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CASE REPORT

CRIMINALISTICS

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Sickle Cell Trait-Associated Deaths: A Case Series with a Review of the Literature*,†

ABSTRACT: This study presents a series of 16 carriers of hemoglobin S (HbS) who died during various circumstances. Many of the cases were associated with mild to moderate exertion. The onset and/or duration of symptoms varied from a few minutes to several hours with many displaying a prolonged lucid interval with stable vital signs. Despite seeking medical treatment, sickle cell trait-related micro-occlusive crisis was never considered in the differential diagnosis. Several cases were associated with sudden death. In those deaths which were delayed, high anion gap and uncompensated metabolic acidosis were typical and were not heat related. Also characteristic were large increases in creatine kinase, alanine aminotransferase, and aspartate aminotransferase along with myoglobinemia. Although the antemortem diagnosis of rhabdomyolysis was made, the underlying cause was never deduced by the clinicians. The sickling found at autopsy is not always a postmortem artifact, and in the right circumstances can be diagnostic.

KEYWORDS: forensic science, sickle cell trait, rhabdomyolysis, anion gap, metabolic acidosis, hemoglobin S, exertional heat illness

As many as one in three Africans living in areas where malaria is indigenous and approximately one in twelve Americans with African ancestry have sickle cell trait (SCT) (1). The affected individuals are generally asymptomatic, and many are not even aware that they carry the HbS gene. The general consensus of the public is that SCT is a relatively benign condition, and affected persons are at no increased risk of morbidity or mortality because of their condition (2). However, the medical and forensic communities are cognizant that under the proper set of circumstances, SCT can be fatal (3–6).

This report demonstrates the wide variety of clinical presentations that persons with SCT may experience in response to certain stressors including clinical symptoms, laboratory abnormalities, and autopsy findings. It also seeks to show how readily the diagnosis can be made by the astute clinician or forensic pathologist, but only if it is considered in the differential diagnosis in the appropriate clinical setting. Most importantly, the authors hope that this report will have a significant impact by showing that SCT is a condition which is not restricted to phenotypic Afro-Americans, and that early recognition of the disease in other individuals carrying the gene can possibly result in a decline in mortality.

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Materials and Methods

The authors have collectively gathered 16 cases that occurred over a 12-year period (1996–2008) where we believed that HbS present in the heterozygous state was either the cause or played a contributory role in the death of the individual. The cases were detected as part of the routine workload of jurisdictions of the authors with two cases referred to one of the authors (J.R.T.) through private consultations and one case detected through a public records request. All of the cases had autopsy reports, microscopic hematoxylin and eosin (H&E) slides, toxicology reports, and investigative/police reports available for examination. Hospital records were reviewed in all relevant cases except one where a relatively complete synopsis was reviewed.

The cases included three females and 13 males with ages varying from 11 to 43 years. Most of the individuals had been subjected to some form of physical exertion or physiological stress which lasted from several minutes to several hours. The onset of symptoms varied from minutes to days as did the survival time. In some cases this resulted in immediate incapacitation with sudden death; in other cases death did not occur for several days. In cases where blood gases were available, the pH was typically below 7.0 and often anion gaps were greater than 30. Table 1 summarizes the pertinent findings in this case study and a more detailed description of six specific individual cases is given below. Case 3 has been previously reported (4). Detailed descriptions of every case are outside the scope of this publication.

Case 1

On a hot July afternoon, a 29-year-old black man was approached by police officers for suspicion of a drug offense. The suspect fled

