Sickle Cell Anemia (Homozygous S) with Aseptic Necrosis of Femoral Head

By Kouichi R. Tanaka, George O. Clifford and Arnold R. Axelrod

Since the advent of the newer techniques for differentiating hemoglobin types, no case of sickle cell anemia (homozygous S) proven by these methods has been described in which aseptic necrosis of the femoral head was present. Aseptic necrosis of the femoral capital epiphysis has been reported by Smith and Conley to occur frequently in the genetic variants of sickle cell anemia. In this report, the complete absence of this lesion in their patients with sickle cell anemia was stressed. Several cases showing femoral head lesions and presumed to represent true sickle cell anemia have been reported, but these were not verified electrophoretically, nor were the clinical and hematologic data sufficient to make a definite clinical diagnosis of sickle cell anemia as distinct from its genetic variants.

It is our purpose to present six patients with sickle cell anemia (homozygous S) proven by paper electrophoresis who demonstrated aseptic necrosis of the femoral head.

Materials and Methods

During the period from January 1, 1954, through December 31, 1955, 51 patients with sickle cell anemia (homozygous S), established clinically and by means of paper electrophoresis, were studied on the wards and in the Hematology Outpatient Clinic of the City of Detroit Receiving Hospital. All patients were seen and evaluated by one or more of the authors. Of this number, 38 patients had adequate x-rays of the femoral and humeral heads. These consisted of anterior-posterior views of both shoulders and anterior-posterior views of the hip joints in neutral position and with the femora in abduction and external rotation. In six cases, aseptic necrosis of the femoral capital epiphysis was encountered and these patients form the body of this report. A summary of the clinical and laboratory data is presented in table 1. The hemoglobin patterns determined by paper electrophoresis are shown in figure 1.

Appropriate hematologic studies were determined by standard methods. Hemoglobin samples for electrophoresis were prepared according to a modification of the technic of Drabkin. Paper electrophoresis was performed using a slight modification of the method of Smith and Conley. The hemoglobin resistance to alkali denaturation was determined by the method of Singer et al.; values to 1.8 per cent are considered normal in our laboratory. In all cases, these determinations were run in duplicate or triplicate by the same technician.

Case Histories

Case 1. C. W., a 31 year old Negro male, had repeated episodes of sickle cell crises since four years of age. He had received blood transfusions yearly since 1951, when he was first...
seen at City of Detroit Receiving Hospital for priapism. In the last two years there was progressive pain and restriction of motion of the left hip with shortening of the left lower extremity. There was no history of trauma or exposure to increased barometric pressure.

Examination revealed an asthenic male with eunuchoidal habitus. There was moderate pallor and scleral icterus. The liver extended 6 cm. below the right costal margin. The spleen was not felt. There were no leg ulcers. There was limitation of abduction and external rotation of the left femur.

The hemoglobin ranged from 6.5 to 8.9 grams per 100 ml., erythrocytes from 2.55 to 3.30 million per cu.mm., reticuloocytes from 7.0 to 18.5 per cent, total serum bilirubin from 5.6 to 18.8 mg. per 100 ml. with indirect bilirubin from 2.2 to 7.2 mg. per 100 ml. The sickle cell preparation was positive and sickling was seen in the counting chamber and in the fixed blood smear. Paper electrophoresis demonstrated SS pattern and alkali denaturation revealed 3.4 per cent F hemoglobin.

X-rays in October, 1955, revealed deformity and flattening of the head of the left femur with some irregularity at the upper border. The joint space was preserved. There was irregularity of the right sacroiliac joint space with sclerosis in the immediate vicinity. These changes were interpreted as aseptic necrosis of the left femoral head and right sacroiliac joint, respectively (fig. 2). In addition, there was coarsening of the bone structure and a slight degree of osteoporosis of all the pelvic bones.

In December 1955, fusion of the left hip joint was done. The histologic description of the surgical specimen was as follows: The material consists of bone in which there is angulation of the lamellae with variation in their widths. Some of the trabeculae are thin, have irregular edges, and contain only a few nuclei. There is no inflammatory exudation. In these areas, the marrow spaces are filled with loose fibrous tissue, containing blood vessels, some of which are thrombosed and in various stages of organization (fig. 3). Sickling of red blood cells is present in the blood vessels. There is no evidence of osteoblastic or osteoclastic activity. The histologic diagnosis was noninflammatory necrosis of bone consistent with aseptic necrosis.

Case 2. F. E., a 13 year old Negro boy, was first seen on September 21, 1955. Since infancy he had experienced periodic abdominal and leg pains and was hospitalized several times, receiving a total of fourteen blood transfusions, but none since 1947. There was no history of trauma to his hip joints or exposure to increased barometric pressure. He denied pain in his hip joints. There was no history of renal disease.

