J Forensic Sci, Jan. 1974, Vol. 19, No. 1

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Sudden Unexpected Death in Hemoglobin SC Disease

Persons with sickle cell anemia have an extensive morbidity and frequently die at an early age. In some instances their deaths occur suddenly [*1*]; such an occurrence in hemoglobin SC disease is rare. This report documents the sudden and unexpected death of a 48-year-old black man whose first symptoms of hemoglobin SC disease were his last.

Case Report

A 48-year-old black man had always been vigorous and athletic; to his family and friends he was the "picture of health." Repeated and detailed interviews with his wife and other members of his family disclosed that he had not consulted a physician for many years except for treatment of minor injuries, had never been seriously ill, and took no medications. From 1947 to 1949 he was on active duty as a corpsman in the U.S. Army, and then served six years in the Active Reserve. He had worked at a steel mill since 1949, first as a laborer and more recently as a truck driver.

His father died at age 77 from chronic renal disease of undetermined etiology which terminated in uremia; his mother died at age 78 from multiple sequelae of arteriosclerotic cardiovascular disease. Of the decedent's six siblings, one 49-year-old brother was said to be in excellent health; another died at age 45 from a head injury sustained incidental to a "fainting spell;" the whereabouts and health of a third brother were unknown. Two of the decedent's sisters died of "pneumonia" in their late teens. The third sister had a fatal intrapartum hemorrhage; allegedly one of her sons has sickle cell trait, and he in turn has a child with sickle cell anemia.

On the day before his death the decedent returned home from work at 4:00 p.m. and shortly thereafter went to a neighborhood tavern. He drank and talked with acquaintances for about two hours, went home briefly to change his clothes, and returned to the tavern. At approximately 8:00 p.m. he joined friends to play cards. Before the card game, all participants consumed a meal of chitlins, yams, and greens; none of the others became ill subsequently.

Shortly after midnight he withdrew from the game because he had lost his money. At

Received for publication 19 March 1973; revised manuscript received 1 June 1973; accepted for publication 12 June 1973.

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that time he voiced no complaint of illness. Since the other players were not yet ready to terminate the game and he was dependent upon one of his companions for transportation home, he retired to a reclining chair in the same room and went to sleep.

The card game finished at 3:00 a.m. and he was awakened easily. As he sat upright from a reclining position he said that he felt "sick" and vomited once. He was able to stand but staggered when he walked. A friend helped him into a car and drove directly to a nearby hospital. En route he complained of abdominal cramps and seemed to gasp for breath. He was transported in a wheel chair from the car into the emergency area, where a nurse noted that he was moaning and bent forward with his arms folded across his abdomen. Without delay he was taken to an examining room and helped onto a table. Within seconds his body stiffened momentarily and then became flaccid. His pulse and blood pressure were unobtainable and his respiration ceased. Attempts at resuscitation were ineffective and were discontinued after 15–20 min.

Autopsy

An autopsy was performed 4 h after death. The decedent's height was 170 cm and he weighed 72 kg. External examination was unremarkable. His thoracic and abdominal viscera were in their normal anatomic relationships, his body cavities were free from hemorrhage or effusion, and his neck organs were normal. Vomitus was not present in the proximal airway or distal respiratory passages.

His 370-g heart was dilated; the valves and myocardium showed no abnormality. The coronary arteries arose in their usual positions, had patent ostia, were normal size, and had a balanced pattern of distribution. Coronary atherosclerosis was focal and slight with no point of more than 30 percent stenosis in the epicardial branches. Microscopic examination showed no inflammatory infiltration in his myocardium and intramyocardial blood vessels were normal.

The lungs were uniform and congested with a combined weight of 920 g. There were no recent thromboemboli; fat emboli were not present. In one microscopic section of lung a branch of the pulmonary artery approximately 0.1 cm in diameter had a double lumen, the probable sequel of a remote thrombus or embolus. A muscular branch of a pulmonary artery contained an organizing, endothelialized, nonobstructive mural thrombus. Minimal, apical subpleural emphysema was present. With the exception of the spleen the remainder of the viscera, including the brain, showed no gross or microscopic abnormality other than vascular congestion to be described presently. His liver did not show fatty metamorphosis, chronic passive hyperemia, or deposition of stainable iron.

His spleen weighed 30 g and had a wrinkled capsule which focally adhered to adjacent structures. Its cut surfaces disclosed accentuation of the normal trabeculae and a reddish-brown parenchyma without discernible follicles. Multiple, irregular, 0.1- to 0.5-cm areas of greyish-white fibrosis with golden yellow margins were distributed randomly throughout the pulp (Fig. 1). Microscopically these foci were typical fibrous siderocalcific nodules. The remainder of the spleen did not contain an excess of stainable iron.

Microscopic study of all the decedent's major organs, including multiple sections from his heart and brain, revealed generalized, marked capillary and venular engorgement by densely packed, sickled red cells. The capillary and venular engorgement by sickled erythrocytes *was not* restricted to his passively hyperemic lungs and abdominal viscera. Similar but less prominent congestion and sickling were present in arterioles and small arteries and veins in a widespread distribution. Erythrophagocytosis by Kupfer cells was prominent.