TABLE 1—*Summary of pertinent findings.*

Case No.	Age/Race/Sex	Exertion	Environmental Temperature (°F)	Exertion Time	Survival Time	HbS%	pH/AG	Mechanism	Autopsy
1	29/B/M	Police foot chase	91°	10 mins	10.5 h	41.4	n/a	Rhabdomyolysis Micro-occlusion	Muscle necrosis/sRBCs
2	15/B/M	Police boot camp	64°	8–12 min	17 h	41	6.78/>40	Micro-occlusion Lactic acidosis	sRBCs DIC
3	30/B/M	Swimming	78° (68° water)	5–10 min	14 h	43.3	6.94/36.0	Micro-occlusion Deconditioning Rhabdomyolysis	BMI = 39.6 Cardiomegaly sRBCs
4	11/B/M	Football practice	92°	15–20 min	9 days	n/a	7.3/17.1	Hyperthermia Renal failure Rhabdomyolysis	BMI = 26.6 Rhabdomyolysis sRBCs
5	36/W/M	Weightlifting Welding	83° Indoors	Hours/weeks	Hours	41.4	n/a	Ruptured spleen Hemoperitoneum	Ruptured spleen Splenic sequestration sRBCs
6	43/B/M	Roofer with leg pain and generalized weakness	88°	Day(s)	1 day	36.1	7.08/31.5	Rhabdomyolysis Renal failure Dehydration Micro-occlusion	Splenic sequestration Rhabdomyolysis sRBCs
7	19/W/M	Assault	68–75°	Minute(s)	24 h	41	6.8/43	Rhabdomyolysis Micro-occlusion Renal failure	sRBCs Splenic sequestration Bronchopneumonia
8	13/B/M	Police foot chase	82°	Minutes	None	38	n/a	Micro-occlusion Asthma	sRBCs Asthma
9	31/B/M	Obstacle course	86°	6 min	2.5 h	44.7	<6.5/>40.0	Rhabdomyolysis	BMI = 29.5 sRBCs
10	21/B/M	Basketball	83°	30 min	None	41.7	n/a	Micro-occlusion	sRBCs Cardiomegaly
11	18/B/M	Football practice	Indoors	90 min	~1.5 h	n/a	6.789‡/n/a	Micro-occlusion	sRBCs
12	12 B/M	Football practice	92°	100 min	20 min	57.4†	n/a	Micro-occlusion	BMI = 25.5 sRBCs HbSE
13	36/B/F	Inversion after MVC	75°	n/a	5 h	51.6*	n/a	Micro-occlusion Mild blunt trauma	sRBCs HbSC
14	40/B/F	Sexual activity Sleep apnea	Indoors	Unknown	n/a	n/a	n/a	Micro-occlusion Hypoxia/sleep apnea	BMI = 34.4 sRBCs
15	30/B/F	Childbirth	Indoors	Minutes	2 weeks	38.9	n/a	Micro-occlusion	sRBCs Benign pancreatic mass
16	20/B/M	Unknown	Unknown	Unknown	n/a	n/a	n/a	Dehydration Micro-occlusion	sRBCs Splenic sequestration

AG, anion gap; BMI, body mass index.
*Had HbSC disease with 42.8% HbC.
†Had HbSE disease with 34.2% HbE.
‡Status post-cardiac arrest.

on foot and jumped over several fences for approximately 400 m. After he was caught, he continued struggling with police for about 5 min and during this time period, two Taser™ electronic control devices were deployed. After the suspect was handcuffed, he was transported to a local hospital where he was orally hydrated, observed for approximately 2 h and released with normal vital signs (temperature [T]: 98.6 F, pulse [P]: 87, respiration rate [RR]: 20, blood pressure [BP]: 117/91 mmHg, O_2 saturation [O sat]: 99% and a normal electrocardiogram [EKG]). An elevated body core temperature was not documented. He was alert and oriented 4×. No blood or urine was sampled and no other tests were performed. He was then transported to the jail where he complained of lower abdominal pain, which resulted in a transfer to the medical wing where all his activities were recorded by a video camera. He was acting somewhat lethargic, and while sitting in a wheelchair, he became unresponsive 5 h later. Resuscitation efforts were immediately initiated. One hour after being found unresponsive, he was pronounced dead at a local hospital after arriving in full cardiopulmonary arrest.

The autopsy revealed a well-nourished 183 lb, 72 in. black male with a few minute puncture sites and punctate thermal injuries of the torso and back that were consistent with injuries from the Taser™ electronic control devices. He had marked vascular congestion of all organs with numerous sickled red blood cells (sRBCs) and gross rhabdomyolysis of the psoas and calf muscles with microscopic vascular congestion with sRBCs. His postmortem urine was dark orange. Toxicology on postmortem samples revealed cocaine and cocaine metabolites only in the urine. Hemoglobin electrophoresis revealed HbA1 = 56.3%, HbA2 = 2.3%, and HbS = 41.4%. The cause of death was "complications of rhabdomyolysis" with contributory conditions of "cocaine intoxication, SCT, physical exertion and restraint."

Case 2

A 15-year-old black male was at his first day at a boot camp-type detention facility where he was required to perform multiple sit-ups and pushups and run 1.5 miles on a dirt track. The exercise began in the morning in cool weather. Approximately 8 min into the run, he stopped and was subsequently advised by the guards to continue running; approximately 1 min later, he collapsed. The temperature at the time of the collapse incident was 64°F (the relative humidity was 73%). After pulling him off the running path, the guards attempted to physically persuade him to resume. Video surveillance cameras showed that the victim appeared lethargic and unable to stand. Attempts to coerce continued exercise included administration of ammonia capsules which met with negative results. These ammonia capsules were episodically held under his nose while his mouth was covered. The officers restrained him, holding him against a post, inflicted leg and torso blows, and at one point held him prone on the ground. He was conversing during the event and seemed alert until someone noted signs of obvious mental obtundation. Approximately 30–45 min after the onset of his initial collapse, emergency medical services (EMS) were requested. Initial vital signs were P of 144; RR of 14; BP of 82/60 mmHg. He remained unresponsive in the hospital and a blood gas drawn at the time of intubation showed profound metabolic acidosis (pH = 6.784, pCO_2 = 20.9, pO_2 = 240.7, bicarbonate = 3.1 mmol/L, and lactic acid = 18.6 mmol/L). His initial body temperature was 99.7°F. Laboratory studies revealed a creatine kinase (CK) level of 8722 IU/L and indicators of disseminated intravascular coagulation (DIC). The severe acidosis was partially corrected with bicarbonate and ventilation. However, despite aggressive bicarbonate infusion his treating physicians struggled with his refractory acidosis until more aggressive ventilator settings were chosen. Blood loss from DIC necessitated multiple blood transfusions. The day after admission (about 14 h after collapse) he expired.

