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Sickle Cell Trait Mimicking Multiple Inflicted Injuries in a 5-Year-Old Boy

ABSTRACT: Sickle cell disease (SCD) and sickle cell trait (SCT) can be associated with sudden unexpected death in the pediatric population, usually due to pulmonary complications occurring within the acute chest syndrome (ACS). Musculoskeletal complications can occur and are classically limited to bone infarcts. The occurrence of bone pathology centered upon the epiphyseal growth plate in SCD/SCT is extremely rare, and multiple such injuries in a single patient have not been previously reported. Herein, we describe a case of sudden unexpected death in a 5-year-old child with undiagnosed SCT due to the ACS, with widespread epiphyseal and periosteal bone lesions mimicking multiple inflicted injuries at autopsy. This case highlights the importance of clinicopathological correlation and is the first to describe SCT pathology as a mimic of nonaccidental injury.

KEYWORDS: forensic science, forensic pathology, sickle cell trait, pediatric, acute chest syndrome, skeletal injury, sudden death

Many medical conditions are of importance to pediatricians, radiologists, and pathologists as potential mimics of inflicted injury in infants and children. Well-known examples of such diseases include osteogenesis imperfecta, *Staphylococcus* scalded skin syndrome, and the various coagulopathies.

Sickle cell disease (SCD), and to a lesser degree, sickle cell trait (SCT), are well described within the forensic pathology literature as causes of sudden, unexpected death in children (1,2). Complications of SCD/SCT are not usually on the differential diagnosis of traumatic injury. Here, we report a case of sudden unexpected death in a 5-year-old child due to pulmonary complications of SCT, and in whom the pattern of bone lesions seen at autopsy mimicked multiple inflicted injuries.

Patient Presentation

Clinical History

A 5-year-old boy of Ghanaian origin was reportedly well except for a dry cough that was initially noted on the morning of the day he died. He had been given a single dose of an over-the-counter cough medication in the early evening, and on his way to bed began to vomit. His parents described copious vomiting from the nose and mouth, and EMS was called. Paramedics arrived to find the child with no vital signs and it appeared to them at the time of initial assessment that he had aspirated. Intubation attempts in the field were unsuccessful; therefore, the boy was bag-ventilated until his arrival at the nearest Emergency Department (ED) *c*. 30 min after the onset of vomiting. He was successfully intubated in the ED, and during the resuscitation efforts it was noted that his abdomen appeared distended, a sign that appeared to worsen over the course of treatment. The anesthetist involved reported thick secretions in the airway and high airway resistance. The resuscitation attempt was unsuccessful and the boy was declared dead 30 min after arriving in the ED. There were no signs of injury, and the child appeared well cared for.

Past medical history was significant only for autism, with moderate to severe global developmental disorder, and although the boy did not speak he was ambulatory and able to follow instructions. During the 3 weeks prior to death, the decedent had been brought to his family physician's office three times with a complaint of left leg pain. Radiographs on two separate days showed only mild soft tissue swelling near the midshaft of the left tibia with no evidence of fractures, arthritic changes, or other bony abnormality. Although the original reports from these imaging studies were obtained from the family physician, the films themselves were not retrospectively reviewed. There was no history of SCD in the decedent or in any first-degree relatives, although it is unknown whether the parents had undergone screening for SCD prior to immigrating to Canada. His only sibling, an older brother, had also been diagnosed with autism, but there were no symptoms to suggest a coexistent hemoglobinopathy. The sibling was subsequently screened for SCD (see below) and was found to be positive for SCT. Appropriate clinical follow-up has been arranged.

Autopsy Findings

An autopsy was performed 14 h after death. A skeletal survey performed during the autopsy was highly suggestive of multifocal metaphyseal fractures of the left humerus, right ulna, bilateral radii, bilateral femora, and bilateral tibiae (Fig. 1). There were no definite features of healed fractures. Characteristic radiologic features of vitamin C or D deficiency were not identified. On external examination, the only abnormalities were small gingival abrasions attributable to intubation during the resuscitation attempt. On internal examination, the most striking findings were in the respiratory and musculoskeletal systems. An endotracheal tube was *in situ* and filled with thick secretions and gastric contents. Gastric contents were also found within the esophagus, trachea, mainstem bronchi and smaller, intrapulmonary airways. The right and left lungs weighed 293 and 126 g, respectively, and the right lower lobe was pale, consolidated, and focally hemorrhagic. There was a

