Pulmonary manifestations of sickle cell disease

A K Siddiqui, S Ahmed

Pulmonary complications account for significant morbidity and mortality in patients with sickle cell disease. Clinical lung involvement manifests in two major forms: the acute chest syndrome and sickle cell chronic lung disease. Acute chest syndrome is characterised by fever, chest pain, and appearance of a new infiltrate on chest radiograph. Sickle cell chronic lung disease, on the other hand, manifests as radiographic interstitial abnormalities, impaired pulmonary function, and, in its most severe form, by the evidence of pulmonary hypertension. Progress has been made in understanding the pathophysiology and management of these complications. In this review the current knowledge of the mechanism, diagnosis, and treatment of pulmonary complications of sickle cell disease are discussed.

Sickle cell disease (SCD) is one of the most prevalent genetic disorders. There are more than 200 million carriers of sickle cell trait worldwide, and 200 000 to 300 000 people are born annually with major haemoglobinopathies. Approximately 0.14% of African Americans children are homozygous for the sickle cell gene and 8% have sickle cell trait, making SCD the most prevalent inherited disorder in African Americans. The protein manifestations of SCD are caused by substitution of glutamic acid by valine in the beta subunits of the haemoglobin molecule. Upon exposure to low oxygen tension the mutant haemoglobin S becomes less soluble and aggregates into large polymers. This results in a distorted erythrocyte with marked decrease in its deformability contributing to the vaso-occlusive and haemolytic aspects of the disease. With improved supportive care the median age of survival has risen to 42 years for men and 48 years for women. As survival into adulthood has become more common in patients with SCD, there has been an increased incidence of chronic organ failure. The lung is among the major organs involved in SCD. The pulmonary manifestations of SCD are both acute and chronic (see box 1). They remain the leading cause of morbidity and mortality in patients with SCD. Clinical lung involvement commonly takes two major forms: the acute chest syndrome (ACS) and sickle cell chronic lung disease (SCCLD). More than 20% of adults with SCD have fatal pulmonary complications. Although pulmonary manifestations of SCD are common, they remain under-diagnosed by physicians. This review summarises the current knowledge and management of pulmonary manifestations associated with SCD.

AIRWAY HYPER-REACTIVITY

Airway hyper-reactivity is a common pulmonary function test abnormality among young subjects with SCD. The reported incidence of obstructive lung defects in children with SCD is 35% to 37%. A prospective controlled trial demonstrated airway reactivity to cold air in 60% patients with SCD compared with none in the control population, suggesting an association between SCD and airway reactivity. The pathogenesis of increased airways reactivity and its relationship to ACS and SCCLD, however, is unknown. In the absence of data on long term benefit, routine use of bronchodilators is not recommended in patients with SCD.

NOCTURNAL OXYHAEMOGLOBIN DESATURATION

Nocturnal oxyhaemoglobin desaturation has been reported in SCD subjects, with a prevalence of up to 40% in children and adolescents. Proposed mechanisms are obstructive sleep apnoea, intrinsic lung disease, and an abnormality in oxyhaemoglobin affinity. Several investigators documented obstructive sleep apnoea in SCD with or without nocturnal oxyhaemoglobin desaturation. Although it has been shown that low nocturnal oxygen saturation is associated with higher rate of painful crisis in childhood, the relationship between nocturnal oxyhaemoglobin desaturation and vaso-occlusive crisis or ACS is poorly understood.

THROMBOEMBOLISM

Patients with SCD are known to be hypercoagulable. A variety of mechanisms are postulated from low levels of protein S and C,
improved after receiving antibiotic therapy and blood transfusion.

ACS showing infiltration of right lower and middle lobes. Patient

671 episodes of ACS in 537 patients with SCD using rigorous

Aetiology

The usual aetiology of ACS is vaso-occlusion, infection, or both

ACUTE CHEST SYNDROME

Incidence and risk factors

ACS is defined as the appearance of a new pulmonary

Fat embolism, with or without

infection

59 (8.8)

Chlamydia

48 (7.2)

Mycoplasma

44 (6.6)

Virus

43 (6.4)

Bacteria

30 (4.5)

Mixed infection

25 (3.7)

Legionella

4 (0.6)

Miscellaneous infections

3 (0.4)

Infarction

108 (16.1)

Unknown

306 (45.7)

Table 1 Causes of acute chest syndrome reported in MACSS

Infection

Patients with SCD are at an increased risk of infection due to

Pulmonary fat embolism

The occurrence of pulmonary emboli containing fat and necrotic bone marrow in patients with SCD is well known. Fat embolism associated ACS was identified in 9% cases of ACS in the MACSS report. The pulmonary signs and symptoms typically are preceded by bone pain, with laboratory evidence of a significant decrease in haemoglobin and platelet count and an increased plasma level of free fatty acids and phospholipase A2. The diagnosis of pulmonary fat embolism is supported by the presence of lipid-laden macrophages in the bronchoalveolar lavage fluid. The Corwin index is used to quantify the amount of lipid in the pulmonary macrophages. ACS due to pulmonary fat embolus is associated with severe haematological and clinical abnormalities and has a fourfold higher mortality rate in adults compared to children.