The autopsy revealed a black male with focal contusions of the scalp and extremities. No fractures or other significant trauma was reported. A retroperitoneal hematoma was found and this was believed to be due to coagulopathy from severe DIC. Microscopically he had sRBCs with vascular congestion of the kidneys, brain, spleen, lungs and liver. Hemoglobin electrophoresis revealed a HbA1 of 55% and a HbS of 41%. The cause of death was certified as "complications of sickle cell trait." A second autopsy found similar anatomic findings but certified the cause of death as related to asphyxia caused by laryngospasm from ammonia inhalation and attributed the microscopic findings of sickling as agonal and/or postmortem artifact.

Case 3

One afternoon in late February, a 30-year-old, muscular, and mildly obese black man was with his family on the beach. After inflating some beach floats, reportedly by manually blowing them up by mouth, he watched his children playing in the water. When one of the floats drifted out too far, he proceeded to swim for about 4–5 min in order to retrieve it. When he approached the float, he began having difficulty swimming. A person on a jet ski noticed the subject having difficulties and assisted him to the shore. On the shore, he was conversing normally. The wife witnessed the event and reported that at no time was the decedent's head submerged. As a precaution EMS were summoned.

Within 5 min of notification, paramedics were at the victim's side. His initial Glasgow coma scale (GCS) was 15 and he was alert and oriented 4×. His radial pulse was strong at 140. His skin was cool, moist, and of normal color. Four minutes later his vital signs were: BP of 90/58 mmHg; P of 140; RR of 26. An EKG revealed sinus tachycardia. While attempting to gain intravascular access, he became lethargic and eventually unresponsive. Forty-one minutes after EMS arrived, the decedent was transferred to a local hospital. His rectal temperature was 100°F. In the emergency room, his breathing pattern became agonal and he was intubated. Initial laboratory findings revealed a profound metabolic acidosis with a pH of 6.94, bicarbonate of 8 mmol/L, lactic acid of 9.6 mmol/L, and an anion gap of 36. A urine drug screen revealed the presence of cannabinoids and a small amount of salicylate. He had elevated calcium, phosphorus, CK, troponin, lactate dehydrogenase, and amylase. Although he was tachycardic, his heart function remained strong until his demise. The clinicians suspected some type of toxic ingestion or diabetes. Approximately 14 h after admission while the clinicians battled his refractory acidosis, he coded and was pronounced dead.

The autopsy findings revealed a healthy appearing black man with no significant external findings. Internal examination showed cardiomegaly (550 g), moderate atherosclerosis of the anterior descending branch of the left coronary artery, congestion of the lungs, liver, and spleen. On microscopic examination there was severe vascular congestion of the spleen, heart, kidney, pancreas, brain, and lungs with many sRBCs. Hemoglobin electrophoresis revealed a HbS level of 43.3%, a HbA1 level of 52.8%, and a HbA2 level of 3.9%. The cause of death was "complications of sickle cell trait" with a contributory cause of "arteriosclerotic cardiovascular disease."

Case 4

An 11-year-old, somewhat obese, black male was at his first day of football practice on a hot and humid July afternoon. After approximately 15–20 min of strenuous exercise, he began to act "abnormally," collapsed and started having "seizures." The seizure activity was mild and self limited. EMS responded and found an initial axillary temperature of 103.5°F (erroneously recorded in the medical chart as 109°F) with a repeat rectal temperature of 106.2°F shortly thereafter. The initial GCS was 10, and the skin was described as "cool and moist." EMS began cooling measures and he was transported to the emergency room. A blood gas 33 min after arrival revealed a pH of 7.307, pCO_2 of 33.8 mmHg, PO_2 of 232.7 mmHg, and bicarbonate of 16.5 mmol/L. The anion gap was 17.1. The initial CK level was 190 IU/L, and the liver function tests were normal as was a CT scan of the brain. Initial urinalysis upon arrival revealed 3 + protein, 2 + glucose, and 3 + blood. A complete blood count revealed a hematocrit of 33.9% with 1 + anisocytosis. The prevailing diagnosis at the time was heat stroke. During the hours following admission, his temperature returned to normal limits and within a day he was alert, ambulating to a degree, and speaking appropriately while on room air. Over his 9 day hospital duration, he had continued anisocytosis (that later resolved) and began exhibiting signs of rhabdomyolysis, liver failure, renal failure, anemia, and progressive acidosis. On the fifth day of admission he began displaying progressive neurological deterioration. At the time of his demise, no family history of SCT was known to any of the treating physicians.