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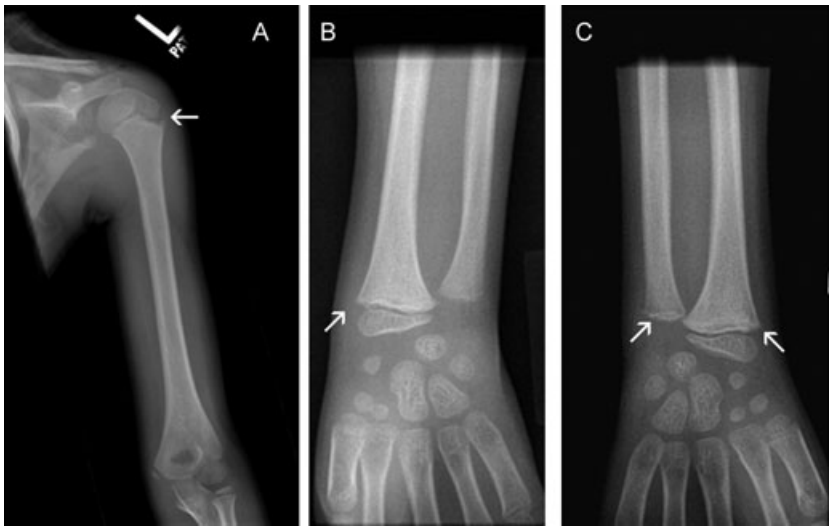

FIG. 1—*Postmortem radiographs demonstrating epiphyseal irregularities and radiolucencies centered about the proximal left humeral epiphysis (A, arrow) and the distal left and right radial epiphyses (B and C, arrows) and distal right ulnar epiphysis (C, arrow).*

right-sided serous pleural effusion of 60 cc and thin, fibrinous adhesions of the visceral pleura. A layered dissection of the muscles of the neck revealed no signs of traumatic injury while a layered dissection of the posterior paraspinal muscles showed focal areas of soft tissue hemorrhage. Layered dissections of all four limbs to the level of the periosteum as well as intra-articular dissections of the shoulders, elbows, wrists, hips, knees, and ankles were then undertaken. Multiple soft tissue and intra-articular hemorrhages were found as well as numerous subperiosteal hematomas associated with the epiphyses of the upper and lower limbs, bilateral ribs and the tempero-mandibular joints (Fig. 2). The epiphyses underlying these hematomas were separated. In addition, the lower limbs had numerous acute myofascial hemorrhages. The spleen weighed 49 g (expected for age = 57.2–81.5 g) and was grossly and microscopically unremarkable. The remainder of the internal examination, including the gross neuropathologic exam, was noncontributory.

Histologic examination of the ribs revealed disruption of the bone immediately beneath the epiphyseal growth plate associated with a fibrinous exudate. The marrow in this area was fibrotic and sickled erythrocytes were easily identified. There were organizing hematomas between the periosteum and the underlying cortical bone with associated foci of reactive bone. Whole mount of the right knee as well as sections from the femur, patella, tibia, and fibula showed both acute and organizing subperiosteal hemorrhages as well as irregular cement lines within the cortical bone suggestive of bone remodeling (Fig. 2). Foci of subcortical and subepiphyseal marrow fibrosis were also identified. In all bones examined, the overall organization of the growth plates was within normal limits (Fig. 3). Sections from the grossly identified areas of soft tissue hemorrhage confirmed the presence of organizing hematomas and granulation tissue.

Sections of most organs showed congestion of vessels and marked sickling of erythrocytes. Both lungs contained foreign material in keeping with aspiration of gastric contents, while the right lower lobe showed marked pulmonary edema associated with an acute fibrinous alveolitis. Focal areas of alveolar hemorrhage, some organizing, were also present. Pulmonary vessels showed focal obliterative endothelialitis and focal fat emboli (Fig. 4). Gram-positive cocci in clumps and clusters were seen within airspaces, consistent with postmortem overgrowth. The brain was histologically unremarkable.