In situ thrombosis

Pulmonary infarction secondary to in situ thrombosis is a potential cause of ACS, though is uncommonly documented pathologically.

Hypoventilation from pain and/or narcotic analgesics

There is a high correlation between thoracic bone infarction on bone scan and the presence of pulmonary infiltrates. It has been suggested that bone pain can cause splinting and atelectasis and can present as ACS. Similarly, postoperative thoracic and upper abdominal pain may predispose to ACS. Incentive spirometry and adequate pain control therefore becomes necessary under such situations. On the other hand, excessive use of narcotics may lead to hypoventilation and ACS as a complication of their use.

Iatrogenic pulmonary oedema

Although it has been suggested that aggressive hydration may lead to ACS in patients with SCD, this association is not established.

Pathogenesis

The mechanism responsible for ACS is not fully understood. It is believed to be a specific form of acute lung injury that can progress to acute respiratory distress syndrome.
injury is caused by various insults superimposed on the genetically based pathophysiology of SCD. In addition to haemoglobin S polymerisation and red cell sickling, increased expression of adhesion molecules on sickle erythrocytes and endothelium, release of inflammatory mediators, interaction of sickle red cell with leucocytes, microvascular thrombosis, and endothelial damage may all contribute to microvascular occlusion and tissue infarction.

More recent data suggest that abnormalities in endothelial cell nitric oxide (NO) production and metabolism as well as oxidant status may contribute to the development of ACS. NO regulates vascular tone and endothelial function, and maintains tissue oxygenation by reducing shunt physiology. Hypoxia induces cytokine and endothelin-1 release which up-regulates expression of the endothelial adhesion receptor vascular cell adhesion molecule-1 (VCAM-1), thereby enhancing adhesion of red cells to endothelial cells. Additionally, fat embolism and release of free fatty acids also enhances the adhesion process by VCAM-1 up-regulation. Under normal conditions NO inhibits both endothelin-1 production and endothelial VCAM-1 expression. During ACS, however, hypoxia and red cell sickling inhibit NO production while free radical species released by leucocytes inactivate locally produced NO. Hence, depletion of NO results in unopposed VCAM-1 up-regulation and increased red cell endothelial adhesion.

Clinical features

The Cooperative Study of Sickle Cell Disease, which prospectively followed up 3751 patients, reported data on 1722 ACS episodes in 939 patients. Patients with ACS presented with fever (80%), cough (74%), chest pain (57%), dyspnoea (28%), productive cough (24%), wheezing (11%), and haemoptysis (2%) accompanied by hypoxia, leucocytosis, and infiltrates on chest radiographs that often progressed to multilobar pulmonary disease indistinguishable from acute respiratory distress syndrome.

The symptoms of ACS are age dependent; ACS is often preceded by febrile episodes in children and by vaso-occlusive crisis in adults. Children are more likely to have fever and cough, whereas adults more commonly experience chest pain and dyspnoea.

Management of acute chest syndrome

General measures

SCD patients admitted for painful crisis should be considered in the prodromal phase of ACS. Prophylactic manoeuvres like close pulmonary monitoring, cautious hydration, optimal pain control, and incentive spirometry remain essential components of therapy. Physicians should have a low threshold for ordering a chest radiograph and arterial blood gas analysis. Vigorous hydration may result in pulmonary oedema and worsening respiratory distress and should be avoided. Judicious use of analgesics is necessary to relieve bone pain and splinting to prevent lung atelectasis. If there is no contraindication, non-steroidal agents should be the part of all pain control regimens as they have a narcotic-sparing effect. Efficacy of incentive spirometry in preventing the pulmonary complications (atelectasis and infiltrates) associated with the ACS has been proven in a randomised controlled trial and should be routinely used in patients with SCD.

Oxygen therapy

Oxygen should be administered for the correction of hypoxia, which if untreated creates a risk of multorgan failure. Pulse oximeter correlation with arterial oxygen tension in patients with SCD may at times be poor and arterial blood gas confirmation is required in hypoxic patients.