The autopsy revealed an appropriately healthy, mildly obese black adolescent with normal gross anatomic findings. Microscopic findings showed congested lungs, liver, and adrenal glands and a non-pathological myocardium. The cause of death was certified as "sequelae of heat stroke." However, 2 years after the autopsy, the microscopic slides were reviewed, and it was found that there were extensive sRBCs in the vascular spaces of all of the aforementioned organs. No hemoglobin electrophoresis was performed. The microscopic descriptions were amended and the family was notified. The death certification was not changed.

Case 5

The decedent was a 36-year-old white man, with a history of drug and anabolic steroid abuse, who was employed as a pipe fitter. One day in April after work, the victim reportedly did a rigorous workout in a gym and returned to his motel room where he complained of "stomach" pain to his roommate. Approximately 7 h after going to bed, the victim was found unresponsive on the floor of his room by his roommate. He was pronounced dead 1 h later.

The autopsy revealed a hemoperitoneum of 1500 cm^3 due to a ruptured 1000 g spleen. The capsule of the spleen had an opaque discoloration and was tense and bulging with an estimated 10.0 cm × 6.0 cm area of rupture. No fractures of the overlying ribs or soft tissue hemorrhages were observed. Microscopy showed congestion of the spleen and lungs with numerous sRBCs. No acute or chronic lung or vascular diseases were identified. Postmortem blood was positive for methadone (260 ng/mL) and benzoylecgonine (660 ng/mL). Hemoglobin electrophoresis revealed a HbA1 of 58.6% and a HbS of 41.4%. The cause of death was listed as "ruptured spleen due to sickle cell hemoglobinopathy."

Further investigation revealed that the decedent would typically complain of pain following gym workouts and had been placed on opiates for back pain. After speaking with the wife of the decedent, it was learned that the son of the deceased had a positive sickle cell screen at birth. Upon learning of the autopsy results, the initially doubtful family physician had the parents of the deceased tested and the father was also found to be positive for SCT.

Case 6

In April, a 43-year-old black man employed as a roofer was nauseated with malaise, generalized weakness, and what the decedent had described as leg pain and leg cramps for a couple of days. The intensity of the illness was such that he missed work the following day and went to the emergency room. The decedent's sister reported that he was a chronic alcoholic. While waiting for a procedure, he collapsed. Vital signs were as follows: BP of 100/78 mmHg; P of 133; RR of 18; T of 96.8°F, and an O_2 sat of 99%. The decedent was intubated and it was noted that his muscles were palpably tense. An initial arterial blood gas revealed a pH of 7.11, pCO_2 = 80 mmHg and a bicarbonate of 25.8 mmol/L; a repeat blood gas, 1 h later, displayed a pH of 7.075, pCO_2 = 56.2 mmHg, and a bicarbonate of 16.4 mmol/L. Acetaminophen and salicylate were detected at low levels but a CK level was 478 IU/L, blood urea nitrogen was 53 mg/dL, and creatinine was 6.5 mg/dL. Hospital urine toxicology was positive for benzodiazepines and cannabinoids with urinalysis findings of 13 red blood cells (RBCs) per high power field and orange colored urine. Despite medical intervention, he died the following day approximately 30 h after admission.

The autopsy revealed congestion of the splenic red pulp, kidneys, and patchy skeletal muscle myocytolysis; the blood vessels of the previously mentioned tissues contained numerous sRBCs. Hemoglobin electrophoresis revealed a HbA1 level of 63.9% and a HbS level of 36.1%. The death was certified as "rhabdomyolysis due to dehydration" with "sickle cell trait and chronic alcoholism" as contributory conditions.

Case 7

A 19-year-old white male of Hispanic ethnicity was hospitalized after he complained of shortness of breath, extremity pain, confusion, and dizziness in the shower. His girlfriend reported that his lips appeared blue. According to law enforcement just before the onset of his symptoms, the decedent had initiated an assault on another person which lasted minute(s). The incident occurred between 5 pm and 7 pm, and the temperature was between 68 and 75°F during those hours. He was functional enough to make it home, and he was able to ambulate and enter his shower. Two weeks prior to the incident he had been involved in a motor vehicle crash where he suffered neck/back soreness and broke the lateral portions of his left sixth and seventh ribs but he was reportedly healing and was having little if any difficulty. He also had been complaining of flu-like symptoms for approximately 2 weeks.

At the time of hospital admission, he was found to have a pH of 6.8 and an anion gap of 43. He was afebrile. Drug testing revealed marijuana. He complained of generalized pain. The only recent trauma reported by the hospital was abrasions to his knees. The clinicians described progressive rhabdomyolysis and renal failure and initially suspected some type of toxic ingestion or diabetes. It was strongly suspected that he had some type of infection, although none was diagnosed. He was initially alert, but his mental status began waxing and waning. Approximately 10 h after his symptoms began, he became unresponsive and coded. His vital signs were restored, and he was mechanically ventilated for the next 3 h. DIC ensued, and he was pronounced dead approximately 24 h after the

initiating event. Despite strong suspicions of an infectious process by the clinicians in the last hours of the decedent's life, no blood cultures were obtained.

