The Natural Progression of Symptomatic Humeral Head Osteonecrosis in Adults with Sickle Cell Disease

Alexandre Poignard, MD, Charles-Henri Flouzat-Lachaniette, MD, Julien Amzallag, MD, Frederic Galacteros, MD, and Philippe Hernigou, MD

Background: Osteonecrosis of the humeral head is a frequent complication in adults with sickle cell disease. However, little is known about the rate of, and the factors influencing, progression of symptomatic shoulder osteonecrosis in patients with this disease.

Methods: Eighty-two adult patients with sickle cell disease and symptomatic osteonecrosis of the humeral head (104 shoulders) were identified with magnetic resonance imaging (MRI) between 1985 and 1993. Nineteen of the eighty-two patients were homozygous for hemoglobin S (S/S genotype), thirty-seven had hemoglobin S/hemoglobin C (S/C), and twenty-six had hemoglobin S/beta-thalassemia (S/T). Shoulder osteonecrosis was graded with the method of Cruess with an adaptation for MRI as proposed by Steinberg et al. for hip osteonecrosis. Annual radiographs were obtained. At the initial evaluation, thirty-eight symptomatic shoulders were designated as stage I (with osteonecrosis seen only on MRI), forty-two symptomatic shoulders were designated as stage II (radiographic evidence without collapse), and twenty-four symptomatic shoulders were designated as stage III or IV (a crescent line or collapse).

Results: Partial or total repair with a decrease in the size of the osteonecrotic lesion or in the stage was never observed on MRI. At the time of the most recent follow-up (average, twenty years; range, fifteen to twenty-four years), collapse had occurred in eighty-nine shoulders (86%). The mean interval between the onset of pain and collapse was six years (range, six months to seventeen years; median, eight years). Of the 104 symptomatic shoulders, sixty-three (61%) with collapse worsened clinically until surgical treatment was needed. The principal risk factors for development of shoulder osteonecrosis in adults with sickle cell disease were the presence of hip osteonecrosis and the S/T or S/C genotype. The rate and risk of progression of the lesion until collapse occurred were significantly related to the S/S genotype, to a stage of II, to a large size of the osteonecrotic lesion, and to a medial or posterior location of the lesion.

Conclusion: Untreated symptomatic shoulder osteonecrosis related to sickle cell disease has a high likelihood of progressing to humeral head collapse, and the natural evolution in the long term requires surgical treatment for many of these patients.

Level of Evidence: Prognostic Level II. See Instructions for Authors for a complete description of levels of evidence.

In patients with sickle cell disease, the humeral head is the second most common site of osteonecrosis. In contrast to femoral head osteonecrosis, there is little information in the literature about the rate of progression of humeral head osteonecrosis or about the risk factors for progression of the osteonecrosis in symptomatic shoulders in adults. Chung and Ralston provided initial descriptions of humeral head osteonecrosis and Milner et al. reported the frequency of the condition in patients with sickle cell disease, but no report has described the natural evolution of symptomatic shoulder osteonecrosis in patients with sickle cell disease. David et al. and, more recently, Lau et al. reported prosthetic shoulder arthroplasty as a treatment option. The delay between the beginning of the disease and the need for an arthroplasty is unknown. Because most of these patients are

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young and have a long life expectancy with appropriate medical treatment, and because of the substantial impact of this type of complication on quality of life, it would be beneficial to know the natural history of a painful shoulder in these patients to better plan treatment.

### Material and Methods

**Patients**

Institutional review board approval was obtained for this study. Three hundred and fifty-six patients who were followed by our sickle-cell disease center became adults (more than eighteen years old) between 1985 and 1990. Two hundred and twelve of the 356 patients were homozygous for hemoglobin S (S/S), seventy-nine had hemoglobin S/hemoglobin C (S/C), and sixty-five had hemoglobin S/beta-thalassemia (S/T). Fifty-two of these 356 patients had preexisting humeral head osteonecrosis demonstrated on shoulder radiographs (performed when they were eighteen years old) and were excluded from this study, leaving 304 patients. These 304 patients had asymptomatic shoulders at the age of eighteen and radiographs of both shoulders (made at the age of eighteen) demonstrating that no osteonecrosis had developed during childhood. The study group (304 patients) included 168 patients with the S/S genotype, seventy-five with the S/C genotype, and sixty-one with the S/T genotype. The inclusion period was between January 1985 and December 1993. During this period all of the patients received specific health education, were prescribed treatment, and because of the substantial impact of this type of complication on quality of life, it would be beneficial to know the natural history of a painful shoulder in these patients to better plan treatment.