Antibiotics

Broad spectrum antibiotics, including a macrolide or quinolone in view of atypical infections such as chlamydia and mycoplasma, should be administered. Penicillin prophylaxis and use of Haemophilus influenzae vaccine has reduced bacterial infection significantly and should be given to all patients with SCD.

Bronchodilators

Bronchodilators are given to patients when airflow obstruction is present, though some investigators recommend their routine use in all patients. Many patients with SCD have airway hyper-reactivity and this fact should be considered when managing these patients on the ventilator to prevent auto-positive end expiratory pressure and dynamic hyperinflation.

Bronchoscopy

Bronchoscopy may be considered in patients not responding to initial therapy. It can be utilised both as an airway clearance technique by removing the thick and tenacious airway secretions often found in patients with ACS and for more accurate diagnosis of the episode.

Transfusion

Simple and exchange blood transfusion may be beneficial by lowering the fraction of sickle haemoglobin and also by improving the oxygen carrying capacity of blood. Both simple and exchange transfusion have resulted in similar improvement in oxygenation in patients with ACS. Transfusion is indicated in individuals with severe disease, multilobe involvement, persistent or worsening hypoxaemia, neurological abnormalities, multiorgan failure, or those with a history of cardiac disease. In patients with severe anaemia, simple transfusion appears to be the modality of choice. However, a post-transfusion increment in haemoglobin levels above 110 g/l may be dangerous due to increased blood viscosity and therefore in individuals with a relatively high haemoglobin exchange transfusion should be performed. Severe episodes may not respond to transfusion therapy and may require support with mechanical ventilation or extracorporeal membrane oxygenation. Efficacy of chronic transfusion has been shown in a randomised controlled trial in the prevention of future episodes of ACS.

Corticosteroids

A short course of corticosteroids has been shown to reduce the need for blood transfusion and the length of hospitalisation in children with ACS. However, its use in vaso-occlusive pain crisis is associated with more rebound attack. Corticosteroids therapy, therefore, should be considered experimental in ACS.

Nitric oxide

NO may be beneficial in severe cases that are refractory to standard therapy. There are isolated reports of significant reduction in pulmonary artery pressure, pulmonary vascular resistance, and alveolar-arterial gradient with concomitant improvement in cardiac output in patients with ACS after the inhalation of NO.

Box 3: Diagnostic testing and laboratory monitoring in acute chest syndrome

- Blood and sputum/tracheal secretion culture.
- Daily blood counts and appropriate metabolic profile.
- Serial measurement of arterial blood gases as necessary.
- Chest radiographs.
- Flexible bronchoscopy with bronchoalveolar lavage as appropriate.
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Box 4: Treatment of acute chest syndrome

- Identify and treat all underlying precipitating factors.
- Supplemental oxygen to treat hypoxia and maintain arterial oxygen tension above 70 mm Hg.
- Optimal pain control and fluid management.
- Ongoing respiratory therapy by using incentive spirometry and chest physical therapy as necessary.
- Provide empirical antibiotic with coverage for atypical organisms.
- Bronchodilators for patients with reactive airway disease.
- Simple or exchange transfusion to reduce haemoglobin S concentration and to enhance oxygen carrying capacity.
- Miscellaneous: NO inhalation, systemic steroids, mechanical ventilation, and extracorporeal membrane oxygenation.

Hydroxyurea
The incidence of ACS is significantly reduced in adult patients treated with hydroxyurea. A double blind, placebo controlled trial of 299 adults with SCD terminated early, because hydroxyurea reduced the frequency of ACS, hospitalisation, and need for transfusion. Hydroxyurea reduces sickling by increasing fetal haemoglobin level and hence decreasing the relative concentration of haemoglobin S in the erythrocytes. It should, therefore, be considered in patients with recurrent episodes of ACS.

SICKLE CELL CHRONIC LUNG DISEASE
The exact incidence, prevalence, natural history, and methods of diagnosis of SCCLD have not been established due to the lack of detailed epidemiological studies. It is suggested that SCCLD has a prevalence of approximately 4% in patients with SCD. SCCLD is presumably related to recurring episodes of infarction and infection and is characterised by a decrease in radiodensity of the lungs, moderate to severe impairment of pulmonary function, and in its most severe form by evidence of pulmonary hypertension.

Radiographic abnormalities
Significant radiographic interstitial lung disease has been seen in patients with SCD. In a prospective study, 41% patients with SCD who had at least one prior episode of ACS were found to have significant multifocal interstitial lung abnormalities on thin section computed tomography scans of the chest. A correlation was found between the severity and extent of interstitial abnormalities on computed tomography and the number of prior episodes of ACS.

