

BRIEF REPORT

Death Due To Asthma in Two Adolescents With Sickle Cell Disease

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In one prospective cohort study, a diagnosis of asthma was associated with an increased risk of mortality in individuals with sickle cell anemia or HbSS. However, a direct relationship between death and asthma exacerbation could not be documented. This report examines two adolescents with sickle cell disease (SCD) who died during worsening symptoms consistent with asthma. Autopsies

in both individuals demonstrated pulmonary airway smooth muscle hyperplasia, basement membrane thickening, and eosinophilia, consistent with bronchial asthma. Individuals with SCD and asthma warrant ongoing education, treatment, and surveillance for life-threatening complications of asthma. *Pediatr Blood Cancer*
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Key words: asthma; autopsy; mortality; sickle cell disease

INTRODUCTION

Asthma is a common co-morbid condition in sickle cell disease (SCD), affecting 17–48% of children [1,2]. A diagnosis of asthma in children with SCD is associated with an increased rate of pain [1] and acute chest syndrome (ACS) [1–3]. One prospective cohort study of 1,963 children and adults with HbSS participating in the Cooperative Study of Sickle Cell Disease (CSSCD) found that asthma is associated with an increased rate of mortality [4].

The reason for premature death in individuals with SCD and asthma is unknown. While the CSSCD data [5] documented the relationship between asthma and an increase rate of mortality, the data did not include autopsy findings and provided no evidence that patients with SCD and asthma died from an asthma exacerbation. Wheezing occurs in people with SCD and many reports of asthma may be due to SCD-related respiratory symptoms [5,6]. Providing pathological evidence consistent with asthma in individuals with SCD who die prematurely would strengthen the causal link between asthma and an increased risk of mortality.

In this report, we describe the circumstance and autopsy findings of two adolescents with SCD who died during increased respiratory symptoms consistent with asthma exacerbations.

METHODS

This study was exempt from review by the Human Research Protection Office at Washington University because the subjects were not living. Family members of the deceased adolescents were interviewed by their primary hematologist to document past history and circumstance of the fatal event. Permission to publish this report was obtained from the families. Autopsy pathology slides were retrospectively reviewed by a single pathologist for this study.

Patient 1

Patient 1 was a 14-year-old male with HbSC and severe persistent asthma (Table). He reported daily albuterol use and coughing 2 nights per week. His past medical history was notable for eight hospital admissions due to asthma exacerbations, although none of those admissions occurred in the year before his death. His controller medications included inhaled fluticasone 110 mcg bid and montelukast 5 mg a day. His family reported adherence to his asthma regiment. Psychological stressors included social withdrawal thought to be related to embarrassment from nocturnal

enuresis. Two months prior to his death, he underwent pulmonary function tests revealing a pre-bronchodilator forced expiratory volume in 1 sec (FEV₁) 1.81 L (66% of predicted), forced vital capacity (FVC) 3.08 L (97% of predicted), and FEV₁/FVC 68% of predicted. Post-bronchodilator, FEV₁ increased 20%. Lung volume testing demonstrated a total lung capacity (TLC) of 4.31 L (100% of predicted) and a ratio of residual volume (RV) to TLC of 38% (upper limit of normal is 30%), indicative of air trapping and small airway disease.

Description of event. Patient 1 awoke from a nap with shortness of breath and chest tightness. While receiving an albuterol nebulizer treatment, he expressed a premonition of death. He then collapsed and became unresponsive. When emergency medical services arrived he was pulseless and apneic. He was transported to the emergency department where resuscitation efforts were continued until he was pronounced dead.

