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CASE REPORT

New pulmonary infiltrates in a 19 year-old with sickle cell crisis

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Summary
Objective: Sickle cell anemia (SCA) is the most common inherited blood disorder. Sickle cell crisis is characterized by episodes of pain, chronic hemolytic anemia and severe infections, usually beginning in early childhood. Sickle cell disease primarily affects those of African descent and Hispanics of Caribbean ancestry, but the trait has also been found in those with Middle Eastern, Indian, Latin American, Native American, and Mediterranean heritage. Recent studies indicate that more than 12,500 people in England have sickle cell disorders. The acute chest syndrome is the leading cause of death and the second most common cause of hospitalization among patients with sickle cell disease. The acute chest syndrome (ACS) is characterized by chest pain with dyspnea and recent radiological abnormalities. Since its cause is largely unknown, rapid recognition and early institution of therapy is paramount as with timely and appropriate intervention majority of these patients survive. The treatment of ACS rests on controlled hydration, antibiotic therapy, oxygen therapy, controlled analgesic therapy, blood transfusion and exchange transfusion. A better understanding of the disease and a close collaborative approach between a primary care physician and a specialist may be the key to improve the quality of care rendered.
Methods: Research studies, review articles, and published scientific meeting abstracts were reviewed.
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Introduction

We present a case of a 19 year-old African-American male with acute chest syndrome (ACS). In the

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United States, Sickle Cell Disease (SCD) is reported to affect 70,000 African-Americans. ACS is the most serious complication and a common cause of death over 5yrs of age in SCD. Recent data from the Clinical Course of Sickle Cell Disease Cooperative Study indicate that this complication occurs with an incidence of 10,500/100,000 patients/year. Our patient initially presented to us with generalized

pain with a normal arterial oxygen saturation and chest X-ray (CXR), and later went into respiratory distress. Early recognition and aggressive therapy may prevent ACS. Here we highlight the risk factors, clinical features, laboratory markers and new treatment options in ACS.

Case

A 19 year-old African-American male with a past medical history of sickle cell disease (SCD) and cholecystectomy presented with excruciating pain in his ribs, back and extremities. He denied smoking, alcohol abuse or drug addiction. On examination he was well nourished and in extreme distress because of his pain. Vital signs were all stable and he was afebrile with an oxygen saturation of 99% in air. His heart and lung examination were noncontributory and his abdomen was soft and non-tender. Laboratory values at the time of admission were significant for a hemoglobin of 9.9 mg/dl, white blood cell count of 9.3, urea nitrogen of 8 mg and creatinine of 0.4 mg. His chest X-ray (CXR) at the time of admission is shown in Fig. 1.

The patient was admitted with a diagnosis of vaso-occlusive crisis (VOC) due to SCD and was started on intravenous hydromorphine initially at 4 mg every two hours together with intravenous fluids and oxygen.

On day 2 of his admission, he was found to be febrile with a temperature of 102 degrees Farenheit. A repeat CXR at this time is shown in Fig. 2. He was confused and drowsy, and his oxygen saturation dropped down to 86% in air. Arterial blood gases revealed a pH of 7.39, pCO_2 of 54 mmHg, pO_2 of 70 mmHg and HCO_3
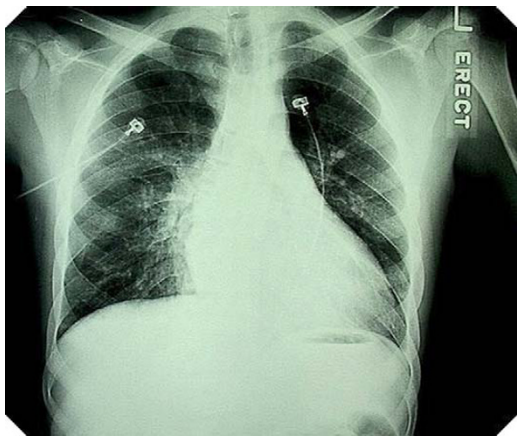

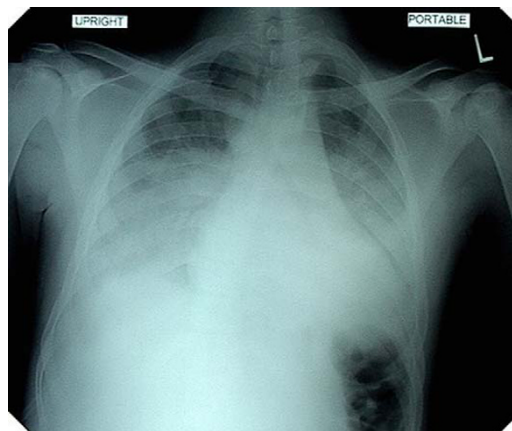**Figure 1** Anterior-posterior admission CXR showing no gross abnormalities.