Ancillary Tests

Cytogenetic analysis showed a normal male karyotype. Toxicologic analysis of peripheral blood drawn in the ED revealed trace amounts of ethanol (<2 mmol/L), attributable to the over-the-counter cough medication. *Staphylococcus aureus* was cultured from lung tissue while blood, cerebrospinal fluid, and pleural fluid were negative. Virological cultures from lung tissue were negative. Ascorbic acid levels were measured in a postmortem blood sample; unfortunately, reference values are not available for ascorbic acid levels in postmortem serum, therefore we could not exclude a diagnosis of scurvy based on biochemical tests alone. Vitamin C deficiency was not felt to be a factor in this case, however, as the child was well nourished and other extraskeletal manifestations of scurvy were not present, including cutaneous hemorrhages, gingival hemorrhages and hypertrophy, hyperkeratosis, and loosening of the teeth (3). Hemoglobin electrophoresis was also undertaken on a postmortem blood sample and showed a distribution consistent with SCT with an HbA of 74.9%, HbF of 1.9%, and HbS of 23.2%.

The cause of death was determined to be pulmonary complications of SCT.

Discussion

With the widespread availability of newborn metabolic screens, the identification of most hemoglobinopathies is generally made within the first few weeks of life. Unfortunately, there are still reports of patients who are not diagnosed until their underlying disorder results in their death (4–6). With SCD in particular, the postmortem diagnosis of both homo- and heterozygous forms generally follows the histologic identification of sickled red blood cells within tissues, and hemoglobin (Hb) electrophoresis is then used to confirm the presence of the abnormal HbS. The complete absence of HbA and a predominance of HbS is diagnostic of homozygous SCD while the presence of both HbA and HbS (with more A than S) confirms the heterozygous form, or SCT. A small proportion of the fetal form of Hb (HbF) may be present in both. Although other abnormal forms of Hb have electrophoretic mobilities that are identical to that of HbS, these variants are not associated with sickling of red cells, therefore the combination of histologic identification of sickled cells and detection of HbS with electrophoresis is

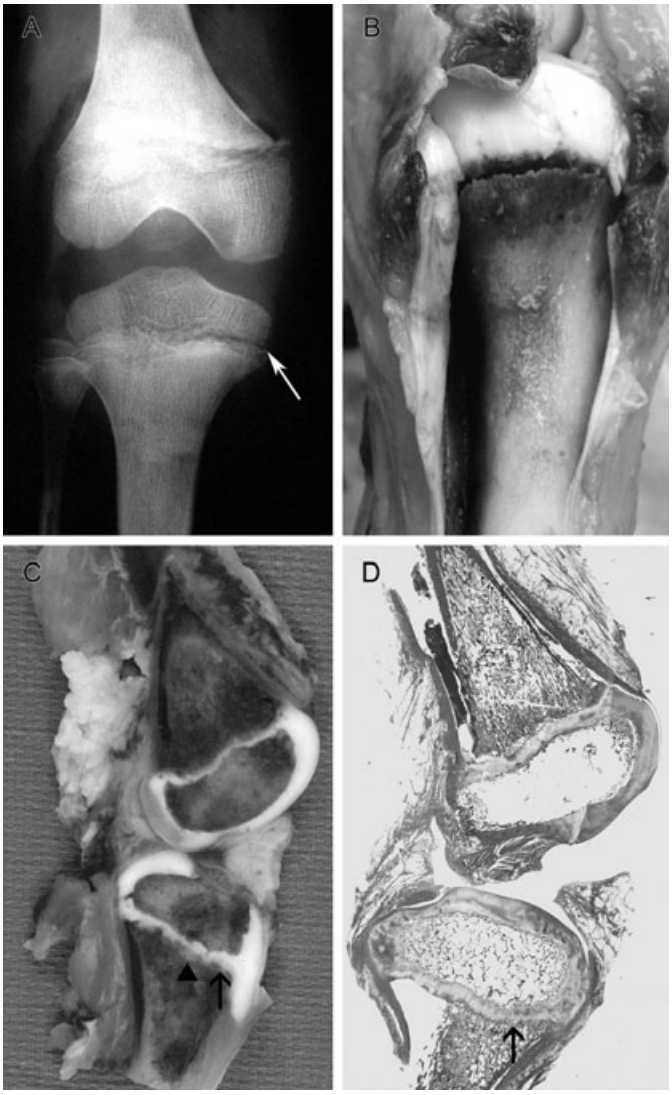

FIG. 2—*Right knee: (A) Postmortem radiograph with lesion interpreted as metaphyseal fracture of tibia (arrow). (B) Tibia* in situ *following layered dissection of knee joint demonstrating the epiphyseal separation under flexural pressure. (C and D) Whole mount of right knee joint showing a fine subepiphyseal tibial fracture line (C and D; arrows) and new bone and cartilage formation (C; arrowhead).*