Examination revealed an asthenic, pale boy with scleral icterus. The liver edge extended 5 cm. below the right costal margin. The spleen was not felt. There was good motion of both hip joints with pain on abduction and external rotation of the right femur. Flexion of the right femur was 10° less than the left. There were no leg ulcers.

The hemoglobin ranged from 6.2 to 7.9 grams per 100 ml., erythrocytes from 2.32 to 2.83 million per cu.mm., and reticuloocytes from 6.2 to 11.3 per cent. The total bilirubin was 3.0 mg. per 100 ml. with 0.4 mg. direct. The sickle cell preparation was positive and paper electrophoresis revealed SS pattern. Alkali denaturation revealed 3.4 per cent F hemoglobin.

X-rays in October, 1955, revealed marked flattening of the capital femoral epiphysis on the right with sclerosis, some fragmentation, and irregular demineralization. On the left side there was a suggestion of slight increase in density of the capital femoral epiphysis with a solitary area of rarefaction within the epiphysis. Normal relationships were maintained at the hip joints. In addition, there was a generalized increase in the trabecular pattern involving all of the osseous structures. These changes were interpreted as aseptic necrosis of the right femoral epiphysis with minimal changes of a similar nature involving the left capital femoral epiphysis (fig. 4).

Case 3. J. W., a 23 year old Negro male, was first seen in October 1954, with typical sickle cell crisis. Since age three he had been hospitalized almost annually elsewhere for crises, receiving fifteen blood transfusions to date. Since April 1954 he had noted intermittent, but progressively severe, pain in the right hip joint. There was no history of trauma or exposure to increased barometric pressure.

Physical examination revealed a normally developed Negro male with icteric sclerae.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Race</th>
<th>Sex</th>
<th>Electro-photometric pattern of Hb.</th>
<th>Alkaline denaturation ° F Hb.</th>
<th>Joint involved</th>
<th>Symptoms and signs</th>
<th>Hb, range Gms.</th>
<th>RBC range millions</th>
<th>Retics. range %</th>
<th>History of trauma</th>
<th>Severity of clinical course (+ to +++++)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C. W.</td>
<td>31</td>
<td>NM</td>
<td>M</td>
<td>3.7</td>
<td></td>
<td>Left femoral head</td>
<td>Yes</td>
<td>6.5-8.9</td>
<td>2.55-3.30</td>
<td>7.0-18.3</td>
<td>No</td>
<td>+</td>
</tr>
<tr>
<td>2. F. E.</td>
<td>13</td>
<td>NM</td>
<td>S</td>
<td>3.4</td>
<td></td>
<td>Bilateral femoral heads</td>
<td>No</td>
<td>6.2-7.9</td>
<td>2.32-2.83</td>
<td>6.2-11.3</td>
<td>No</td>
<td>++++</td>
</tr>
<tr>
<td>3. J. W.</td>
<td>23</td>
<td>NM</td>
<td>S</td>
<td>4.6</td>
<td></td>
<td>Bilateral femoral heads</td>
<td>Yes</td>
<td>7.1-9.4</td>
<td>3.24-3.64</td>
<td>6.8</td>
<td>No</td>
<td>+++</td>
</tr>
<tr>
<td>4. D. G.</td>
<td>23</td>
<td>NM</td>
<td>S</td>
<td>1.8</td>
<td></td>
<td>Bilateral femoral heads</td>
<td>Yes</td>
<td>7.0-9.2</td>
<td>2.63-3.93</td>
<td>13.9-29.1</td>
<td>No</td>
<td>++</td>
</tr>
<tr>
<td>5. A. A.</td>
<td>20</td>
<td>NM</td>
<td>S</td>
<td>1.6</td>
<td></td>
<td>Left fem. head, left humeral head</td>
<td>Yes</td>
<td>9.3-10.0</td>
<td>3.90-4.26</td>
<td>3.6-5.0</td>
<td>No</td>
<td>++</td>
</tr>
<tr>
<td>6. M. S.</td>
<td>21</td>
<td>NF</td>
<td>S</td>
<td>2.1</td>
<td></td>
<td>Right fem. head</td>
<td>No</td>
<td>4.5-9.5</td>
<td>1.40-3.18</td>
<td>4.6-27.2</td>
<td>No</td>
<td>+++</td>
</tr>
</tbody>
</table>
Fig. 1

Fig. 2.—Case 1. Aseptic necrosis of the left femoral head. Deformity and flattening of the head of the left femur with some irregularity at the upper border.

The liver and spleen were not palpable. There was slight limitation of motion of the right hip joint on flexion, extension and abduction. No leg ulcers were present.

Hemoglobin ranged from 7.1 to 9.4 grams per 100 ml., with erythrocytes of 3.24 to 3.64 million per cu.mm. Total bilirubin varied between 2.0 and 4.0 mg. per 100 ml. with majority
FIG. 3.—Photomicrograph (14X) of bone removed at operation in case 1. See text for histologic description.

