hypoxemic which progressed to diffuse infiltrates on chest x-ray, suggestive of adult respiratory distress syndrome. He had a rapidly fatal course. Autopsy showed bone marrow infarction, fat embolism, splenomegaly, and widespread congestion with sickle erythrocytes. Hemoglobin electrophoresis done postmortem showed hemoglobin (Hb) SC disease that was undiagnosed antemortem. To the best of our knowledge, it is unusual for Hb SC to be diagnosed postmortem in adults. This case suggests that sickle cell disorders should be ruled out in patients at risk for hemoglobinopathy in the presence of signs and symptoms compatible with the disease, irrespective of age.

Introduction

Hemoglobin SC disease (Hb SC) is a compound heterozygosity that results from the inheritance of the Hb S gene from one parent and the Hb C gene from the other parent leading to the synthesis of both Hb S and Hb C in nearly equal amounts. The estimated incidence of Hb SC disease in African Americans is 1 per 833 live births compared to 1 per 625 live births within those who are affected with sickle cell anemia (SS).1 The prevalence of the Hb C trait in African Americans is about 2.3 percent,2,3 whereas in West Africa it is as high as 25 percent in some regions.4

Although Hb SC disease and SS share some similarities, there are distinct differences between the two entities.5,6 The extent of

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the anemia and the frequency of acute painful episodes are milder in Hb SC disease than in SS. Retinopathy and thromboembolic complications, however, seem to be more common in Hb SC disease than in SS. With few exceptions, the patients with Hb SC disease and fatal fat embolism described in the literature had a morbid antemortem clinical picture. The exception, to the best of our knowledge, include: (1) sudden death of a previously healthy young man owing to fat embolism, and (2) massive fat and necrotic marrow embolization in a previously undiagnosed 37-year-old woman whose death followed an anaphylactic reaction to intramuscular injection of iron.

In this report a previously healthy 52-year-old patient is described who had fatal fat embolism which was a complication of Hb SC disease that was diagnosed postmortem. Review of the literature showed no previous reports of patients where Hb SC disease was diagnosed postmortem in a quinquagenerian.

Case Report

The patient was a 52-year-old African American male previously in good health who presented to the Emergency Room complaining of sudden onset of severe abdominal pain which had begun early that morning. The pain was primarily located in the periumbilical region and the right lower quadrant. The pain was constant, sharp, stabbing, and excruciating in nature with no radiations. There was no history of fever, chills, nausea, vomiting, chest pain, shortness of breath, urinary symptoms, diarrhea, constipation, or alcohol consumption. His past history was significant for sudden loss of vision in the left eye one week prior to admission, but no definite diagnosis was made. He also had a history of limping with occasional weakness of his left lower extremity. There was no history of hypertension, diabetes mellitus, coronary artery disease, hemoglobinopathy, coagulopathy, smoking, or use of illicit drugs. He worked in a print shop.

Physical examination revealed an alert and oriented 52-year-old African American male, uncomfortable and writhing in pain. The vital signs were stable (see table I, day 1). There was mild scleral icterus. Examination of the abdomen revealed hypoactive bowel sounds, periumbilical and right lower quadrant tenderness without any guarding or rebound. Liver span was 7 cm at the mid-clavicular line. The rest of the physical exam was unremarkable. Laboratory data are summarized in table I and are significant for mild anemia, elevated bilirubin, and normal serum amylase and lipase.