Patient 2

Patient 2 was a 20-year-old male with HbSS and severe persistent asthma (Table). His past medical history was notable for one hospitalization for an asthma exacerbation, but the hospitalization did not occur in the year before his death. His asthma controller medications included fluticasone/salmeterol 250/50 bid and montelukast 10 mg a day. His family reported adherence to his asthma

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TABLE I. Table Past Medical History and Autopsy Lung Findings of Two Adolescents With Sickle Cell Disease (SCD) and Asthma

	Patient #1	Patient #2
Past medical history		
SCD		
Phenotype	SC	SS
# Hospitalizations, lifetime (yr before death)		
Pain	1 (0)	13 (4)
ACS	0 (0)	4 (0)
History of stroke	No	No
Hydroxyurea use	No	No
Asthma		
# Hospitalizations, lifetime (yr before death)		
Asthma	8 (0)	1 (0)
Pulmonary function tests ^a	FEV ₁ 1.80 L (73%) FVC 2.76 L (96%) FEV ₁ /FVC 68%	FEV ₁ 2.90 L (77%) FVC 3.72 (81%) FEV ₁ /FVC 78%
Asthma severity classification	Severe persistent	Severe persistent
Asthma mortality risks ^b		
Chronic prednisone	No	No
ICU admissions	None	None
Psychological stressors	Grade failure, social withdrawal because of nocturnal enuresis	Depression
Medication non-adherence	No	No
Autopsy		
Lung histopathology	Airway smooth muscle hyperplasia, basement membrane thickening Airway associated lymphoid tissue Airway eosinophilia Minimal luminal mucus Mild goblet cell hyperplasia	Airway smooth muscle hyperplasia, Basement membrane thickening Airway associated lymphoid tissue Airway eosinophilia Minimal luminal mucus Focal luminal eosinophils and neutrophils with adjacent acute bronchopneumonia

^aPulmonary function tests performed 2 months before death for Patient #1 and 6 months for Patient #2; ^brisks for asthma severity based on NHLBI guidelines [13], Strunk et al. [15] and Miller et al. [16].

regiment. At his last clinic visit, oxygen saturation was 97% on room air. Spirometry testing 6 months before the fatal event was consistent with mild restriction, with a pre-bronchodilator FEV₁ 2.90 L (77% of predicted), FVC 3.72 L (81% of predicted), and FEV₁/FVC 78% of predicted, but restriction was not apparent on lung volume testing (TLC was 4.17 L or 94% of predicted). Post-bronchodilator, there was only an 8% increase in FEV₁. Psychological stressors included depression. The day prior to his death, he expressed concern that he was going to die.

Description of event. Patient 2 had three episodes of emesis the morning of his death. He did not have shortness of breath until he presented to the outpatient hematology clinic that afternoon where he described wheezing and pain in his chest and back. On physical examination, he demonstrated increased effort with breathing. He was severely hypoxic and was treated with supplemental oxygen and albuterol by nebulization. Shortly thereafter he had a seizure and progressed to full cardiopulmonary arrest. Resuscitation efforts were initiated and the patient was intubated and transported to the intensive care unit where he died a short time later.

RESULTS

Patient 1

At autopsy, the lungs were heavy (1,010 g combined weight, normal range: 573–901 g). Mucus plugs were not appreciated.

Microscopic examination revealed congested lung parenchyma with mild edema. There was prominent airway associated lymphoid tissue with germinal centers. Bronchi and large bronchioles had smooth muscle hyperplasia, marked basement membrane thickening, and prominent eosinophilic infiltrate (Fig. 1). In a few airways, there was mucus cell hyperplasia and small amount of luminal mucus. Arteries and arterioles did not show changes of pulmonary hypertension. Additional autopsy findings included cardiac left ventricular hypertrophy (heart weight 480 g, normal range 189–237 g, LV wall thickness 1.5 cm) and congestive hepatosplenomegaly (liver weight 1,950 g, normal range 1,095–1,313 g, spleen weight 550 g, normal range 111–191 g). Sickled red blood cells were present.

Patient 2

At autopsy, the lungs were heavy (1,150 g combined lung weight, normal range 685–1,050 g), congested and edematous. Mucus plugs were not appreciated. On microscopic examination, airway findings were similar to that of Patient 1, including airway associated lymphoid tissue with germinal centers, smooth muscle hyperplasia, marked basement membrane thickening, and prominent eosinophilic infiltrate. Focally, airways contained sloughed epithelium admixed with neutrophils, eosinophils, and a small amount of mucus, with adjacent bronchopneumonia. Arteries and arterioles did not show changes of pulmonary hypertension.