### Table I: Stage of Osteonecrosis at the Initial Visit and at the Time of Final Follow-up

<table>
<thead>
<tr>
<th>Criteria for Staging</th>
<th>No. of Shoulders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At Initial Visit</td>
</tr>
<tr>
<td>Stage I</td>
<td>38</td>
</tr>
<tr>
<td>Abnormal MRI, normal radiograph</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>42</td>
</tr>
<tr>
<td>Abnormal radiograph with sclerotic or cystic changes in the humeral head, but no crescent line</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>5</td>
</tr>
<tr>
<td>Abnormal radiograph showing a crescent sign with humeral head flattening of &lt;1 mm</td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>19</td>
</tr>
<tr>
<td>Collapse of the humeral head of &gt;1 mm without joint space narrowing</td>
<td></td>
</tr>
<tr>
<td>Stage V</td>
<td>0</td>
</tr>
<tr>
<td>Joint space narrowing</td>
<td></td>
</tr>
<tr>
<td>Stage VI</td>
<td>0</td>
</tr>
<tr>
<td>Advanced degenerative changes</td>
<td></td>
</tr>
</tbody>
</table>

### Location

The measurement of the lesion in contact with the articular surface of the glenoid was performed on the transverse MRI, with the arm always in the same anatomical position (the arm along the body and the palm of the hand in a supinated position). The diameter of the glenoid, as it appeared on the transverse image, was divided into two parts: anterior and posterior. The measurement of the necrotic area at the articular margin of the adjacent humeral head was expressed as anterior if it was anterior and in contact with less than one-half of the glenoid rim, as posterior if it was posterior and in contact with less than one-half of the glenoid rim, and as medial if it was in contact with all of the glenoid rim.

### Progression of the Disease

During the inclusion period (from 1985 to 1993), the natural history of shoulder osteonecrosis in sickle cell disease was not well known; there was little conclusive evidence about the risk of progression of shoulder osteonecrosis in these patients, and there was no evidence of a favorable benefit-to-risk ratio of early surgery. Therefore, no therapeutic intervention was carried out if no collapse had occurred. The natural progression of the shoulder osteonecrosis was followed clinically and radiographically every six months for the first two years and then every year until 2008. All patients were followed at the same institution by the sickle-cell disease center. The follow-up evaluations consisted of serial radiographs, a review of the office charts, interviews, and clinical examination of the patients. Changes in lesion size were determined on MRIs two and four years after the diagnosis of osteonecrosis (the first MRI) for...
shoulders that remained without collapse after two or four years of follow-up after the first MRI. Patients with symptomatic shoulders without collapse at the time of the most recent follow-up had another MRI at the last follow-up visit. If a change in size was detected, the ratio of the lesion volume change was calculated on the basis of the lesion volume at baseline and at the time of follow-up. During the study, no patient was lost to follow-up.

The results were classified according to the radiographic progression of the disease or the clinical evolution until surgery. Radiographic progression of the disease was defined as an advance in stage or progressive collapse. Clinical evolution was evaluated by assessing pain, the Constant Shoulder Score\(^3\), and need for surgical intervention. At each follow-up evaluation and immediately before surgery, shoulder function was assessed with the Constant Shoulder Score, and surgical intervention was discussed with the patient when the score was approximately 60 points (out of 100). This score (60 points) was accepted before surgery, shoulder function was assessed with the Constant Shoulder Score, and surgical intervention was discussed with the patient when the score was approximately 60 points (out of 100). This score (60 points) was accepted by all patients as warranting surgical intervention (except for one patient who refused surgery due to medical conditions), and the mean score of the patients undergoing surgery was 52 points (range, 23 to 59 points). Therefore, the clinical evolution of the disease was defined as surgical intervention for these symptomatic shoulders.

**Statistical Analysis**

Survival curves for the shoulders before collapse were calculated with Kaplan-Meier survival analysis, and these survival curves were compared by using the log-rank test. To construct the “life table,” the number of shoulders at each stage was closely followed and the number of events (change of stage, collapse, or surgery) was determined for each year. When an event occurred, the shoulder was registered and the “number at risk” for the stage was calculated again and so on for each successive year. Multivariate analyses were performed by using the Cox proportional-hazards model to identify the independent factors (genotype, association with hip osteonecrosis, stage, extent, and location of the lesion) associated with radiographic progression of the disease, clinical progression of the disease, and need for surgical treatment.