### TABLE I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td>36.5</td>
<td>39.7</td>
<td>ND</td>
</tr>
<tr>
<td>Pulse</td>
<td>69</td>
<td>154</td>
<td>ND</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>24</td>
<td>32</td>
<td>ND</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>135/78</td>
<td>114/63</td>
<td>86/50</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>11.9</td>
<td>10.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Hct, %</td>
<td>35.8</td>
<td>31.1</td>
<td>36.6</td>
</tr>
<tr>
<td>MCV, fL</td>
<td>91</td>
<td>90</td>
<td>91</td>
</tr>
<tr>
<td>WBC, 10^9/ul</td>
<td>10.2</td>
<td>14.9</td>
<td>15.8</td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td>82</td>
<td>46</td>
<td>ND</td>
</tr>
<tr>
<td>NRBC, per 100 WBC</td>
<td>0</td>
<td>16</td>
<td>ND</td>
</tr>
<tr>
<td>Platelet count, 10^9/ul</td>
<td>306</td>
<td>56</td>
<td>61</td>
</tr>
<tr>
<td>Bilirubin T/D, mg/dl</td>
<td>2.5/1.0</td>
<td>3.6/1.3</td>
<td>ND</td>
</tr>
<tr>
<td>ALK, IU/L</td>
<td>111</td>
<td>412</td>
<td>ND</td>
</tr>
<tr>
<td>AST, IU/L</td>
<td>29</td>
<td>100</td>
<td>ND</td>
</tr>
<tr>
<td>ALT, IU/L</td>
<td>23</td>
<td>39</td>
<td>ND</td>
</tr>
<tr>
<td>GGT, IU/L</td>
<td>23</td>
<td>39</td>
<td>ND</td>
</tr>
<tr>
<td>LD, IU/L</td>
<td>238</td>
<td>2430</td>
<td>ND</td>
</tr>
<tr>
<td>PT/TT, sec</td>
<td>11.9/21</td>
<td>13.1/24</td>
<td>14.4/25</td>
</tr>
<tr>
<td>Fibrinogen, mg/dl</td>
<td>ND</td>
<td>386</td>
<td>388</td>
</tr>
<tr>
<td>D-Dimer, μg/ml</td>
<td>ND</td>
<td>&gt; 4.0</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>Antithrombin III, %</td>
<td>87</td>
<td>74</td>
<td>ND</td>
</tr>
<tr>
<td>PO2, mmHg</td>
<td>ND</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>PCO2, mmHg</td>
<td>ND</td>
<td>34</td>
<td>45</td>
</tr>
<tr>
<td>PH</td>
<td>ND</td>
<td>7.46</td>
<td>7.31</td>
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<tr>
<td>O2 Saturation, %</td>
<td>ND</td>
<td>71</td>
<td>50</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.2</td>
<td>1.3</td>
<td>ND</td>
</tr>
</tbody>
</table>

**ND** = Not determined.

Hb = Hemoglobin.

Hct = Hematocrit.

MCV = Mean corpuscular volume.

WBC = White blood cell count.

NRBC = Nucleated red blood cells.

Bilirubin T/D = Total and direct bilirubin.

ALK = Alkaline phosphatase.

AST = Aspartate aminotransferase.

ALT = Alanine aminotransferase.

GGT = γ-glutamyltranspeptidase.

LD = Lactate dehydrogenase.

PT = Prothrombin time.

PTT = Partial thromboplastin time.

The peripheral blood smear revealed 1+ poikilocytosis and 2+ target cells. Gastrointestinal obstruction series and abdominal ultrasound showed no evidence of obstruction, ileus, free air, appendicitis, cholecystitis, or hydronephrosis, and the electrocardiogram (EKG) was normal. On chest x-ray, the right heart border was prominent and there was minimal right basilar atelectasis. Diagnostic con-
sideration included appendicitis vs. ischemic bowel syndrome. The patient was treated with intravenous (IV) hydration with normal saline and pain control with morphine sulfate 4 mg IV plus ketorolac 60 mg intramuscularly (IM) with moderate pain relief. He was admitted to the hospital for further observation.

On the next day the patient was found to be arousable but lethargic and incoherent. Physical examination now revealed tachypnea, tachycardia, and a temperature of 38.6°C (table I). The abdomen was rigid and distended with hypoactive bowel sounds. Arterial blood gases showed severe hypoxia with a PaO₂ of 35 mm Hg. His liver enzymes and bilirubin increased dramatically to include lactate dehydrogenase (LDH): 2430 IU/L; alkaline phosphatase (ALK): 412 IU/L; aspartate aminotransferase (AST): 100 IU/L; total bilirubin: 3.6 mg/dl; and an EKG showed T wave inversion across the precordium. Suspecting a ruptured viscus with resulting sepsis, he was emergently taken to the operating room for an exploratory laparotomy. A pleural effusion of 650 cc was present on the left and blood typing and crossmatch. It showed Hb S (51.8 percent) and Hb C (43.6 percent) with 4.6 fetal hemoglobin.