Figure 2 Follow up anterior-posterior CXR from second day admission showing new bilateral predominantly basal pulmonary infiltrate.

of 32.9 mmol on 4 L of oxygen. The patient was put on 100% oxygen via non-rebreather mask. His hydration was increased and he was commenced on Rocephin and Zithromax and transferred to the intensive care unit (ICU) for monitoring and with pre-emptive plans for exchange transfusion for ACS. He improved remarkably after two sessions of exchange transfusion, was moved out of ICU after two days, and remained stable until discharge.

Discussion

Acute chest syndrome (ACS) is the most common pulmonary complication of SCD and affects approximately half of SCD patients [1]. It is the leading cause of death in SCD. The Cooperative Study on Sickle Cell Disease recently reported an increase in life expectancy for individuals with SCD [2]. The median life expectancy for men and women with sickle cell anemia is 42 and 48 years, respectively [2]. For hemoglobin (Hb) SC disease, the median life expectancy is reported to be in the 60s for both sexes. High Hb S concentrations, high steady-state white blood cell counts, and low Hb F concentration are risk factors that predispose a patient to the development of ACS. The cause of this disorder remains largely unknown; however, it is postulated that the most common causes are infection, fat embolism and thromboembolism. When considering the diagnosis of ACS, pneumonia deserves special consideration. Although an infectious pathogen is identified in slightly more than one third of ACS episodes, pneumonia may contribute to more than one half of the deaths from ACS [3]. Several pathogens have been associated with the development of ACS. The

Table 1 Characteristics of high risk groups for acute chest syndrome[a].

1. Younger patients
2. Those presenting in winter months
3. High white blood cell count at baseline
4. History of vasoocclusive crisis, acute chest syndrome or aseptic necrosis of hip joints
5. Homozygous sickle cell or sickle cell −Beta+ Thalasemia genotype
6. High Hemoglobin S concentration
7. Low fetal hemoglobin concentrations

[a] Modified from Powars D., Weidman J.A., Odom-Maryon T., et al. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine 1988; 67:66-76.

Table 3 Common signs, symptoms & laboratory findings in patients with ACS.

Symptoms	Signs	Laboratory findings
Fever	Tachycardia	Hypoxia
Chest pain	Tachypnoea	Pulmonary infiltrate
Cough	Rales	Low Haemoglobin
Wheeze		High White cell
Dyspnoea		Increase Phospholipase A2

Modified from:Platt OS. The acute chest syndrome of sickle cell disease. N Engl J Med 2000;342:1994, Vichinsky EP, Neumayr LD, Earles AN, Williams R. Causes and outcomes of the acute chest syndrome in sickle cell disease. National acute Chest Syndrome Study Group. N Engl J Med 2000;342:1855., Taylor C, Carter F, Poulose J, Rolle S, Babu S, Crichlow S. Clinical presentation of acute chest syndrome in sickle cell disease. Postgrad Med J 2004;80:346−9.

more prevalent treatable microorganisms include Chlamydia and Mycoplasma [4]. Among viruses, the respiratory syncitial viruses have been shown to be major offenders (Tables 1 and 2).

The definition of ACS is a new radiographic pulmonary infiltrate that is usually associated with a combination of fever, chest pain, hypoxemia, cough or wheeze, and tachycardia in patients with SCD [3,4]. The diagnostic criteria employed in management are clinical, radiological and laboratory. A 30-centre cooperative study of 671 patients [4] showed that 58% of patients were males, with the first episode occurring under the age of 20 in almost 60% of these patients. Half of the patients were admitted for a diagnosis other than ACS with 72% being admitted for VOC. Mean time of development of radiological and clinical

Table 2 Commonest causes of ACS in SCD patients.