sufficient for diagnosis of SCD (7). Other mimics of SCD on Hb electrophoresis include the coexistence of HbS with α or β thalassemia. Although the distinction from homozygous SCD in these cases can be challenging and require DNA-based studies, the distinction from SCT is relatively straightforward as the proportion of HbS is greater than that of HbA in HbS-α/β thalassemia while the reverse pattern is seen in SCT. In general, it can be said that DNA-based studies for the detection of hemoglobinopathies are more accurate than electrophoresis, especially for rare variants. As such, methods such as DNA sequencing of polymerase chain reaction-amplified samples are preferentially used for prenatal diagnosis; however, electrophoresis has the advantage of being rapid, inexpensive, widely available, and extremely effective at separating normal Hb from the common abnormal forms such as HbS (7). Therefore, there is no disadvantage in using this technique for the diagnosis of SCD or SCT.

Two additional features of this case are of importance to the pediatric primary care physician. First, it reminds us that SCT can be a cause of the acute complications normally associated with SCD, including the acute chest syndrome (ACS). Such complications may be the initial presentation in a patient with SCT, and they may, rarely, result in sudden death (1). Of greater interest is the fact that the skeletal manifestations of SCT in this patient were thought to represent multiple inflicted injuries on the initial imaging studies.

Acute chest syndrome is the leading cause of morbidity and mortality among patients with SCD (8). It is defined by the presence of new pulmonary infiltrates on chest imaging, accompanied by fever, chest pain, and respiratory symptoms such as wheezing, coughing, and tachypnea (1). There are numerous causes of ACS, including fat embolism following bone infarction, infection, and pulmonary infarcts due to occlusion of pulmonary vessels with sickled red cells (8,9). Although more common in adult patients, it is a well-recognized complication of SCD in the pediatric population as well (8). The occurrence of ACS in SCT is rare, and is usually associated with significant stressors such as dehydration, heat stress, and viral illness (10,11). Postmortem examination of the current case showed generalized hyperplasia of gastrointestinal-associated lymphoid tissue, consistent with a viral-like illness. While the parents reported only a short history of cough and viral-like symptomatology, it is possible that the child's developmental disorder delayed the recognition of the illness. Although the clinical information required for a diagnosis of ACS was missing in our case, the histologic findings, including acute fibrinous and organizing alveolitis, pleural effusion, endothelialitis, and fat emboli, have been previously described in patients with ACS (1,12,13). Therefore, ACS was felt to be the major contributing factor to the cause of death.

The numerous well-known orthopedic complications of SCD/SCT in children include dactylitis (hand-foot syndrome), acute long bone infarction, osteomyelitis, and sickle cell arthropathy (14,15). Most of these complications are secondary to vaso-occlusive crises, which are also the most common cause of extremity and joint pain in pediatric sickle cell patients. Although several of the individual features that we describe in our case have been previously reported in patients with SCD, including subperiosteal hemorrhage (16), hemarthrosis (14), and marrow fibrosis (17), no one has yet described a similar constellation of findings, nor widespread epiphyseal separations. Similar separations have been described as a complication of osteomyelitis and septic arthritis in neonates, however not in the context of SCD/SCT (18). Although a single report describes a case of slipped capital femoral epiphysis in an adolescent with SCD (19), it is unclear in the report whether the orthopedic injury was directly due to the underlying SCD, or if the two pathologies were merely coincident. The most likely cause of the epiphyseal separations in the current case is microinfarction and hemorrhage of the underlying bone, given the combination of marrow fibrosis, subperiosteal hemorrhage, and focal reactive new bone formation.

In Canada, *c.* 3% of children who are physically abused will sustain fractures (20), while in the United States, prevalence rates have been quoted as high as 55% (21). Metaphyseal fractures are considered to be the most specific radiographically detectable injury in abused children (21), hence the concern for nonaccidental injury in our case. However, the symmetrical nature of the injuries, together with the temporal homogeneity, were not consistent with inflicted injuries, facts which precipitated the layered dissections of all four limbs. The histology confirmed that the epiphyseal lesions were not traumatic injuries, but rather secondary to a sickle cell crisis, and this case quickly evolved from one of inflicted injury to a cautionary tale for pediatric clinicians, radiologists, and pathologists. Although SCD/SCT is not one of the classic mimickers of child