FIG. 4.—Case 2. Aseptic necrosis, advanced, right femoral head; early, left femoral head. Marked flattening, sclerosis, fragmentation and irregular demineralization of right femoral head. Slight increase in density with area of rarefaction, left femoral head.

of the bilirubin indirect. The sickle preparation was positive and sickling was seen in the counting chamber and in the fixed blood smear. Reticulocytosis of 6.8 per cent was present. Hemoglobin pattern by paper electrophoresis was SS. Alkali denaturation revealed 4.6 per cent F hemoglobin.

SICKLE CELL ANEMIA WITH ASEPTIC NECROSIS OF FEMORAL HEAD
Case 5. A. A., a 20 year old Negro male, was first seen in 1953 for severe sickle cell crisis. There had been frequent crises every five to six months since age seven with repeated hos-
pitealizations at other institutions. Crises had become more severe during his late teens. A leg ulcer developed six months before admission and was not completely healed. Trans- fusions were not required. In June 1950 the patient noted a “snap” in the left lower extremity while walking and since then has had intermittent pain in his left hip and limitation of motion. There was no history of trauma or exposure to increased barometric pressure.

Physical examination revealed a normally developed Negro without definite eunuchoidal habitus, who walked with an obvious limp. There was slight scleral icterus. The liver was palpable 4 cm. below the right costal margin and the spleen could not be felt. An old ulcer scar was present on the right lower lateral leg and a 1 cm. granulating superficial ulcer was present on the medial aspect of the lower one-third of the left leg. On standing, the left side of the pelvis was lower than the right. There was pain and moderate limitation of internal and external rotation of the left hip, with slight limitation of abduction and adduction, flexion and extension. Motion at the right hip joint was normal.

Hemoglobin ranged between 9.3 and 10.9 grams per 100 ml. Erythrocytes ranged between 3.90 and 4.26 million per cu. mm. The serum bilirubin varied between 0.8 and 1.4 mg. per 100 ml. total with 0.2 to 0.4 mg. per 100 ml. direct. Reticulocytosis of 3.6 to 5.0 per cent was noted. Sickle preparation was positive and sickling of erythrocytes was noted on the fixed blood smear. The electrophoretic pattern of hemoglobin was SS, and alkali denaturation revealed 1.6 per cent F hemoglobin.

In March 1958, X rays revealed flattening of the superior half of the left femoral head, as well as marked irregularity of the articular margin. These changes were regarded as old osteochondrosis by the radiologist. Generalized osteoporosis with coarsening of trabeculae and increase in the biconcavity of the vertebral bodies was present. Films in December 1955 revealed more severe destructive changes in the left hip joint (fig. 7) plus the appearance of a small area of irregularity on the articular surface of the left humeral head with loss of bone substance, indicating a destructive process. There was increase in the trabeculation of the left humeral shaft and head. This was interpreted as compatible with an early aseptic necrosis of the left humeral head, as well as the advanced changes present in the left femoral head previously described.

Case 6. M. S., a 21 year old Negro female, was first diagnosed as having sickle cell anemia at 8 years of age. She had been jaundiced since early childhood with several crises yearly.
I.

Case 5. Aseptic necrosis of the left femoral head. Marked loss of joint space in the left hip joint with flattening, sclerosis, and partial absorption of the left femoral head. Slight irregularity of the articular surface of the right femoral head.

She exhibited enunchoidal habitus with slight scleral icterus. The liver was palpated 5 cm. below the right costal margin. The spleen was not felt. There was no limitation of motion of either hip joint. Two chronic superficial ulcers, each 6 by 8 cm., were present over the medial and lateral malleoli of the left ankle.

Hemoglobin ranged from 4.5 to 9.5 grams per 100 ml. Erythrocytes ranged from 1.4 to 3.18 million per cu.mm.; total bilirubin was 0.8 to 2.4 mg. per 100 ml. with major component indirect. The sickle preparation was positive and sickling was noted in the counting chamber and on the fixed blood smear. Reticulocytosis of 4.6 to 27.2 per cent was present. Hemoglobin pattern by paper electrophoresis was 88 and alkali denaturation revealed 2.1 per cent F hemoglobin.

X-rays in April 1953 revealed slight irregularity of the articular surface of the right fem-

Fig. 7.—Case 5. Aseptic necrosis of the left femoral head. Marked loss of joint space in the left hip joint with flattening, sclerosis, and partial absorption of the left femoral head.

Fig. 8.—Case 6. Early aseptic necrosis of right femoral head. Slight irregularity of the articular surface of the right femoral head.
oral head, compatible with early aseptic necrosis (fig. 8). Repeat x-rays in January 1959 showed suggestive improvement, although the changes of aseptic necrosis were still present. Some osteoporosis of the vertebral bodies with bilateral concavity on the adjacent articular surfaces was present.

