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Pulmonary Edema in Hb S/β+ thalassemia Patient Leading to Acute Chest Syndrome. A Case Report and Review of Literature

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Abstract Acute chest syndrome (ACS) is associated with prolonged hospitalization and high mortality in sickle cell population. The etiology of ACS is often multifactorial. It is well known that any chest pain that limits ventilation, blood flow or oxygenation establishes the risk of ACS. The independent contributory mechanism is fluid overload, resulting in pulmonary edema. In this report, we present a case of compound heterozygous Hb S/β+ thalassemia in a 32-year-old woman who presented with chest pain complicated by the development of pulmonary edema advancing to acute chest syndrome. We discuss the putative mechanisms might have led to pulmonary edema in this patient including hydration with underlying renal defect, along with a vicious cycle of vascular changes that resulted into pulmonary edema and consequently ACS.

Keywords: *acute chest syndrome, Sickle cell, thalassemia, Hb S/β+ thalassemia, pulmonary edema*

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1. Introduction

Sickle cell disease occurs due to structural defect in the globin gene, whereas beta thalassemia is due to defect in globin chain production [2]. Acute chest syndrome is the second most common cause of hospitalization with characteristics of pulmonary infiltrates on chest X ray, and premature mortality [3]. Pulmonary edema is one of the earliest signs of hypervolemia which could develop with conventional interventions such as fluid replacements and parental narcotics [5]. It is manifested as hypoxia, dyspnea, and atelectasis. In this case report of ACS associated with pulmonary edema, we provide some insights into the pathophysiology of atypical mechanisms of sickle cell crisis that not only helps with early diagnosis of disease exacerbation, but also focuses on conservative approach to standard therapeutic strategies.

2. Report of the Case

A 32-year-old woman with Hb S/β+ thalassemia, on folic acid and hydroxyurea, presented with chest and lower back pain for 4 days. Her previous history included an episode of acute chest and 3-4 painful crisis per year requiring hospitalizations. She had 1 unit of blood transfusion prior to this admission. On physical examination, the patient was afebrile with a temperature of 99.6 °F, normotensive 123/65mm Hg, tachycardic114 bpm and in mild distress due to pain. Her respiratory rate was 19 and her oxygen saturation was 100% on room air. She had no palpable enlargement of the liver or spleen. Initial lab work showed hemoglobin of 10.4g/dl, WBC 9.2 k/uL, and platelets of 204 k/uL. There was no record of her baseline hemoglobin. Her creatinine was 0.6 mg/dL, LDH 278 U/L (normal value 140-271 U/L), total bilirubin 0.7 mg/dL and haptoglobin 104 mg/dL (normal value 50-220mg/dl). Respiratory panel and HIV test were negative. Hemoglobin electrophoresis showed HbA 27.6%, HbS 62.8% and HbF 5.3%. Radiograph of chest was normal (Figure 1a) and she also had normal radiographs of the hip and spine. EKG was normal without ischemic changes. She was given 2 liters of hypotonic saline at maintenance rate of 80cc/hr. Pain regimen included ketorolac 15mg every 6 hours for moderate pain and hydromorphone 1mg every 4 hours for severe pain.

On the second hospital day, patient developed a fever of 100.8°F. Her labs were significant for thrombocytopenia

of 102 k/uL, a 50% drop from her baseline of 204 and LDH was increased to 2026 U/L with reticulocyte of 1.86%. However, her hemoglobin and white count remained unchanged. On the third hospital day, patient remained alert but was oriented only to person and she also became hypoxic with oxygen saturation in high 80s on room air. Arterial blood gas showed pH 7.57, pC02 24 mmHg, pO2 86 mmHg, HCO3 20 mmol/L. Pt was given supplemental oxygen with improvement in her O2 saturations. Antibiotics were prescribed to cover community acquired pneumonia and she was transferred to Medical Intensive Care unit (MICU) for close monitoring.