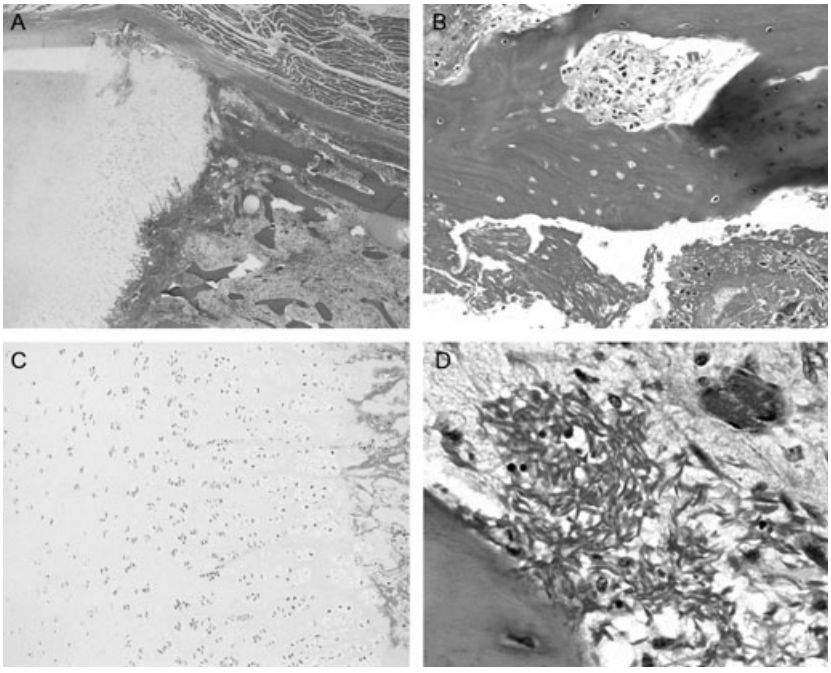

FIG. 3—*Histologic findings within the right knee epiphysis. (A and B) Low and high power views of the metaphyseal bone marrow showing fibrosis and fibrinous exudate. (C) Growth plate with normal organization. (D) Sickled erythrocytes within the marrow space.*

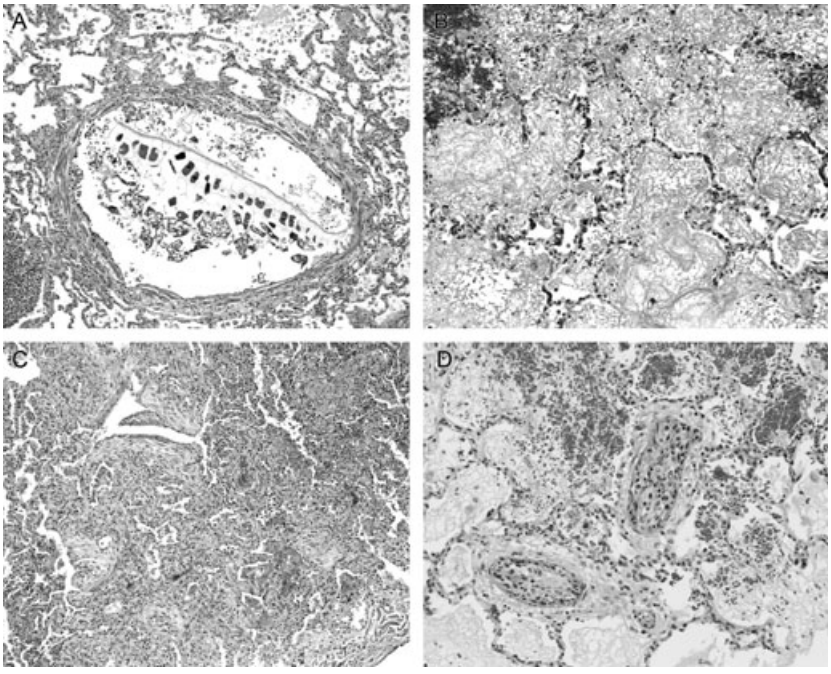

FIG. 4—*Histologic findings within the lung: (A) aspirated vegetable matter; (B and C) acute and organizing fibrinous alveolitis; and (D) obliterative endothelialitis.*

abuse, unusual orthopedic pathologies can and do occur, and may appear as inflicted injury on skeletal survey.

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