**Source of Funding**

There was no funding source for this study.

**Results**

During the inclusion period of the study (from January 1985 to December 1993), symptomatic humeral head osteonecrosis developed in 104 of the shoulders, in eighty-two patients. There were thirty-five men and forty-seven women. Nineteen of the eighty-two patients were homozygous for hemoglobin S (S/S genotype), thirty-seven had hemoglobin S/hemoglobin C (S/C), and twenty-six had hemoglobin S/beta-thalassemia (S/T) (see Appendix). Thirty-two patients had bilateral symptomatic humeral head osteonecrosis and forty, unilateral symptomatic osteonecrosis.

This population of eighty-two patients with 104 shoulders affected by osteonecrosis had a mean age of twenty-three years (range, eighteen to twenty-six years) at the time that they became symptomatic and osteonecrosis was diagnosed. At the time of diagnosis, thirty-eight shoulders were stage I, forty-two were stage II, and twenty-four were stage III or IV (Table I). The average duration of follow-up, after inclusion of the shoulder with humeral head osteonecrosis in the study, was twenty years (range, fifteen to twenty-three years).

**Evolution of Osteonecrosis on Imaging Studies**

Progression of the disease until humeral head collapse was seen on radiographs and/or MRI studies was observed in many shoulders regardless of the stage at the time of the diagnosis of the osteonecrosis. Stage regression (from stage II to stage I, or total repair of stage I, as seen on MRI) was never observed in this population. At the time of diagnosis of the 104 shoulders with symptomatic osteonecrosis (Table I), eighty were stage I (thirty-eight shoulders) or stage II (forty-two) and twenty-four were stage III (five) or IV (nineteen). At the time of the most recent follow-up, none of the eighty shoulders with stage-I or II osteonecrosis (at the time of diagnosis) was stage I; fifteen were stage II, and sixty-five (twenty-eight of the thirty-eight that were stage I at diagnosis and thirty-seven of the forty-two that were stage II at diagnosis) had progressed to collapse. Hence, radiographic progression of the disease until collapse occurred was observed in 81% of the eighty shoulders that had stage I or II at the time of diagnosis of osteonecrosis (Fig. 1). The five shoulders with stage-III osteonecrosis at diagnosis had collapse within six months after symptom onset and diagnosis, and the nineteen shoulders with stage-IV osteonecrosis at diagnosis had collapse on the first radiograph made (at an average of fourteen weeks; range, two to four months) after the occurrence of symptoms; the symptoms in those twenty-four shoulders appeared when the patients were an average of twenty-two years old (range, twenty to twenty-five years old). The mean time between pain occurrence and collapse was six years (range, six months to seventeen years), with a median of eight years. Progression from collapse to osteoarthritis with joint space narrowing (Table I) occurred in most of the shoulders within a period of five years after collapse.

Progression in the size of the lesion was diagnosed on sequential MRIs of twenty-four shoulders before they progressed to collapse. The mean volume of the lesion involved 36% (range, 8% to 48%) of the humeral head at the time of the first MRI and progressed to a mean of 47% at the time of the second MRI. These twenty-four shoulders (sixteen in patients with the S/S genotype) had two or several separate low-intensity bands, either surrounding the other area of the lesion or separate from the other area, thus indicating possible recurrence of osteonecrosis in these patients. Sequential MRI showed no enlargement of the osteonecrotic lesion in the humeral head in the other eighty shoulders. Patients in whom the osteonecrosis was still stage II at the most recent follow-up evaluation had another MRI, which showed no spontaneous decrease in the size of the lesion.

**Clinical Evolution of Osteonecrosis**

Of the 104 symptomatic shoulders, sixty-three (61%) worsened clinically until surgical treatment was needed. Of these sixty-three shoulders, twenty were stage I at the time of diagnosis of the osteonecrosis, twenty-six were stage II, and seventeen were stage III or IV (see Appendix). There was a significant difference between the mean Constant Shoulder Score of the forty-one shoulders that had not undergone surgery by the time of the latest follow-up (73 points [range, 62 to 88 points] out of 100 points) and the preoperative mean Constant Shoulder Score of the sixty-three shoulders that required surgery (mean, 52 points [range, 23 to 59 points]) (p = 0.02).
Risk Factors for Occurrence and Progression of the Disease