Pulmonary function abnormalities in sickle cell disease
Pulmonary function abnormalities in SCD are frequent and are characterised by airway obstruction, restrictive lung disease, abnormal diffusion capacity, and hypoxaemia. However, a restrictive airways abnormality is typically seen in patients with SCCLD. A recent prospective study based on echocardiograms in 154 patients with SCD, however, revealed a prevalence of 34% and approximately 27% of these patients found to have severe pulmonary hypertension.

Pulmonary hypertension
Prevalence
Secondary pulmonary hypertension has become an increasingly recognised complication in patients with SCD. It is associated with impaired exercise tolerance, progressive heart failure, and a high mortality. Retrospective studies of echocardiograms of patients with SCD suggested a prevalence of pulmonary hypertension from 30% to 56%. A recent prospective study based on echocardiograms in 154 patients with SCD, however, revealed a prevalence of 34% and approximately 27% of these patients found to have severe pulmonary hypertension.

Right sided cardiac catheterisation is the gold standard test for the diagnosis of pulmonary hypertension. Haemodynamic studies of patients with cardiopulmonary symptoms by right sided heart catheterisation have also demonstrated a raised pulmonary systolic and diastolic pressure. Although SCD patients with echocardiographic evidence of pulmonary hypertension may not have the symptoms of cardiac dysfunction, mortality is significantly increased in these patients compared with patients without pulmonary hypertension.

Pathophysiology
Pulmonary hypertension is characterised by progressive obliteration of the pulmonary vasculature. The mechanism of pulmonary hypertension complicating SCD is unknown and likely to be multifactorial. Possible causes include: sickle cell related vasculopathy due to sequestration of sickle erythrocytes, fat embolism, or recurrent infection; chronic hypoxic stress causing irreversible remodelling of the vasculature with smooth muscle proliferation and fibrosis; recurrent pulmonary thromboembolism; increased blood viscosity with consequent right ventricular volume or pressure overload; and pulmonary scarring from repeated episodes of ACS. Regardless of the pathophysiology of pulmonary hypertension, once it becomes established, the patients are at risk for right sided heart failure.

Clinical features
Patients tend to be asymptomatic in the early stage, though with moderate to severe pulmonary hypertension they experience chest pain, dyspnoea, and hypoxaemia at rest. With disease progression they are at risk for right heart failure and sudden death from pulmonary thromboembolism, systemic hypotension, and cardiac arrhythmia.

Management
Limited data are available in the literature regarding management of pulmonary hypertension related to SCD. The efficacy of continuous intravenous epoprostenol (prostacyclin) and calcium channel blockers, which are effective therapy in primary pulmonary hypertension, are of unknown efficacy in pulmonary hypertension secondary to SCD. Patients with significant parenchymal lung disease may develop considerable shunt and increased oxygen requirement while receiving epoprostenol. Likewise, systemic blood pressure is lower than normal in patients with SCD and it is not known whether SCD patients can tolerate vasodilators. Various other agents including prostaglandin analogues such as subcutaneous
Inhaled NO directly acts on pulmonary vasculature and improves oxygenation by reducing V/Q mismatch and pulmonary artery pressure. NO down-regulates the expression of endothelial adhesion molecules, thereby reducing vaso-occlusion. NO inhibit platelet aggregation and may prevent thrombotic complication in patients with pulmonary hypertension. NO may contribute to the induction of fetal haemoglobin by hydroxyurea. NO inhibition enhance NO delivery to the peripheral vasculature by increasing nitrosylated haemoglobin.

Advanced disease, intravenous epoprostenol should be started and atrial septostomy may be considered. Lung transplantation is less likely to be beneficial in patients with SCD due to an expected high procedure related mortality in these patients.

CONCLUSION

Pulmonary complications are common and account for a large proportion of deaths among adults with sickle cell disease. They result from the complex pathophysiology of sickle cell disease. New therapies are being developed that may prove to be beneficial in the various complications. Clinicians should be aware of acute and chronic complications of sickle cell disease, as they have emerged as major threats to the health and longevity of patients with this condition.

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Authors’ affiliations

A Siddiqui, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Long Island Jewish Medical Center, New Hyde Park, the Long Island Campus for the Albert Einstein College of Medicine, Bronx, New York

S Ahmed, Division of Hematology and Oncology

REFERENCES

5 Farber MD, Konysh M, Kinney TR. Cooperative study of sickle cell disease: demographic and socioeconomic characteristics of patients and families with sickle cell disease. J Chronic Dis 1983;38:495–505.

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