

**CRISIS IN SICKLE CELL TRAIT**

ALDEN W. DUDLEY, JR, MD, AND CAROLINE C. WADDELL, MD

*A 34-year-old black male with hemoglobin AS was admitted for renal failure, polydipsia, hypertension, schizophrenia, mental confusion, and visual hallucinations. Abnormal electrolytes were corrected by dialysis, but blood specimens were reported as hemolyzed with hyperkalemia. Peaked T waves on electrocardiographic analysis were followed by cardiac arrest. An autopsy revealed sickled cells in the visual cortex and other symptomatic organs, but normal erythrocytes in most of the vascular tree. These findings suggest true progressive sickle cell crisis in a hemoglobin AS patient. HUM PATHOL 22:616-618. This is a US government work. There are no restrictions on its use.*

Fully 8% of black Americans carry hemoglobin AS (hgb AS) and are described as having sickle cell trait (SCT)—an “innocuous” genotype.<sup>1</sup> Several investigators have described symptoms and death which they attributed to a sickle cell crisis in patients with hgb AS.<sup>2-4</sup> However, others have questioned these reports because of “undue reliance on postmortem findings of intravascular sickling” without supportive laboratory data.<sup>5</sup>

Failure to anticipate a diagnosis of sickle cell crisis in this patient precluded a full spectrum of laboratory tests or hematology consultation. However, there remain sufficient laboratory, electrocardiographic (EKG), clinical, and autopsy features to be pathognomonic for a sickle cell crisis. Sickled cells were restricted to symptomatic organs and regions of the brain. These findings support the hypothesis that patients with hgb AS may develop a sickle crisis under physiologic duress (hypoxia, acidosis, or dehydration).

**CLINICAL HISTORY**

A 34-year-old black male with paranoid schizophrenia, progressive dementia, hypertension, and end-stage renal disease was hospitalized January 23, 1987 for visual hallucinations and tremors of 3 days' duration. Past history included surgery for right facial and abdominal stab wounds in 1967. In 1981, the patient was first noted to be hypertensive. By 1983, blood pressure was 214/158 mm Hg with grade 3 fundus. In March 1984, blood urea nitrogen level was 126 mg/dL (45 mmol/L) and creatinine level was 18.7 mg/dL (1,650  $\mu$ mol/L). The patient was given an arteriovenous access graft for triweekly hemodialysis. He was a thin man who frequently drank entire quarts of water. After 1984, the patient had multiple hospitalizations for acute psychosis with auditory hallucinations and paranoia. A bleeding peptic ulcer was treated by gastrojejunostomy in March 1986.

In May 1986, a screening Sickledex test was positive and hemoglobin showed hgb A and S without other abnor-

malities. Because the density of the A and S bands was typical of sickle cell trait (approximately 60%/40%), studies for thalassemia were not performed. The level of glucose-6-phosphate dehydrogenase was tested and found to be normal. Hematology consultation was not requested; test results were considered irrelevant to the patient's illness.

Upon admission, the patient described visual hallucinations without paranoid ideation. He could not stand up because his legs became shaky and he had a severe intention tremor. All four extremities were restrained. Because of the serum sodium of 117 mg/dL, fluid intake was restricted to 1,200 mL daily. By the third hospital day he became increasingly confused, occasionally “violent,” and lay staring at the ceiling.

Hemodialysis was performed on January 26, 1987; the blood sample received by the laboratory was reported as “hemolyzed” (Table 1). Subsequent samples were also hemolyzed and showed rapidly climbing potassium (despite sodium polystyrene sulfonate therapy), uric acid, aspartate aminotransferase, and lactate dehydrogenase levels, concurrent with falling hematocrit, hemoglobin, platelet count, albumin, and globulin levels. An EKG showed peaked T waves, tachycardia, and left bundle branch block. On January 27, 1987, he had a generalized tonic-clonic seizure and suffered cardiac arrest at 1:45 AM, was resuscitated briefly, and finally pronounced dead at 5:00 AM.