Labs at that point revealed WBC 11.6 k/uL and Hb 9.3 g/dl, with worsening thrombocytopenia of 56 k/uL. Her LDH was further elevated to 3036 U/L with haptoglobin of 160 mg/dL (normal value 50-220mg/dl) and total bilirubin of 1.7 mg/dL. Blood cultures were negative. CT head showed no evidence of stroke. Repeat chest radiograph showed bilateral hazy opacities with prominent and indistinct pulmonary vasculature (Figure 1b). CTA was negative for PE but showed patchy airspace opacities within bilateral lower lobes consistent with pulmonary edema (Figure 2). Pt was diagnosed with of severe ACS. Despite an exchange transfusion, she continued to deteriorate and was eventually intubated and placed on a ventilator. Resuscitative efforts were ultimately unsuccessful and the patient expired.

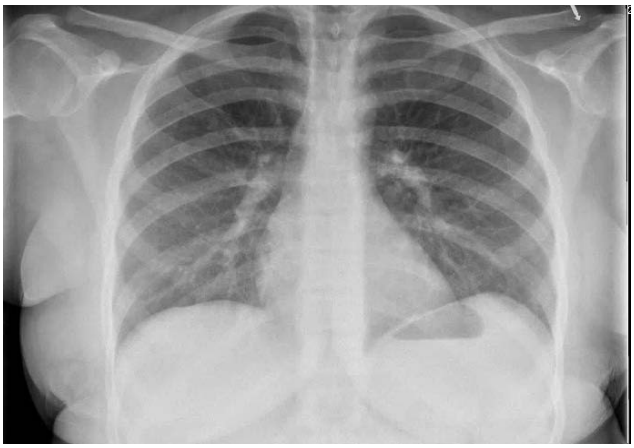

Figure 1a. Day 1: Normal Chest X-ray

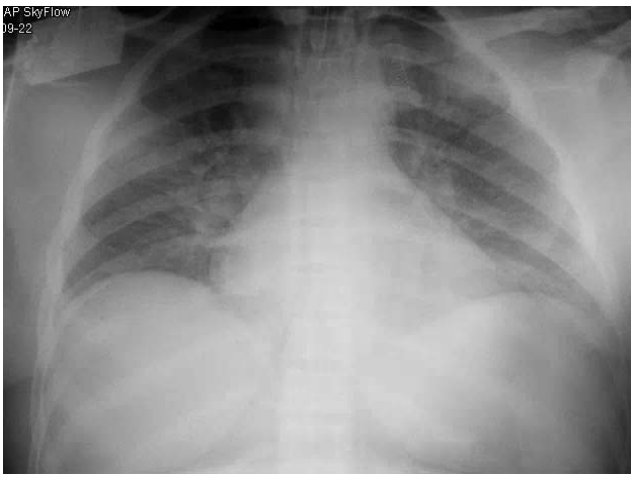

Figure 1b. Day 3: Bilateral hazy opacities with prominent pulmonary vasculature

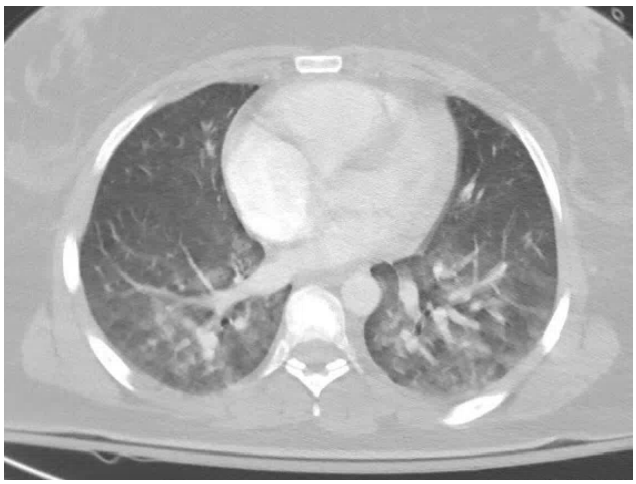

Figure 2. Day 3: Patchy airspace opacities within bilateral lower lobes consistent with pulmonary edema. No evidence of pulmonary embolism