The autopsy findings revealed a healthy appearing man with no significant external findings. The autopsy report indicated that the decedent had a white phenotype, marked congestion of the lungs, and no significant trauma. Microscopic examination showed pulmonary edema, hemosiderin laden macrophages, and some alveolar spaces filled with neutrophils. Several organs were noted to contain sRBCs. The spleen was described as markedly congested. The sRBCs were dismissed as postmortem artifact. Hemoglobin electrophoresis performed on hospital admission blood revealed a HbS level of 41% and a HbA level of 57%. No drugs were detected. In a lengthy opinion discussion about the case, streptococcus septicemia was suspected, but this could not be supported by the postmortem bacterial studies or the gross or microscopic examination. Thus, the cause of death was certified as "rhabdomyolysis with renal failure of unknown etiology" 6 months after the death occurred.

Four years after the autopsy, the microscopic slides were reviewed, and they revealed extensive sRBCs in the organs as discussed in the file. The spleen had lakes of sRBCs with the central portion of the spleen showing vascular and red pulp sRBCs while much of the peripheral and subcapsular portions of the spleen had virtually acelluar red pulp. The kidneys, liver, and lungs had extensive collections of sRBCs. No sections of skeletal muscle were taken. The alveolar collections of neutrophils described in the lungs were more consistent with collections found after mechanical ventilation and respiratory collapse than those resulting from an underlying preadmission infectious process. No abscesses or other indications of overwhelming sepsis or infection were seen.

Discussion

One of the earliest published papers involving deaths associated with SCT was a case series of four deaths of military recruits in 1970 (5). Since then other authors have added to the wealth of knowledge and understanding regarding exertion-related deaths in people with SCT (3,4,6–14). In addition to the reported deaths associated with exertion or altitude that are apparent in the literature, anatomic and functional differences in cerebral vasculature, urine concentrating ability, and red cell rigidity all have been described in individuals with SCT (15–17). Pulmonary, renal, and cerebral infarction/thrombosis apparently unrelated to exertion have also been described in those with SCT (18–22). Despite this, the clinical recognition of people exhibiting signs and symptoms related to SCT is sorely lacking. The cases presented here illustrate the varying circumstances that can be associated with SCT.

The typical clinical manifestations are sudden death, rhabdomyolysis, renal failure, high anion gap metabolic acidosis, splenic sequestration, or some combination of these. All these cases except for cases 4 and 7 were certified as being related to SCT. It is our opinion that SCT played a significant contributory role in case 4 and a major causative role in case 7 even though it was not considered in the death certification. Case 13 had HbSC disease which is considered as sickle cell disease by clinicians. Cases 14–16 were certified as related to SCT, but this was primarily due to the absence of other identifiable causation and/or a relative lack of reliable or available circumstantial information.

Although the onset of severe symptoms is typically minutes, these cases show that the onset can be as much as several days or weeks from the initiating event. As described by Eichner (23), the more strenuous the activity, the earlier the onset of symptoms. Perhaps the prolonged and sustained nature of the exertion (such as the sustained type of work involved in cases 5 and 6) accounts for the increased time prior to the onset of symptoms in some of the cases. Survival time is also highly variable, from sudden death at or near the time of exertion to prolonged hospital survival of up to 9 days (case 4). Case 15 was 2 weeks postpartum and had been complaining of leg pains since the home delivery when she collapsed in front of the boyfriend. Deaths associated with pregnancy and SCT are not uncommon (24). Several of the cases had increased body mass indices (cases 3, 4, 9, 12, and 14) (25) or other comorbidity factors such as asthma, dehydration, or deconditioning.

The literature is replete with references associating SCT with exertional rhabdomyolysis. In fact, those with SCT have been shown to be 100–200 times more likely to suffer rhabdomyolysis after exertion than those with normal hemoglobin (12,13). Of the deaths presented here, many had either clinical evidence of rhabdomyolysis or it was demonstrated at autopsy. Typical clinical symptoms of muscle pathology in SCT related deaths include flaccidity, pain, cramps, and induration in involved muscles.

Several reports and studies of military recruits and others have concluded that exertional heat illness (EHI) is the underlying cause of death in those with SCT-associated rhabdomyolysis (12,13,26,27). These authors opine that SCT does not increase the incidence of EHI but SCT increases the mortality of EHI; therefore if EHI is the underlying culprit, controlling EHI will prevent the deaths.

The latest and largest military study includes cases over a 29-year period (27). This study used a broad definition of EHI and included cases of apparent actual exertional heatstroke along with cases without hyperthermia or exposure to hot environments which also had laboratory-documented rhabdomyolysis, renal failure, and certain enzyme/electrolyte anomalies. Even cases with normal body temperatures exercising in cool environments were considered EHI simply because they had lived long enough for laboratory evidence of rhabdomyolysis to be obtained (12,13). Rhabdomyolysis related to exertion can be caused by many factors of which only one is heat (28,29).