**AUTOPSY**

An autopsy revealed intimal thickening throughout large medium-sized renal arteries in kidneys weighing only 75 g each. Glomeruli were severely atrophic. The heart weighed 625 g, had complete pericardial fibrosis, and showed concentric thickening of both ventricles without scars. The lungs had a combined weight of 1,705 g, were deeply congested, and edematous with mild anthracosis. Whereas most pulmonary vessels had normal erythrocytes, some peripheral small vessels contained sickled cells. The gastrojejunostomy was open and adequate. Mucosal vessels were normal, but submucosal venules were often filled with sickled cells. The liver weighed 1,900 g, had a tense capsule, and irregular areas of mottled yellow or dark red-brown. Microscopy of the liver revealed thrombosis, infarction, and necrosis alternating with congestion and hemorrhage, a pattern characteristic of disseminated intravascular coagulation. All red cells in the infarcted areas, and most in the congested or hemorrhagic sites, were sickled.

The spleen weighed 250 g, was tense, densely packed with sickled red cells, and several splenic veins contained hemosiderin and red cell-laden macrophages. It had siderosis reflecting excessive chronic destruction of erythrocytes. The bone marrow was grossly hyperemic, had 70% cellularity, and showed a particular increase in erythroid precursors, including normoblasts. The thymus revealed extramedullary hematopoiesis. Sickled red cells were found in selected vessels of the kidneys and testes as well.

The fresh brain weighed 1,500 g, was extremely pale, and had uniformly mildly swollen gyri without herniation of the uncus or tonsils. The ventricles were mildly reduced in volume but there were no grossly discernible lesions in gray or white matter. Luxol Fast blue-periodic acid-Schiff stains revealed multiple sites of ischemic malacia, with the largest focus 4 by 1 mm in the left occipital watershed zone of white matter. Arterioles to these sites were plugged with

Received from the Departments of Pathology and Medicine, Veterans Administration Medical Center, Houston, TX; and Baylor College of Medicine, Houston, TX. Accepted for publication August 27, 1990.

*Key words:* sickle cell trait, sickle crisis, autopsy, dialysis, hyperkalemia, stroke.

Address correspondence and reprint requests to Alden W. Dudley, Jr, MD, Veterans Administration Medical Center (113), 2002 Holcombe Blvd, Houston, TX 77030.

This is a US government work. There are no restrictions on its use.

0046-8177/91/2206-0018\$0.00/0

**TABLE 1.** Serum Hematology and Chemistry

Analysis	Date				
	1/21/87	1/23/87	1/26/87	1/27/87	1/28/87
Hematocrit (%)	32.9	39.0	—	—	22.4
Platelets ( $10^9/\text{mL}^3$ )	—	341	—	—	152
Sodium (mmol/L)	132	117	125	126	142
Potassium (mmol/L)	4.3	3.6	4.5	6.8	8.1
Chloride (mmol/L)	91	81	87	80	96
Total $\text{CO}_2$ (mmol/L)	18.5	19.0	15.0	13.2	7.9
Urea N (mmol/L) (mg/dL)	17.8 (50)	16.4 (46)	23.5 (66)	31.0 (87)	39.2 (110)
Albumin (g/L) (g/dL)	37 (3.7)	31 (3.1)	49 (4.9)	—	26 (2.6)
Globulin (g/L) (g/dL)	42 (4.2)	53 (5.3)	45 (4.5)	—	19 (1.9)
Uric acid (mmol/L) (mg/dL)	580 (9.8)	380 (6.5)	720 (12.2)	—	1,120 (19.0)
AST (SGOT) (U/L)	14	27	466	—	1,900
LDH (U/L)	157	155	564	—	2,870

Abbreviations:  $\text{CO}_2$ , carbon dioxide; N, nitrogen; AST (SGOT), aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); LDH, lactate dehydrogenase.

sickled cells and often surrounded by hemosiderin macrophages (Fig 1), while arterioles to other sites contained normal, donut-shaped red cells (Fig 2). Sections taken at random showed occasional vessels occluded by sickled cells causing microinfarcts varying from acute to chronic in all lobes.