Femoral head osteonecrosis and an S/T or S/C genotype were the principal risk factors for the occurrence of a symptomatic shoulder osteonecrosis (p < 0.01) at the adult age. During the inclusion period (when the patients were adults), those with the S/T or S/C genotype had the highest incidence of humeral head osteonecrosis: humeral head osteonecrosis was observed in nineteen (11%) of the 168 patients with the S/S genotype, in thirty-seven (49%) of the seventy-five patients who had the S/C genotype, and in twenty-six (42%) of the sixty-two patients who had the S/T genotype. At the most recent evaluation, hip osteonecrosis was present in eighty of the eighty-two patients who had symptomatic humeral head osteonecrosis during the inclusion period: twenty-two had hip osteonecrosis during childhood before the shoulder osteonecrosis, thirty-nine presented with symptomatic hip osteonecrosis before the shoulder osteonecrosis as adults, six had asymptomatic hip osteonecrosis diagnosed at the time of the symptomatic shoulder osteonecrosis, thirteen had hip osteonecrosis diagnosed after the shoulder osteonecrosis, and two had no hip osteonecrosis on MRI at the most recent follow-up.

The S/S genotype was a risk factor for an increase in the size of the lesion, rapid progression of the disease, and collapse. The size of the lesion increased in sixteen of the twenty-eight shoulders with the S/S genotype. The time between symptoms and collapse was less than six months in ten of these twenty-eight shoulders. The duration of survival before collapse (Fig. 2) for shoulders that presented with stage I or stage II was significantly (p = 0.01) shorter for the shoulders with the S/S genotype than for the shoulders with the S/C or S/T genotype. At the time of the most recent follow-up, twenty-seven (96%) of the twenty-eight osteonecrotic shoulders in patients with the S/S genotype had collapse compared with sixty-two (82%) of the seventy-six shoulders without collapse.
osteonecrotic shoulders in patients who had the S/C or S/T genotype.

The stage, extent, and location of the lesion were the most relevant to the rate of progression of the humeral head disease and collapse in the seventy-six shoulders in patients with the ST or S/C genotype. The duration of survival before collapse was significantly different between the two groups (p < 0.01, log-rank test). The survival rate before collapse was significantly different between the two groups (p < 0.01, log-rank test). The end point is defined as progression of the disease from the time of diagnosis of the osteonecrosis until collapse occurred. The survival rate before collapse was significantly different between the two groups (p < 0.01, log-rank test). The y axis represents shoulders with the hemoglobin S/beta-thalassemia or hemoglobin S/hemoglobin C genotype without collapse. Fig. 4 Kaplan-Meier curves depicting the influence of the extent of involvement on the risk of collapse in symptomatic shoulders of patients with the S/T or S/C genotype (p < 0.01, log-rank test). The size of the lesion was graded A (mild), B (moderate), or C (severe). The y axis represents shoulders without collapse.

Fig. 3 Kaplan-Meier curves depicting radiographic failure of stage I and stage-I symptomatic shoulders in the patients with the hemoglobin S/beta-thalassemia or hemoglobin S/hemoglobin C genotype. The end point is defined as progression of the disease from the time of diagnosis of the osteonecrosis until collapse occurred. The survival rate before collapse was significantly different between the two groups (p < 0.01, log-rank test). The y axis represents shoulders with the hemoglobin S/beta-thalassemia or hemoglobin S/hemoglobin C genotype without collapse. Fig. 4 Kaplan-Meier curves depicting the influence of the extent of involvement on the risk of collapse in symptomatic shoulders of patients with the S/T or S/C genotype (p < 0.01, log-rank test). The size of the lesion was graded A (mild), B (moderate), or C (severe). The y axis represents shoulders without collapse.

Discussion

The purpose of our study was to determine the natural history of humeral head osteonecrosis in patients with sickle cell disease. As was reported in another study on humeral head osteonecrosis related to other causes, we examined the rate of progression of the disease on radiographs and MRIs and the clinical evolution of the symptomatic osteonecrosis in the shoulders of these patients. Because shoulders were evaluated with MRI as soon they became symptomatic, analysis of the outcome of early osteonecrosis (stage I) was also possible in our

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**Fig. 3** Kaplan-Meier curves depicting radiographic failure of stage I and stage-I symptomatic shoulders in the patients with the hemoglobin S/beta-thalassemia or hemoglobin S/hemoglobin C genotype. The end point is defined as progression of the disease from the time of diagnosis of the osteonecrosis until collapse occurred. The survival rate before collapse was significantly different between the two groups (p < 0.01, log-rank test). The y axis represents shoulders with the hemoglobin S/beta-thalassemia or hemoglobin S/hemoglobin C genotype without collapse.