Without the presence of SCT or other known risk factors, exertional rhabdomyolysis is often localized and relatively benign. Exertional rhabdomyolysis unrelated to heat exposure or hyperthermia can occur in well-hydrated individuals even after workouts in climate-controlled environments and usually involve repetitive severe exertion with resulting rhabdomyolysis but without severe or fatal systemic illness (30,31). Cases of severe rhabdomyolysis in athletes unrelated to SCT or other risk factors have been reported, but these involve severe, sustained activity, and they do not necessarily have adverse or fatal outcomes (29). Conversely, many cases of severe exertional rhabdomyolysis associated with SCT do not involve severe exertion or hot environments and frequently involve disturbance in mentation with generalized severe systemic illness and metabolic acidosis.

With respect to body temperature and exertion, elevation of core temperature during exercise is a normal physiologic response which decreases upon cessation of the exertion (32,33). Benign exertion-related hyperthermia occurs even in cool environments and therefore, elevated body temperature is not necessarily the underlying cause of fatal rhabdomyolysis to the exclusion of all other etiologies (34).

An example of one of the military cases involved the reported EHI death of a 30-year-old soldier with SCT undergoing the mountain phase of U.S. Army Ranger training (13). The death occurred

in cool (50–55°F), misty conditions. The soldier had a rectal temperature of 98°F and suffered severe exertional rhabdomyolysis which the authors attributed to EHI. The local major metropolitan newspaper quoted an Army report stating that the soldier died from renal failure caused by SCT (35). No mention was made of heat or heat illness. The location of the incident, as indicated by the newspaper, was Camp Merrill, Georgia which is at a mild altitude of 3700–4000 ft. Altitude is a major risk factor for exertional sickling as previously described in military and civilian cases (12). Although this altitude was mild by comparison to the typical reported cases, the case report described this Ranger training as extremely strenuous.

In contrast to the military interpretation that exertional rhabdomyolysis equates with heat illness, this case series shows that exertional rhabdomyolysis in those with SCT occurs even in cool environments with short-term exertion. For instance, the exertion involving case 3 occurred while swimming in water with a temperature that has been shown to be one of the most effective treatments of heat illness (36). Indeed, the conditions and time exposed to water of that temperature could have induced mild hypothermia (37,38). A previous case report described a person with SCT drowning during a sprint distance (~100 yard) swim race in a lake (3). The circumstances involved in case 3 (particularly a location with rapid medical response) simply allowed him to survive long enough to have laboratory tests performed.

The clinical findings of heat stroke and SCT-related micro-occlusive crisis have overlapping findings (12,23,26,27,39). In fact, case 4 had the prominent features of both heat stroke and SCT with rhabdomyolysis and metabolic acidosis found in both conditions. In such circumstances, one may argue that it may be difficult to distinguish the two entities although an article by Eichner (23) describes the difference in the acute setting.

In the deaths associated with exertion that are presented here, evidence of rhabdomyolysis is an almost universal finding in those whose survival times were long enough to allow the diagnosis to be made. Although his collapse and death were sudden, case 1 was unique not only due to the 10.5 h delay between exertion and collapse and his medical release from an emergency room after prolonged evaluation, but also for how the postmortem diagnosis of rhabdomyolysis was initially made: direct visualization of the damaged muscles. This unique diagnostic route was due primarily to the anatomic location of the muscles being in the direct field of view of any routine autopsy. The follow-up confirmation of the gross diagnosis from that point forward was relatively straightforward.

Rhabdomyolysis is an extremely serious medical illness and can be devastating even with aggressive treatment (40). It is likely that other instances of apparent sudden death such as case 1 are actually prolonged brewing insults with inapparent loci of rhabdomyolysis. The other cases in this series that had rhabdomyolysis were diagnosed clinically due to prolonged survival and extensive laboratory analysis. The finding of muscle biopsy-confirmed sickling-induced rhabdomyolysis has been previously described (40,41).

Of course renal failure would be a concern in any case where rhabdomyolysis occurs (11,14,23,26,40). However, the renal insufficiency and pathology found in those with SCT is not merely secondary to rhabdomyolysis but a direct result of the effects of sickled erythrocytes on the kidneys (16,20,21). Hyposthenuria and other urinary anomalies have been well described in those with SCT. Specific microscopic glomerular differences have been described in those with SCT in addition to renal infarction (21,42). Cases 3 and 4 showed urinary anomalies immediately upon presentation.

High anion gap metabolic acidosis was another common feature of the cases with any significant antemortem survival. The differential diagnosis of metabolic acidosis with increased anion gap includes many diagnoses, but SCT-related micro-occlusive crisis is not one of them even when specifically dealing with lactic acidosis from hypoperfusion (43,44). Of the cases presented where pH was documented, the acidosis was severe with many cases having pH levels below 7 including the deaths involving exertion in cool conditions. Acidosis of such an extreme nature is not unusual for exertional-related deaths of HbS carriers (11,12,26,45). Of the 14 cases in our series, six (cases 2–4, 6, 7, and 9) were admitted to a hospital with sufficient time for a diagnosis of metabolic acidosis to be made; however, in none of those cases was SCT entertained as the etiology even when the metabolic acidosis was ongoing, unrelated to heat exposure, and virtually refractory to therapy. Case 1 was evaluated at a hospital for hours on the day of his death, yet SCT and the associated fatal sequelae were not considered and, thus, the critical laboratory examinations were not performed. Recent studies on the preoptic area and anterior hippocampus indicate that metabolic acidosis and/or hypercapnia can induce central hyperthermia by inhibiting heat loss mechanisms (46,47) thus suggesting a causal relationship for hyperthermia induced by metabolic acidosis from short-term exercise as seen in case 4.