#### DISCUSSION

Intimal fibromuscular hyperplasia is ordinarily a disease of major arteries such as the origin of the internal carotids or renal arteries, is familial, and is most common in women.<sup>6</sup> A similar disorder has been described in smaller arteries of the brain,<sup>3</sup> spleen, and kidneys of patients with sickle cell disease. This patient had the renal vascular pattern of sickle cell disease (small arteries in hilum without major renal artery involvement). Progressive renal failure and hypertension appear to have been secondary to this lesion.

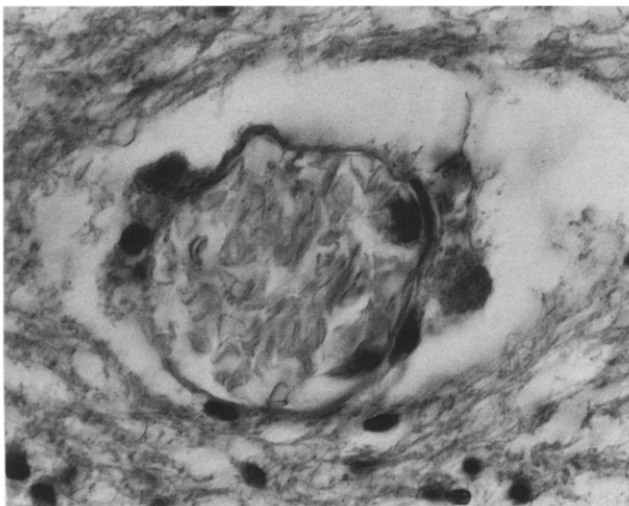
Sickling is reversible to a point, but repeated sickling damages the plasma membrane irreversibly.<sup>4</sup> These phenomena are worsened by acidosis (between dialyses), dehydration, hypertonic solutions, anesthesia, fever, or polycythemia, and relieved by water or alkalization.<sup>7</sup> Sickled

cells marginate, adhere to endothelium, and induce reactive intimal hyperplasia.<sup>8</sup> Hemoglobin AS erythrocytes will most likely sickle in vessels with relatively stagnant circulation. This would include capillaries and veins in the legs, the double capillary bed of the kidneys, the watershed region of the brain, the sinusoids of the spleen, and the portal segment of the intestines.

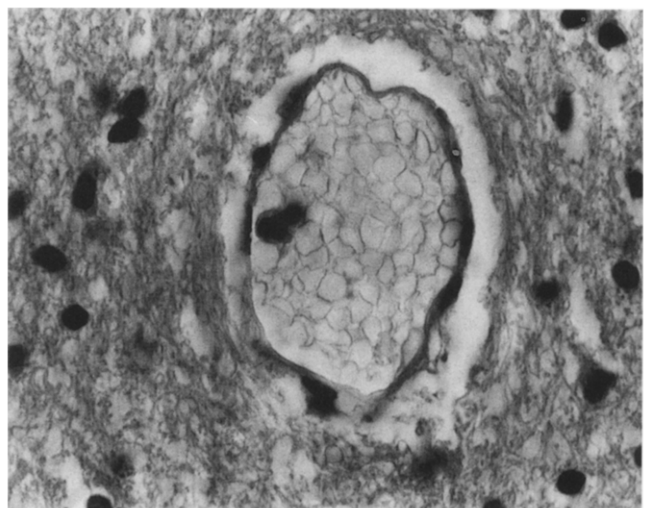
Since 1930, it has been known that cells sickle in vivo when  $\text{pO}_2$  is less than 40 mm Hg.<sup>9</sup> Thus, the distribution of sickled cells in this patient could have been predicted. The unexpected autopsy finding was the apparent free flow of round erythrocytes in most of the pulmonary and other major arteries, veins, and even capillaries.

It is often taught that formalin causes red blood cells to sickle. However, Ham et al<sup>10</sup> demonstrated that red cells containing sickle hemoglobin are not adversely affected by buffered formalin or glutaraldehyde. They will maintain their donut shape indefinitely; therefore, cells found sickled in tissue fixed in buffered formalin were sickled before fixation. While one might expect that cells would sickle during the anoxic phase of death, surviving round erythrocytes in this patient demonstrate that such is not the case. The selective distribution in our patient of sickling and siderosis in areas with infarction is serendipitous.