The final diagnoses included hemoglobin SC disease with acute abdominal sickle pain crisis and pulmonary fat embolism; recent and remote splenic infarction; and widespread hemorrhagic infarcts of the bone marrow. The immediate cause of death was acute right heart failure secondary to massive pulmonary fat emboli from bone marrow necrosis. The underlying cause of death was fat embolism owing to marrow necrosis secondary to sickle cell vaso-occlusion.

**Discussion**

The most important feature of this case is that adults with Hb SC disease may escape prior diagnosis and that bone marrow embolism should be considered in certain clinical situations like the one presented. The patient described was previously healthy with no documented history of previous acute painful episodes despite his age of 52 years. Platt et al.\(^1\) reported that the median age of death among patients with Hb SC disease was 60 years for males and 68 years for females. In retrospect, this patient did have some salient features suggestive, but not diagnostic, of Hb SC disease. These included the limp with occasional weakness of the left lower extremity possibly owing to avascular necrosis of the left femoral joint and the sudden onset of blindness in the left eye possibly owing to sickle retinopathy. The latter complication is typically more common in Hb SC disease than in SS.\(^5,6\) The absence of previous acute painful episodes is surprising and may represent a high threshold for painful stimuli in this patient and/or the presence of factors that are known to ameliorate the severity of sickle cell disease.

Factors that have a salutary effect on the clinical picture of sickle cell anemia include a white blood cell count below 15,000/\(\mu\)l and a high Hb F level.\(^19,20\) Relatively high total Hb levels, on the other hand, constitute a high risk factor for morbidity and mortality in patients with SS. Whether or not the same factors contribute to the phenotypic expression of Hb SC disease is not known. Nevertheless, this patient had a white blood cell (WBC) count of
Figure 1. Histologic sections of lung showing (A) occlusion of a small artery (large arrow) by a fat embolus, intraalveolar edema (small arrow) and dilated “empty” capillaries (inset arrows) in the interstitium (H&E 100X; inset 400X); and (B) positive staining for fat within the embolus occluding a small artery and within the surrounding capillaries (Oil red O; 400X).
10,200/μl when first seen in the Emergency Room (ER), and his Hb F level was 4.6 percent which is relatively high for an adult patient with Hb SC disease. Therefore, it is speculated by us that in this patient the low WBC count and high Hb F may have contributed to the mildness of the clinical picture as far as painful crises are concerned.

Sickle cell crises that involve the abdomen are often mistaken for an acute surgical abdomen. Careful examination of the peripheral smear in this patient may have suggested the associated diagnosis antemortem. It should be emphasized in this regard that sickle cell disease is a great mimic among African American patients. Recurrent episodes of pain and/or unexplained signs and symptoms of organ failure in patients of this ethnic group should alert the care provider to the possibility of sickle cell disease as the underlying etiology. The chances of Hb SC disease being missed in African Americans in the United States is not as likely in the future since all newborns, irrespective of ethnicity, are now tested for sickle hemoglobinopathies in most states.

Undoubtedly this patient had a fatal episode of pulmonary fat embolism. The subdiaphragmatic pain, hypoxia, tachypnea, fever, changes in mental status, fever, worsening anemia, necrotic bone marrow, increase in NRBC, and thrombocytopenia are all typical features of fat embolism syndrome. This is usually a serious complication of sickle cell disease. Early diagnosis based on a high index of suspicion and early treatment with aggressive transfusion or exchange transfusion has been reported to be of life saving value in an occasional patient.

Previous reports have suggested that fat embolism appears to be more common in SC disease than in sickle cell anemia. A recent study, however, has shown that acute chest syndrome is more common in SS than SC disease. Previous reports have shown that fat embolism in sickle cell disease is characterized by prior painful episodes and severe toxemia. The sequence of events in this patient suggests that ischemia and necrosis of the bone marrow in thoracic or lumbar vertebrae occurred first and led both to the abdominal painful crisis and fat embolism. Had an autopsy not been done in this patient, the diagnosis of fat embolism owing to SC disease would have never been made. This suggests that the incidence of fat embolism in adults with sickle cell disease may be higher than reported so far. This diagnosis may be missed in those adult patients who die suddenly at home after a brief severe painful episode and on whom no autopsy is performed. The national study on acute chest syndrome that is underway may clarify these issues in the future.

Acknowledgment

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