While SCT fatalities have usually resulted from intense levels of exertion, cases 13–15 had relatively innocuous methods of exertion. Case 13 involved the death of a black female driver with hemoglobin sickle cell disease who was involved in a motor vehicle crash. Due to the crash the woman was inverted for approximately 20 min. She was stable at the scene and upon arrival at the hospital and had sufficient time for a differential workup, but concerns for her mild blunt injuries probably superseded any concerns of a hemoglobinopathy. The physicians noted numerous varicose veins in the upper torso and were concerned about superior vena cava syndrome. Cases 14 and 15 involved the physiological exertions of sexual activity and childbirth, respectively. Of note in case 14 was the possible incorporation of consensual asphyxiation by her life partner, and the decedent also suffered from obstructive sleep apnea. Obstructive sleep apnea has been strongly linked to nocturnal hypoxia in those with sickle cell disease and it has been proposed to have similar effects on some with SCT (48,49).

Case 5 shows that Caucasians can also carry the HbS gene. Despite autopsy, microscopic findings, and hemoglobin electrophoresis, the family physician had great difficulty believing the results. Complications of SCT including splenic syndrome in Caucasians have been described in the literature primarily due to exposure to altitude (50–55). Interestingly, the deceased reportedly previously experienced abdominal pain after working out in the gym; one can only speculate that SCT-related splenic syndrome may have been the cause. Certainly, the 1000 g spleen did not develop acutely, and the spleen likely enlarged after repetitive sickling episodes for weeks or even years. A working knowledge and acceptance of his condition, or perhaps even a thorough physical exam, might have resulted in an appropriate diagnosis of his significantly enlarged spleen. From a clinician's perspective, splenomegaly, such as in case 5, is often related to malignancy and splenectomy to avoid rupture is life saving in addition to being diagnostic (56). Certainly, splenectomy would have prevented this death.

If HbS is not entertained in the differential, the diagnosis will not be made in a timely manner, if ever. Micro-occlusive sickling is treatable if diagnosed. Fluids, dialysis, and supportive care were generally received by all of these cases. However, techniques as simple as supplemental oxygen or more specialized treatments for sickle cell disease-related micro-occlusive crisis such as transfusion

or exchange transfusion would be expected to yield favorable results (57).

Although SCT is indeed not a typical part of the clinical differential diagnosis of sudden death or metabolic acidosis in living patients, pathologists performing postmortem diagnoses do not fair much better. In cases 2, 4, 6–8, and 12–16 the diagnosis of SCT and its role in these deaths initially eluded the pathologists. In case 5, one would hope that the presence of an enlarged, ruptured spleen would have at least entertained the possibility of SCT to most forensic pathologists, but the decedent's Caucasian race was initially confounding.

According to the file in case 7, the decedent's attending physicians dismissed the role of SCT in his rhabdomyolysis and renal failure. The decedent's family notified the physicians that he had SCT. Due to his white phenotype, it is highly unlikely that SCT would have been considered without this historical information. Despite the knowledge of his SCT and its well-published connection with rhabdomyolysis and renal failure, a causative relationship was never established by the clinicians. Similarly, the prominent postmortem sRBCs were dismissed as a postmortem artifact by the attending forensic pathologist. No other reasonable explanation was discovered although streptococcal septicemia was suspected. The negative postmortem cultures were dismissed as being due to antibiotic therapy. The histology slides of the spleen show unequivocal splenic sequestration that with longer survival would have likely progressed to frank infarction.

Case 4 was not originally diagnosed as having SCT. The decedent's SCT became generally known only after a request to review the slides was made by one of the authors (C.I.W.). He did not have any hemoglobin electrophoresis performed or any genetic testing. The certifying forensic pathologist confirmed the presence of sRBCs, but these were dismissed as postmortem artifact. The decedent's family confirmed that SCT was identified by neonatal screening. He had chronic low grade anemia documented for a period of 2 years prior to his demise (with hemoglobin levels ranging from 9.5 to 11.9 g/dL) but no hemoglobin or other metabolic studies were performed by his pediatrician to elucidate the cause of his refractory mild anemia. Based on the history, it is possible that case 4 had another hemoglobinopathy that, in concert with his SCT, caused his anemia and perhaps contributed to his demise.