**Fig. 4** Kaplan-Meier curves depicting the influence of the extent of involvement on the risk of collapse in symptomatic shoulders of patients with the S/T or S/C genotype (p < 0.01, log-rank test). The size of the lesion was graded A (mild), B (moderate), or C (severe). The y axis represents shoulders without collapse.
study. We identified risk factors that were associated with rapid progression of the disease until collapse occurred. In particular, we found that patients with the S/S genotype had a greater risk of rapid collapse and the need for shoulder arthroplasty than did patients with other genotypes. For these patients, the delay between symptoms and collapse was sometimes as short as three months and was always less than five years, even for stage-I shoulders. The patients with the S/C or S/T genotype had a longer delay between symptoms and collapse, and the size and location of the humeral head osteonecrosis were associated with the risk of rapid radiographic or clinical failure.

In contrast to other reports on humeral head osteonecrosis, we observed extension of some stage-I and II necrotic lesions. This finding differs from those in most previous reports, in which an increase in the volume of femoral head or humeral head osteonecrosis was not observed on repeated MRIs. Our observation is in agreement with histological analyses of hip osteonecrosis in sickle cell disease that demonstrated the possibility of recurrent hip osteonecrosis in these patients. In addition, spontaneous regression was never observed on MRI, even in stage-I disease. This is in contrast to reports on shoulder osteonecrosis related to the use of corticosteroids.

There were several other findings of interest in our study. Isolated shoulder osteonecrosis without associated hip osteonecrosis was a rare event in adults with sickle cell disease. This is consistent with findings of shoulder osteonecrosis related to corticosteroids. Therefore, when a patient with symptomatic shoulder osteonecrosis presents without hip pain, he/she should be informed that there is a high risk of symptom hip osteonecrosis being observed over the following years with a distinct probability that collapse will occur. We also recommend that patients with shoulder osteonecrosis related to sickle cell disease have bilateral hip MRI at the time of the diagnosis of the humeral head osteonecrosis.

Discussion of treatment of shoulder osteonecrosis in patients with sickle cell disease is beyond the scope of this report. However, the young mean age of the patients at the initial examination, the frequency of unfavorable clinical outcomes after collapse, and the risks of arthroplasty in young patients argue for considering a surgical procedure to avoid collapse in symptomatic shoulders with stage-I or II osteonecrosis, as is the case for the hip. Even after collapse, arthroplasty is not the only solution for these patients. Hattrup and Cofield found that 43% of patients with osteonecrosis required shoulder replacement three years after diagnosis, but most of their patients had stage-III or IV involvement, and sickle cell disease was not a frequent cause of the osteonecrosis in their series. We recommend a more cautious indication for shoulder arthroplasty in patients with osteonecrosis related to sickle cell disease, even after collapse. Nonoperative treatment with exercises to preserve shoulder motion, arthroscopic or operative debridement, core decompression, or other conservative treatments can provide pain relief and delay the need of arthroplasty over the long term in patients with osteonecroses (of whatever cause). Although some reports have discussed shoulder osteonecrosis in sickle cell disease, to our knowledge ours is the first extensive report with a long-term follow-up on the natural history of symptomatic osteonecrosis of the humeral head in adults with sickle cell disease. Because the shoulders were evaluated with MRI as soon as they became symptomatic, it was possible to analyze outcomes in patients with early osteonecrosis (stage I).

Nevertheless, our study has some limitations. Importantly, given the fact that most of the patients had humeral head collapse, it was difficult to model the factors that were most predictive of rapid progression of the disease until collapse occurred.

In conclusion, humeral head collapse occurs very quickly (in as early as six months) after the onset of pain due to osteonecrosis, particularly in patients with the S/C genotype. Collapse of the humeral head tended to occur later but at a high rate in patients who had the S/C or S/T genotype. Therefore, in the majority of the patients, symptomatic osteonecrosis of the humeral head should be considered as a disease with substantial clinical and radiographic progression over time.

Appendix

Tables showing the size of the lesion graded according to the quantification of the extent with the system of Steinberg et al., the number of osteonecrotic lesions according to genotype, and progression of the disease and surgery at the most recent follow-up evaluation according to the stage at the time of diagnosis of osteonecrosis are available with the online version of this article as a data supplement at jbjs.org.

References