DISCUSSION

Aseptic necrosis of bones in sickle cell anemia was treated as an established fact prior to the advent of hemoglobin electrophoresis. This technic permitted the separation of sickle cell anemia from its generally milder genetic variants. To our knowledge, since the use of these methods, no case of aseptic necrosis of the femoral capital epiphysis in sickle cell anemia (homozygous S) proven by electrophoresis has been reported. In fact, Smith and Conley, in their recent review, emphasize the absence of aseptic necrosis in patients with true sickle cell anemia. A few of the previously reported cases met clinical criteria for sickle cell anemia, but were not confirmed by electrophoresis; however, the majority of cases in the literature are atypical for sickle cell anemia and almost certainly represent genetic variants on the basis of data given. This is in keeping with recent studies which indicate the frequency of this finding in sickle cell-hemoglobin C disease and sickle cell-thalassemia. Our experience in patients with sickle cell-hemoglobin C disease concurs with these reports. Presumably the sickling phenomenon accounts for the presence of aseptic necrosis by the production of capillary thromboses with resulting bony infarction. In our operated case (C. W.), thromboses of the blood vessels in the necrotic area, presumably due to the sickling phenomenon, were demonstrated. It is surprising, therefore, that aseptic necrosis of the femoral head is not seen more often in sickle cell anemia, since it has been reported to occur frequently in sickle cell-hemoglobin C disease.

Since the introduction of electrophoresis, we have studied a total of 51 cases of sickle cell anemia (homozygous S). Of these, 6, or 12 per cent, were found to have aseptic necrosis of the femoral head; however, of these 51 patients, only 38 were studied by adequate detailed x-rays and it may well be that the incidence of aseptic necrosis is greater than reported here. In this respect, two of our six patients (F. E. and M. S.) complained of no symptoms referable to the joints involved and the aseptic necrosis was detected only after x-rays of the femoral heads were taken as part of a bone survey or as part of this study.

Despite the fact that x-rays were obtained of the shoulders and hip joints in all 38 patients, we found only one case (A. A.) demonstrating changes suggestive of early aseptic necrosis of the humeral head. This is in keeping with the uncommon finding of aseptic necrosis in the humeral heads in the variants of sickle cell anemia as reported by others.

Aseptic necrosis due to Caisson's disease and trauma can be dismissed in all of our cases because of negative history. In one of our cases (F. E.), we cannot exclude the possibility of coincidental Legg-Calve-Perthes Syndrome because of the patient's age; however, the bilateral involvement and the patient's race make Legg-Calve-Perthes Syndrome unlikely.

In one series of cases reported, it was observed that there was no progression of the aseptic necrosis of the femoral capital epiphysis over a period of four years. In the author's description, regression of the lesion of the humeral head occurred...
in one patient. In our material, with the exception of one case (M. S.), in which
the lesion apparently improved over a period of three years, all the lesions demon-
strated both clinical and roentgenologic progression.

It might be implied, from the data presented by Smith and Conley,\(^4\) that the
presence of aseptic necrosis in a patient whose red blood cells can be made to
sickle indicates that the patient has a genetic variant of sickle cell anemia rather
than sickle cell anemia (homozygous S). Our material demonstrates, however,
that aseptic necrosis may also be found in sickle cell anemia and that this lesion
cannot be utilized to discriminate between sickle cell anemia and its genetic
variants. In addition, although our series is small, it appears that aseptic necrosis
of the femoral head in sickle cell anemia is not an uncommon finding and that
it may be an incapacitating complication.

**Summary**

1. Six patients with sickle cell anemia who exhibit aseptic necrosis of the
femoral head are presented.
2. All patients were proven homozygous S by paper electrophoresis.
3. In our material, aseptic necrosis of the femoral capital epiphysis in patients
with sickle cell anemia is not an uncommon finding, 12% of 51 cases demonstrat-
ing this lesion.
4. The incidence of this lesion may be even greater than we report, inasmuch
as some of our patients were asymptomatic, although typical roentgenographic
changes of aseptic necrosis of the femoral head were present.

**Summario in Interlingua**

1. Es presentate sex patientes con anemia a cellulhas falciformi qui exhibiva
necrosis aseptic del capite femoral.
2. Omne le patientes esseva homozygote S, provate per electrophorese a
papire.
3. In nostre material, necrosis aseptic del femoral epiphyse capital in patientes
con anemia a cellulas falciforme non es un constatatia infrequente. In un serie
de 51 casos, 12% demonstrava iste lesion.
4. Le incidentia de iste lesion es possibilemente mesmo plus alte que lo que
nos reporta, proque un numero de nostre patientes esseva asymptomatic, ben
que typic alterationes roentgenographic de necrosis aseptic del capite femoral
esseva presente.

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