Pulmonary infarction - in situ sickling
Fat embolism syndrome
Hypoventilation secondary to rib infarction/narcotic administration
Pulmonary edema induced by narcotics or fluid overload

Infections
  Chlamydia
  Mycoplasma
  Viruses - RSV, CMV, Influenza, Adenovirus, Parvovirus
  Bacteria - Staph. aureus, Strep. pneumonia, Mycoplasma
  Mixed infections
  Legionella
  Miscellaneous infections
Unknown

Modified from Vichinsky EP, Neumayr LD, Earles AN. et al. Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease…The National Acute Chest Syndrome Study Group. N Engl J Med 2000;342:1855−65, Jun 22, 2000.

findings from time of admission was 2.5 days. The three most common factors in the past medical history were previous VOC in 80%, prior exchange transfusion in 74%, and a previous history of ACS or pneumonia in 67%. The three most common symptoms at the time of diagnosis were fever in 80%, cough in 62% and chest pain in 44%. The three most common findings on physical examination were respiratory rate >30/min in 67% (mean peak respiratory rate of 38/min); a mean peak temperature of 38.9 °C; and rales on examination in 76% [5,6].

Laboratory findings at the time of diagnosis included a mean initial hemoglobin of 7.7 g/dl, a mean decrease in hemoglobin from steady state value of about 0.78 g/dl, a mean white cell count of 23,300 per cu mm, relative thrombocytopenia (200,000/cu mm) and a mean partial pressure of arterial oxygen at diagnosis of 70 mmHg. There are no laboratory abnormalities diagnostic of ACS, although interestingly, an increase in serum phospholipase A_2 has been suggested as an early marker of fat embolism syndrome (FES) and the development of ACS during an episode of VOC [7]. Vitamin E-deficient patients with SCD were also found to have significantly higher irreversibly sickled counts, indicating that vitamin E is an important inhibitor of the irreversibly sickled cell formation [8]. Radiological findings at the time of diagnosis included upper lobe involvement in 34%, lower lobe involvement in 92%, middle lobe involvement in 40% and the presence of effusions in 35% [9] (Table 3).

Hypoxia leads to increased hydrolysis of phospholipids to produce free fatty acids and lysophospholipids, which are both known to be active mediators in acute lung injury [10,11]. One such secretory mediator is phospholipase A2, a

potent inflammatory mediator. Studies indicate that phospholipase A2 levels rise 24—48 hours prior to the development of ACS and can alert a physician to impending ACS [12]. In addition, monitoring phospholipase A2 may be useful for instituting early therapies and in preventing or reducing the clinical morbidity of ACS.

Other markers of ACS include VCAM-1. Decreased production of nitric oxide (NO), as occurs in hypoxia, results in up-regulation of VCAM-1 production. VCAM-1 induces increased adhesion of sickled erythrocytes to the vascular endothelium via VLA-4 integrin [13]; studies have indicated values much higher in ACS as compared to sickle cell patients at baseline or during VOC. Lopez et al found patients with persistent pain had significantly low initial NO levels while those with pain improvement had higher initial NO levels [14].

With repetitive injury to the lung, the patient may develop a form of pulmonary dysfunction called sickle cell chronic lung disease (SCLD). The most significant risk factors associated with SCLD were the number of ACS episodes and the presence of avascular necrosis. The number of ACS episodes has also been positively correlated with interstitial lung disease and obstructive lung disease (OLD) [15,16]. Pulmonary hypertension is increasingly recognized as a complication of sickle cell anemia [17]. Retrospective studies of echocardiograms performed at tertiary care SCD centres have reported that up to 40% of patients have moderate to severe pulmonary hypertension [18,19] (Table 4).

Current management of ACS is largely supportive and symptomatic. Antibiotics should always be considered. In the presence of hypoxemia, supplemental oxygen therapy must be implemented to keep PaO_2 at 70 mmHg or above or oxygen saturation at 92% or more. Good pain control and incentive spirometry is essential to prevent splinting and resultant hypoventilation. Adequate hydration should be maintained, with care taken to avoid over-hydration. In moderate to severe cases, therapy with exchange transfusion is directed to reduce Hb S to 20 to 30% without exceeding a haematocrit of 30%.

It has been shown that hydroxyurea reduces the number of ACS episodes by 50% in two-thirds

Table 4　Management of acute chest syndrome[a].