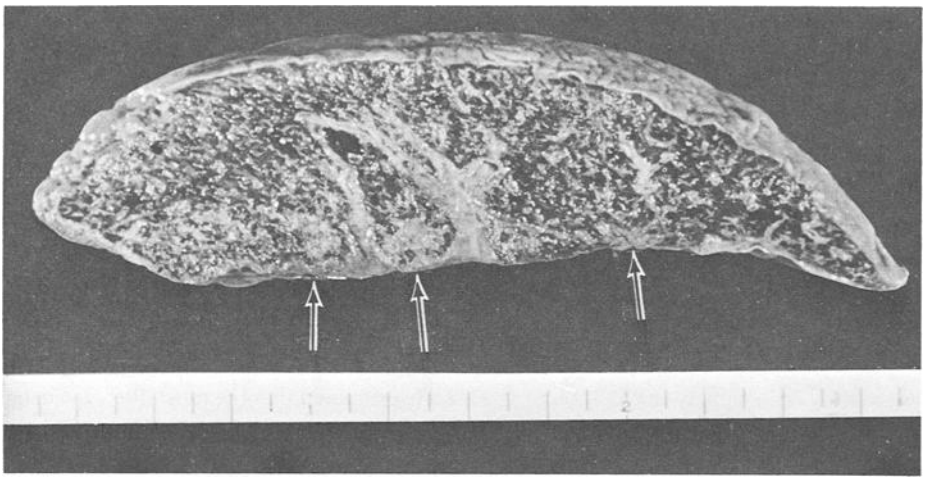

FIG. 1—*Cross section of atrophic spleen showing wrinkled capsule and prominent trabeculae. Arrows indicate some of the larger siderocalcific nodules. Follicles are indistinct. (Scale is in inches.)*

Toxicological Studies

The decedent's blood and urine contained 60 and 130 mg of ethanol per 100 ml, respectively. (Ethanol does not dissipate from these fluids in the interval between death and autopsy.) Methanol, isopropanol, or other alcohols were not present. His blood contained no barbiturate or carboxyhemoglobin and his urine was free of sugar, acetone, aldehyde, phenothiazine, salicylate, narcotics, amphetamine and related compounds, and antihistamines. His bile did not contain morphine.

Hemoglobin Analysis

A diagnosis of the hemoglobin SC disease was made on the basis of the following studies carried out on blood obtained postmortem. A carboxyhemoglobin solution prepared in glycerol was used. Electrophoresis on thin-layer starch gel, using a discontinuous buffer system at pH 8.6 [*2*] and on cellulose acetate using a Tris-EDTA-borate buffer at pH 8.9 showed two major hemoglobin fractions migrating with mobilities identical to Hb-S and Hb-C. Hb-F, determined by alkali denaturation, comprised less than 1 percent of the specimen. A solubility test (Sickledex, Ortho Diagnostics, Inc.) was positive. Solubility was further studied by Itano's method [*3*]. Approximately 50 percent of the hemoglobin was precipitated. The remaining soluble hemoglobin had the mobility of Hb-C on starch gel.

Discussion

This 48-year-old black man had hemoglobin SC disease with a non-sickling C hemoglobin, which had produced no symptoms during his previously vigorous life. He became ill precipitously with vomiting, abdominal cramps, and labored breathing and died less than an hour after the onset of his symptoms. Autopsy and laboratory studies indicate that a thrombotic sickle crisis, characterized by widespread sickling of red cells in small vessels, is the only reasonable explanation for his death.

The noxious stimulus which initiated the lethal intravascular sickling remains enigmatic. He was not dehydrated, and there is no valid basis for assuming that he became hypoxic or acidotic while he was sleeping in the reclining chair. Therefore, none of the usual initiators of sickling can be identified in this instance. To hypothesize that he slept in a peculiar position which caused venous stasis in his legs or viscera requires a degree of speculation which strains one's pathophysiologic imagination.

The concentrations of ethanol in his blood and urine were insufficient to have caused respiratory depression. Furthermore, he could not have metabolised sufficient ethanol during his three hours of sleep to support a hypothesis that he was markedly intoxicated before going to sleep. His slight (insignificant) coronary atherosclerosis and minimal pulmonary abnormalities are not acceptable as important contributory factors or causes of his death.

Motulsky [*4*] calculated the frequence of SC hemoglobinopathy in U.S. blacks at birth as possibly ranging between 1:311 and 1:3333. He estimated that the most likely incidence is 1:833. These individuals may live long, asymptomatic lives, but adverse effects of this hemoglobinopathy may be manifested in bones [*5*, *6*, *7*], eyes [*8*], lungs (with or without cor pulmonale) [*5*, *6*, *9*, *10*, *11*], gallbladder [*12*], spleen [*6*, *9*, *10*, *12*, *13*], and genitourinary tract [*14*]. In pregnancy, fetal and maternal mortality and morbidity are high [*15*, *16*].

Exclusive of pregnancy we found two reports of sudden death due to thrombotic sickle crisis in patients with hemoglobin SC disease [*9*, *10*]; however, neither of these occurred in a previously asymptomatic individual. The decedents were 34- and 38-year-old black men, both of whom had prior treatment for pulmonary vascular occlusions with cor pulmonale. These two patients and the individual reported here had atrophic spleens. This finding stands in contrast to a high incidence of splenomegaly [*13*] in patients with hemoglobin SC disease and may have significance. Splenic atrophy with formation of siderocalcific nodules, which may be demonstrable radiographically [*6*], is a sequel of previous episodes of visceral sickling and may indicate that the patient is at risk for sudden death on the basis of his hemoglobinopathy.

Summary

A 48-year-old, vigorous, ostensibly healthy black man died suddenly and unexpectedly. Autopsy and laboratory studies established that he had hemoglobin SC disease with a non-sickling C hemoglobin, and that the only reasonable explanation for his death was extensive sickling of red cells in the small vessels of all of his major organs.

Acknowledgment

Toxicological studies were performed at the Toxicology Laboratory of the Cuyahoga County Coroner's Office under the supervision of Irving Sunshine, Ph.D.

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