Specimen handling and postmortem artifacts causing reversible sickling of HbS RBCs can make the diagnostic link with death difficult for physicians. Clinicians expect that patients in the midst of a SCT-related micro-occlusive crisis will have sickling readily apparent on their peripheral blood smears. They commonly rely upon the reported lack of poikilocytosis as evidence that SCT was not a causal element in the illness or death. Sickling is reversible and, depending on how the specimen or slide is handled, artifacts will cause changes to the cell morphology even in those with sickle cell disease (58,59). Similarly, a somewhat common belief held by forensic pathologists and promulgated by hematologists is that the sRBCs in autopsies of those with SCT were due to postmortem fixation artifact or immediate agonal hypoxia. Thus, the sRBCs depicted on the microscopic slides were not a reflection of antemortem occlusive events (12,41).

Several cases encountered by the authors and several published case reports offer convincing arguments against sRBCs being pure artifact at autopsy. A study by one of the authors (C.I.W.) demonstrated that carriers of HbS show minute but manually detectable anomalies in RBC shape on their peripheral smears (60). In a similar study published by several of the authors (J.R.T., C.I.W., N.A.P., and S.S.I.) (61), it was found that all carriers of HbS showed sRBCs in postmortem histology slides. Such baseline RBC anomalies in those with SCT could indeed present diagnostic difficulties. However, the postmortem histology study included a control case that had multiple antemortem blood transfusions as a result of treatment for trauma. Due to these transfusions, the postmortem measured HbS was lowered to 14.4%, and this inhibited the typical finding of sickling on the microscopic slides. In fact, unlike the other SCT control cases in the study that did not receive such voluminous transfusions, no sickling was evident and the RBCs appeared histologically indistinguishable from control cases with normal hemoglobin. A decedent with a prolonged hospitalization for West Nile Virus who received antemortem transfusions was included as a control in the same histology study. This decedent had a postmortem HbS of 28.5%. Detecting sickled cells on his postmortem histology slides proved difficult. The authors have encountered similar phenomena in even a double heterozygous HbSC decedent with HbS and C fractions below 30% due to transfusions. In an incidental case, a 2-month-old infant who died of a cause unrelated to SCT had a postmortem HbS of 10% due to the presence of HbF, and sRBCs were undetectable on the infant's histology slides.

These postmortem findings of lowered evident sickling with lower HbS percentage are consistent with the clinical findings and justification of transfusion therapy for sickle cell disease patients. Maintaining HbS concentrations of less than 30% by transfusion therapy has been proven efficacious in preventing strokes and treating other sickle cell disease complications (62,63).

These transfusion findings apply to cases 2 and 4. Prior to his first dialysis treatment, case 4 received 1000 cm^3 of packed RBCs for treatment of anemia. Based on previous published calculations of hematocrit and hemoglobin corrections and his pretransfusion hematocrit, these transfusions would have likely lowered his HbS to about 25% (64). It is unlikely that significant postmortem sickling would be evident and certainly the degree of sickling would have been less than what was seen in the histology slides. His readily evident sickling was likely antemortem (61).

During his hospitalization, case 2 experienced hemorrhagic diathesis from DIC which is not unusual in these cases and in this case required relatively aggressive blood transfusions. At the time of death, an expert for the criminal prosecution of the guards charged in this death, calculated these transfusions were extensive enough to mitigate perimortem sickling. This would have included the massive micro-occlusive sickling in all tissues, particularly the remarkably congested spleen.

As is customary in the field of forensic pathology, the laboratory analyses including Hb electrophoresis, to determine the cause of death in case 2 were performed on admission blood. This reflected his HbS status at the time of the incident (see Table 1). This level does not reflect his status at the time of death. Our calculations, based upon the laboratory reports and transfusion records, indicate that his HbS percentage at the time of death would have been approximately 19–20% (64) and the large number of sRBCs seen at autopsy were not postmortem artifact.

A prominent case of an exertional sickling death in a college football player described widespread marked intravascular sickling, splenic sequestration, and muscle necrosis despite 10 units of packed RBCs during his hospitalization (41). Similarly, two other reports described nearly identical clinical courses with one case of a naval recruit who received 10 units of packed RBCs (65) and the other receiving "multiple units" of packed RBCs (8). Both of these cases had widespread intravascular sRBCs and splenic sequestration at autopsy. Both of these case reports, including one that excluded the sRBCs as postmortem artifact (65) were included in a previous

case series and discussion that specifically dismissed sRBCs found at autopsy to be purely postmortem artifact (12). Such massive antemortem transfusions would have precluded the massive amount of sickling found in the autopsies of these cases.

The cases presented here reveal that SCT is associated with deaths, delayed and sudden, in many different environments and circumstances. Rhabdomyolysis, renal failure, and high anion gap metabolic acidosis are common features found in those with sufficient periods of survival, and, rather than being heat-related phenomena, these complications occur in those with SCT with exertion in cool environments. High environmental temperatures, dehydration, increased body mass index, altitude, deconditioning, asthma, or other co-morbidities are often present, and these function in heightening the physiologic stress of any given type of physical exertion. The sRBCs found at autopsy are not always a postmortem artifact, and in the right circumstances can be diagnostic. The understanding of the clinical course and potential lethal outcomes in those with SCT may help prevent deaths in these otherwise healthy individuals.

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