In 1961, McCormick<sup>11</sup> reported a series of 120 autop-



**FIGURE 1.** Occipital arteriole plugged with degenerating sickled red blood cells and with perivascular red cell and hemosiderin-laden macrophages. (Luxol Fast blue-periodic acid-Schiff stain; magnification  $\times 1,000$ .)



**FIGURE 2.** Neighboring patent arteriole with nonsickled intraluminal erythrocytes. (Luxol Fast blue-periodic acid-Schiff stain; magnification  $\times 1,000$ .)

sies on SCT patients with 22 (18%) showing massive sickling and cerebral infarcts, 15 (13%) having massive sickling of cerebral vessels without proven infarcts, and the remaining 83 (69%) containing multiple vessels with sickled cells but no impactions. Thus, 30% of SCT patients had significant sickling and may have had central nervous system symptoms. Patients with SCT have had slow, progressive infarction of the brain and spinal cord,<sup>12</sup> pituitary, and retina.<sup>13</sup>

Hemoglobin AS is not an innocuous genotype. Kark et al<sup>14</sup> have recently shown an increased incidence of sudden death in SCT recruits. High altitude encampment, exercise, and flying without compression are accepted causes of sickling in heterozygous disease. Many military personnel are exposed to all three of the above hazards.

The visual hallucinations without paranoid ideation were a clue to sickling. The cerebral component of sickle cell anemia and SCT emphasizes bilateral watershed areas with sluggish circulation (relative hypoperfusion), stagnation, and the potential for sickling. Subcortical white matter in the occipital pole is most frequently involved,<sup>9</sup> and is the most logical site for visual hallucinations of organic origin. Frontal pole, centrum ovale, internal capsule, and pons follow in descending order of frequency as sites of ischemia and infarction.

The laboratory report of "hemolysis" of the blood was reasonable in view of elevated serum potassium level and pigmentation. However, it was not due to phlebotomy, transport problems, or heating of the blood. The sickle crisis led to apparent disseminated intravascular coagulation, and infarction of multiple organs (liver, spleen, etc) caused lysing of their cells. Repeat blood samples showed progressive elevation of serum potassium to 7.5 mg/dL, the EKG T wave spiked, and the patient died.

Treatment of sickle cell crisis is both physiologic and symptomatic. Bicarbonate, transfusion with hgb AA blood hypotonic saline (up to three to four liters), and hyperbaric oxygen are recommended.<sup>7</sup> Curiously, intravenous fluids may actually flush enough red cells from capillaries to raise

the hematocrit level.<sup>15</sup> Routine high intake of water is a strong prophylactic as well as therapeutic regimen for sickle cell anemia or SCT.