3. Discussion

While risk factors for acute chest syndrome (ACS) consists of various precipitants, a common pathway include reduced ventilation with hypoxia and increased sickling [1]**.** In our case report, we highlight the putative etiology of pulmonary edema by reviewing three pathophysiologic processes i.e kidney and vascular dysfunction, and hydration. One factor is undergoing nephropathy in these patients. Hyperosmolar environment of inner medulla promotes sickling which results in microinfarcts demonstrated with loss of vasa recta, and obliteration of medullary capillaries in radio- angiographic studies [4]. Therefore, patients lose the ability to concentrate urine which is not restricted to SS disease but is also seen in sickle beta thalassemia [5]. Furthermore, high GFR secondary to prostaglandins release in response to sickling leads to hyperfiltration-mediated sclerosis of glomerular capillaries. This compromises the glomerular filtration barrier, thus setting the stage for age-dependent proteinuria [4,6].

There is a growing body of literature on mechanisms of vasculopathy in sickle cell patients involving endothelial dysfunction, nitric oxide deficiency, oxidative stress, inflammatory cytokine release, and hypercoagulability [1]. Nitric oxide (NO) induces vasodilation and regional blood flow by suppressing cell adhesion molecules expression. It is synthesized within the endothelium from L arginine by a family of enzymes, NO synthases [8]. Sickle cell patients have low NO reserves which has been demonstrated in various studies with suppressed plasma L-arginine levels [7,8]. Although production of reactive oxygen species in this population is multi-factorial but tissue ischemia from occlusion and tissue re-perfusion when occlusion is relieved generates an environment of oxygen free radicals [7,8]. Reactive oxygen species generated during ischemia-reperfusion cycles scavenge NO [7]. Moreover, cell-free plasma hemoglobin released from on-going intravascular hemolysis further depletes NO [8]. In pulmonary vascular beds predisposed to injury, this constant endothelial damage, and decreased oncotic pressure due to hypotonic saline enhance vessel permeability [8]. Due to such vasomotor instability, these

patients cannot tolerate small excess volume as compared to normal population. Furthermore, during non-crisis steady state vasorelaxant systems in kidney are maximally upregulated, therefore vessel expandability to respond to high plasma volumes is limited [6].

Furthermore, about one third of patients develop pulmonary hypertension, which is a predictor of early death in SCD [11]. A retrospective MICU level study with 58 sickle cell patients that assessed clinical variables associated with poor outcome showed lower steady state HbF, higher admission hemoglobin and DIC to be correlated with higher mortality rate [10]. Our patient presented with Hb level of 10.4, a low HbF of 5.3% and rising LDH. Normal haptoglobin and bilirubin suggest LDH to be a marker of lung injury than hemolysis secondary to tissue infarct from micro emboli that cannot be picked up on imaging. Also, low NO state serves as a pro-coagulant milieu as NO has the properties to prevent platelet activation and tissue factor activation that further contribute to vascular obstruction [8]. Similarly, the concomitant development of ACS was seen with up-trending troponins. An independent 10% decrease in platelet count from baseline is also reported to be a significant predictor for developing ACS [9]. Hence, it could be postulated that vascular dysfunction, and chronic hyperosmolar state from impaired kidney concentrating ability predispose the SCD population to develop pulmonary edema with slight volume overload especially with underlying pulmonary hypertension.

4. Conclusion

In this report, we presented a case of a 32-year-old woman with compound heterozygous Hb S/β+ thalassemia who presented with chest pain and developed pulmonary edema and ACS. The putative mechanisms for pulmonary edema in our case includes chronic hyperosmolar state from impaired kidney concentrating ability predispose the SCD population, low baseline HbF levels, normal haptoglobin and bilirubin suggesting that the rising LDH a marker of lung injury than hemolysis likely due to underlying NO dysfunction in these patient population. Understanding these mechanisms by the practicing physicians could lead to avoidance of large volume replacement with standard sodium content for hemodynamic support, painful crisis, and dehydration. Hydration is generally administered intravenously in the form of hypotonic fluids with close monitoring of urine output and pulmonary auscultation with cautious administration of fluids and narcotic analgesics in this high-risk patient population to minimize the risk of pulmonary edema and the unpredictable progression to acute chest syndrome.

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