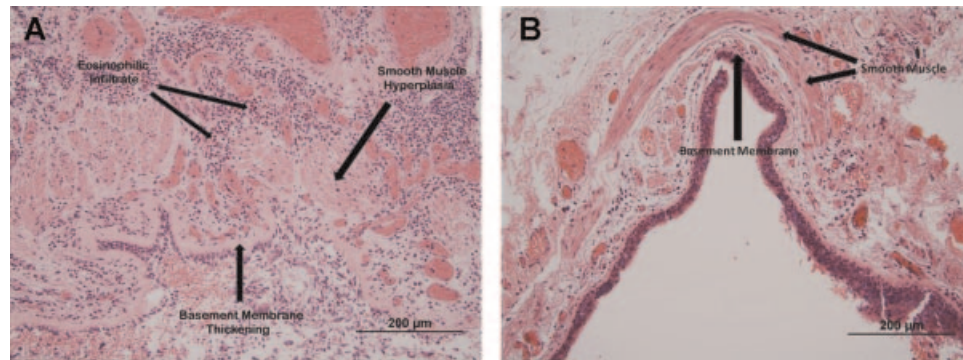


Fig. 1. Patient 1. Histologic section of medium sized airway with smooth muscle hyperplasia, marked basement membrane thickening, and partial epithelial denudement. There are numerous eosinophils in peribronchiolar tissue and airway wall (A). For comparison, an airway from a surgical resection for tumor shows no smooth muscle hyperplasia, basement membrane thickening, or significant eosinophilic infiltrate (B); (hematoxylin and eosin, 200 $\times$).

Additional findings included cardiac left ventricular hypertrophy and dilatation (heart weight 420 g, normal range 272–318 g, LV wall thickness 1.4 cm) and splenic fibrosis (weight 75 g, normal range 167–225 g). Sickled red blood cells were present.

DISCUSSION

A previous study demonstrated that asthma in individuals with HbSS is associated with increased all-cause mortality [4]; however, immediate causes of death were not known. In this report, we have presented two adolescents who died during asthma exacerbations. Microscopic examination of autopsy lung tissue from both patients revealed airway smooth muscle hyperplasia, thickened basement membranes, and prominent eosinophilia, consistent with bronchial asthma.

Only one prior report has described a death in an individual with SCD that was temporally related to an asthma exacerbation and supported by autopsy findings [7]. The cause of death in this case study was fat emboli and not an asthma exacerbation. However, the fat emboli may have been caused by asthma or corticosteroid-induced vaso-occlusion [8,9].

Fatal asthma exacerbations are rare among children in the general population without SCD. Asthma-related deaths occur at a rate of approximately 1–2/100,000 patient-years [10]; however, death may occur more frequently in those with severe asthma, especially adolescents and young adults [11,12]. Risks for fatal asthma include a history of severe exacerbations requiring ICU admission [13], poorly controlled symptoms [14], oral steroid dependency [13], psychological stress [15], and non-adherence with asthma therapies [16]. In the present study of SCD, our two cases had histories of psychological stress suggesting that some established risks for fatal asthma in the general population also apply to individuals with SCD.

Prior studies have categorized asthma-related deaths as slow onset-late arrival and sudden onset [17,18]. Individuals in the slow onset-late arrival scenario present to medical attention after the presence of symptoms for many hours or days, and lung histopathology is characterized by a predominance of eosinophils in the airway submucosa [19]. In contrast, sudden onset deaths typically occur within an hour from the onset of symptoms and airway submucosa shows a high proportion of neutrophils [19]. Although both participants in the present study had an eosinophilic

infiltrate in the airway submucosa, Both patients had a rapid onset of symptoms consistent with sudden onset.