1. General Preventive Measures
　Regular periodic visits to physicians
　Immunizations and penicillin prophylaxis- especially in children
　Prevention of acute chest syndrome with hydroxyurea treatment[b]

2. Symptom-directed medical treatments
　Supplemental oxygen therapy
　Adequate Pain control[c]
　Incentive spirometry
　Adequate hydration- Oral or IV fluid replacement[d]
　Blood transfusion- packed red blood cells or exchange type[e]
　Exchange transfusion
　Bronchodilators
　Antibiotic therapy[f]

3. Experimental therapeutic modalities under investigations
　L-Arginine butyrate therapy
　Inhaled nitric oxide administration
　Membrane Active Drugs- Clotrimazole, Magnesium salts
　Non-ionic surfactant compound
　Gene therapy
　Bone marrow transplants

[a] Modified from Steinberg M.H. Drug Therapy: Management of Sickle Cell Disease; New England Journal of Medicine 1999; 340:1021-1030, Apr 1, 1999.
[b] Blood counts should be monitored frequently.
[c] Preferably frequent, fixed interval, parenteral opioids until pain is under control and then oral analgesics on an as needed basis.
[d] Four to five liters of PO or IV fluids per day may be needed.
[e] Specially if patient is hypoxic despite oxygen therapy.
[f] May or may not be indicated depending on local bacterial patterns and by the results of sputum smear analysis.

of patients [20] and in a recently published observational study by Steinberg et al. [21] the overall mortality in adult patients taking hydroxyurea was reduced by 40%. Its beneficial effects related to its ability to increase Hb F level, to decrease the number of leukocytes, and to serve as a donor of NO [22].

Newer forms of therapy include administration of L-arginine, NO, gene therapy and BMT. Studies have shown decreased levels of arginine in patients with ACS [23]. Arginine is known to be a precursor of nitric oxide and it is postulated that administration of arginine will lead to increased production of nitric oxide. In a report by Morris et al, a five-day course of arginine therapy was associated with a modest reduction in estimated pulmonary artery pressure in ten SCD patients with pulmonary hypertension [24]. A decrease in irreversibly sickled erythrocytes was noted in sickle cell anemia patients given vitamin E [25].

Inhaled NO may emerge as a cytoprotective strategy facilitating vascular homeostasis, thereby preventing or attenuating the recurrent ischemia/reperfusion in the lung. In addition, its ability selectively to dilate pulmonary vasculature, reduce pulmonary pressure, improve ventilation-perfusion mismatch and to increase oxygen tension, means that its benefit has been noted in ACS as well as in mechanically ventilated patients with severe ACS [22,26].

Sickle cell anemia has long been recognized as a potential candidate for the development of gene therapy approaches. Walters and colleagues suggest that bone marrow transplantation has the potential to cure all these patients. Indeed, in a group of 22 children with SCD in their study who received marrow from HLA-matched siblings, 15 (68 percent) were cured [27]. Studies are underway to test the outcome of this hypothesis and the efficacy of arginine, NO, gene therapy and bone marrow transplantation.

Summary

Since ACS is the leading cause of death in SCD patients, a close collaborative approach between primary care physicians and other specialists can lead to prompt diagnosis and treatment. Early diagnosis and institution of therapy can significantly reduce the risk of death in patients with ACS. Diagnostic suspicion should be raised especially for high risk groups such as younger SCD patients, those who present during winter months, are febrile, have a high white blood cell count at baseline, and who have a past history of VOCs, ACS or aseptic necrosis of the hip joints. Patients with a homozygous sickle cell or sickle cell −Beta+ Thalasemia genotype, and those with High Hb S concentration and/or a low fetal hemoglobin concentration, are also more at-risk for ACS. ACS should be considered in all SCD patients who complain of chest pain, especially if it is associated with tachypnoea, dyspnoea, cough, hypoxia and signs of respiratory distress. New infiltrates on the CXR are highly suggestive. Since patients can deteriorate suddenly and go into respiratory failure, all SCD patients with such a presentation should be admitted to hospital. ACS can mimic pneumonias, pulmonary emboli, bone marrow infarctions and emboli, myocardial ischemia, or in situ lung infarction. All of these disorders are more common in SCD patients as compared to healthy individuals, and may be extremely difficult to distinguish from ACS solely on the basis of clinical presentation. ACS is a medical emergency and may require ICU admission. Management includes oxygen therapy, hydration, adequate analgesia and blood transfusions. Empirical antibiotics may be needed. Management of patients with sickle cell syndromes and their complications such as ACS requires ongoing continuity of care. Familiarity with the pattern of symptoms related to ACS appears to be the best safeguard against misdiagnosis and subsequent delay in appropriate life saving therapy.

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