## REFERENCES

1. Bunn HF: Disorders of hemoglobin, in Wilson JD, Braunwald E, Isselbacher KJ, et al (eds): *Harrison's Principles of Internal Medicine*. New York, NY, McGraw-Hill, 1991, pp 1544-1547
2. Butkus DE: Sickle cell trait (SCT): An opposing view. *Milit Med* 149:164-165, 1984
3. Kozlowski PB, Rao C, Sher JH: Subintimal fibromuscular hyperplasia (SFH) of large cerebral blood vessels as a complication of sickle cell anemia (SCA). *J Neuropathol Exp Neurol* 46:382, 1987
4. Serjeant GR: *Sickle Cell Disease*. New York, NY, Oxford, 1985, pp 1-478
5. Sears DA: The morbidity of sickle cell trait. A review of the literature. *Am J Med* 64:1021-1036, 1978
6. Dudley AW Jr: Cerebrospinal blood vessels: Normal and diseased, in Haymaker W, Adams RD (eds): *Histology and Histopathology of the Nervous System*. Springfield, IL, Thomas, 1982, pp 714-799
7. Knoche JP: Hematuria in sickle cell trait: The effect of intravenous administration of distilled water, urinary alkalinization, diuresis. *Arch Intern Med* 123:160-165, 1969
8. Barabino GS, McIntire LV, Eskine SZ, et al: Rheological studies of erythrocyte—endothelial cell interactions in sickle cell disease, in Nagel RL (ed): *Progress in Clinical and Biological Research*, Vol 240, Pathophysiological Aspects of Sickle Cell Vaso-Occlusion. New York, NY, Liss, 1987, pp 113-127
9. Scriver JB, Waugh TR: Studies on a case of sickle cell anemia. *Can Med Assoc J* 23:375-380, 1930
10. Ham TH, Dunn RF, Sayre RW: Physical properties of red cells as related to effects in vivo. I. Increased rigidity of erythrocytes as measured by viscosity of cells altered by chemical fixation, sickling, and hypertonicity. *Blood* 32:847-861, 1968
11. McCormick WF: Abnormal hemoglobins. II. The pathology of sickle cell trait. *Am J Med Sci* 211:329-335, 1961
12. Wolman L, Hardy AG: Spinal cord infarction associated with the sickle cell trait. *Paraplegia* 7:282-291, 1970
13. Conrad WC, Penner R: Sickle cell trait and central retinal artery occlusion. *Am J Ophthalmol* 63:465-468, 1967
14. Kark JA, Posey DM, Schumacher HR, et al: Sickle cell trait as a risk factor for sudden death in physical training. *N Engl J Med* 317:781-787, 1987
15. Erlanson ME, Schulman I, Smith CE: Studies on congenital hemolytic syndromes. III. Rates of destruction and production of erythrocytes in sickle cell anemia. *Pediatrics* 25:629-644, 1960

## OSTEOCLAST-LIKE GIANT CELL TUMOR OF THE PANCREAS: IMMUNOPHENOTYPIC SIMILARITY TO GIANT CELL TUMOR OF BONE

RUTH D. GOLDBERG, MBBCh, FABRIZIO MICHELASSI, MD, AND ANTHONY G. MONTAG, MD

*An immunophenotype was performed on an osteoclast-like giant cell tumor of the pancreas using a panel of antibodies to epithelial and leukocyte antigens. Several antibodies to cytokeratin and carcinoembryonic antigen were negative in the tumor. Osteoclast-like cells were positive for CD4, CD13, CD45, CD68, CD71, and vimentin, but negative for lysozyme and HLA-DR. Mononuclear tumor cells were positive for CD4, CD11c, CD13, CD14, CD45, CD68, CD71, HLA-DR, and vimentin, but negative for lysozyme. The phenotype is similar to that previously described for giant cell tumor of bone. The osteoclast-like cell phenotype is also similar to that*

*reported for normal osteoclasts. The findings support a nonepithelial origin for osteoclast-like giant cell tumor of the pancreas, and suggest a derivation similar to giant cell tumor of bone. HUM PATHOL 22:618-622. Copyright © 1991 by W.B. Saunders Company*

Osteoclast-like giant cell tumor of the pancreas (OGTP) is an unusual entity originally described by Rosai,<sup>1</sup> and characterized by osteoclast-like giant cells and mononuclear stromal cells identical to those seen in giant cell tumor of bone. It is distinct from the pleomorphic giant cell tumor of the pancreas, lacking the marked nuclear pleomorphism associated with that entity. Often a histologically recognizable pancreatic carcinoma accompanies OGTP, and the majority of the 15 previously reported cases<sup>2-4</sup> have favored an epithelial origin for the giant cells. We report a case of OGTP with immunohistochemical characterization of the tumor using a panel of antibodies to leukocyte and epithelial antigens. The findings indicate that the immunophenotype of OGTP resembles that of giant cell tumor of bone, and suggest a nonepithelial origin for the tumor.

From the Departments of Pathology and Surgery, University of Chicago, Chicago, IL. Accepted for publication September 17, 1990.

*Key words:* giant cell tumor, osteoclast, immunoenzyme techniques, pancreatic neoplasms, leukocyte antigens.

Address correspondence and reprint requests to Anthony G. Montag, MD, University of Chicago, Box 274, 5841 S Maryland Ave, Chicago, IL 60637.

Copyright © 1991 by W.B. Saunders Company  
0046-8177/91/2206-0019\$5.00/0