This study does not explain the pathogenesis for premature death among individuals with SCD and asthma. Asthma exacerbations can result in regional hypoxia in the lungs, acidosis, and/or inflammation in the pulmonary vascular bed [20], all of which could promote vaso-occlusion. In the absence of randomized studies to guide management, patients with SCD and asthma should be closely monitored, ideally under the care of an asthma specialist, and treated according to NHLBI asthma guidelines [13].

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REFERENCES

1. Boyd JH, Macklin EA, Strunk RC, et al. Asthma is associated with acute chest syndrome and pain in children with sickle cell anemia. *Blood* 2006;108:2923–2927.
2. Knight-Madden JM, Forrester TS, Lewis NA, et al. Asthma in children with sickle cell disease and its association with acute chest syndrome. *Thorax* 2005;60:206–210.
3. Bernaudin F, Strunk RC, Kamdem A, et al. Asthma is associated with acute chest syndrome, but not with an increased rate of hospitalization for pain among children in France with sickle cell anemia: A retrospective cohort study. *Haematologica* 2008;93:1917–1918.
4. Boyd JH, Macklin EA, Strunk RC, et al. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica* 2007;92:1115–1118.
5. Vichinsky EP, Styles LA, Colangelo LH, et al. Acute chest syndrome in sickle cell disease: Clinical presentation and course. Cooperative Study of Sickle Cell Disease. *Blood* 1997;89:1787–1792.
6. Delclaux C, Zerah-Lancner F, Bachir D, et al. Factors associated with dyspnea in adult patients with sickle cell disease. *Chest* 2005; 128:3336–3344.
7. Johnson K, Stastny JF, Rucknagel DL. Fat embolism syndrome associated with asthma and sickle cell-beta(+)-thalassemia. *Am J Hematol* 1994;46:354–357.

8. Glassberg J, Spivey JF, Strunk R, et al. Painful episodes in children with sickle cell disease and asthma are temporally associated with respiratory symptoms. *J Pediatr Hematol Oncol* 2006;28:481–485.
9. Darbari DS, Castro O, Taylor JG VI, et al. Severe vaso-occlusive episodes associated with use of systemic corticosteroids in patients with sickle cell disease. *J Natl Med Assoc* 2008;100:948–951.
10. Anderson HR, Gupta R, Strachan DP, et al. 50 years of asthma: UK trends from 1955 to 2004. *Thorax* 2007;62:85–90.
11. Turner MO, Noertjojo K, Vedal S, et al. Risk factors for near-fatal asthma. A case-control study in hospitalized patients with asthma. *Am J Respir Crit Care Med* 1998;157:1804–1809.
12. Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501–506.
13. Expert report panel 3: Guidelines for the diagnosis and management of asthma. NIH publication No: 08-5846. Bethesda, MD: US Department of Health and Human Services; National Institutes of Health; National Heart, Lung and Blood Institute; National Asthma Education and Prevention Program, 2007.
14. McFadden ER, Jr., Warren EL. Observations on asthma mortality. *Ann Intern Med* 1997;127:142–147.
15. Strunk RC, Mrazek DA, Fuhrmann GS, et al. Physiologic and psychological characteristics associated with deaths due to asthma in childhood. A case-controlled study. *JAMA* 1985;254:1193–1198.
16. Miller TP, Greenberger PA, Patterson R. The diagnosis of potentially fatal asthma in hospitalized adults. Patient characteristics and increased severity of asthma. *Chest* 1992;102:515–518.
17. Strunk RC. Death due to asthma. New insights into sudden unexpected deaths, but the focus remains on prevention. *Am Rev Respir Dis* 1993;148:550–552.
18. Hyzy RC, Travis WD, Hanna E, et al. Slow-onset asthma deaths have more eosinophils and health care utilization than rapid-onset deaths. *Respir Med* 2008;102:1819–1826.
19. Sur S, Crotty TB, Kephart GM, et al. Sudden-onset fatal asthma. A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Am Rev Respir Dis* 1993;148:713–719.
20. Busse WW, Lemanske RF, Jr. Asthma. *N Engl J Med* 2001;344:350–362.