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Acute Splenic Sequestration Crisis

Jorge Peña Siado and Julian Londono Hernández

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Abstract

Acute splenic sequestration crisis (ASSC) is a life-threatening complication associated with sickle cell anemia (SCA) that consists of an acute fall in hemoglobin produced by red blood cell (RBC) sickling within the spleen. It is also one of the leading causes of death in children with SCA. Occlusion of the splenic vascular supply leads to parenchymal ischemia and tissue necrosis. ASSCs are considered an emergency because of their high morbidity and mortality. Untreated patients may die within 1–2 h due to circulatory failure. Management is supportive, sometimes with blood transfusion and total or partial splenectomy.

The aim of this chapter is to bring the up-to-date knowledge of the epidemiology, pathophysiology, diagnosis, and treatment of ASSC. Other important items considered are the spleen dysfunction, susceptibility to infections, and its prevention, disease expression, and to address the different managements for improving prognosis.

Keywords: Sickle cell anemia (SCA), acute splenic sequestration crisis (ASSC), splenomegaly, hypersplenism, splenectomy

1. Introduction

In 1904, Herrick was the first to describe sickle cell anemia (SCA) in a West Indian student [1]. SCA is one of the most frequent hemoglobinopathies in the world. This disease may affect any part of the body, and one of the most commonly affected organs is the spleen. This disease results from a change of the amino acid valine instead of glutamic acid in the sixth position of the beta chain of hemoglobin. This change will produce rigid sickle-shaped red blood cells (RBCs) that hemolyze easily and adhere to each other blocking blood vessels [2].

The SCA is associated with several problems that can acutely or chronically affect health of children or adults with this disease: vasoocclusive crisis, aplastic crisis, acute splenic crisis sequestration, acute chest syndrome, stroke, priapism, and impaired growth and development. This type of anemia is inherited in an autosomal recessive manner. When there is only one abnormal copy of the gene, patients do not experience symptoms [3].

In children with SCA, spleen may be clinically palpable or not, functional or not, and not have existing correlation between size and function. The spleen is the organ most affected in SCA. Often, hyposplenism occurs before 1 year of age. Autosplenectomy is caused by fibrosis of the spleen as a result of multiple repeated vasoocclusive crises and usually is present between 5 and 6 years. Splenomegaly, sometimes with hypersplenism, can occur with the loss of function of the spleen. Hyposplenism increases the risk of infections with encapsulated bacteria [4].

The first person who conceptualized the term acute splenic sequestration crisis (ASSC) was Topley in 1981, who defined it as acute splenic enlargement with a fall in the hemoglobin (Hb) level of at least 20 g/l (or 2 g/dL) and abnormal basal reticulocyte count [5]. It is also defined as the sudden onset of splenomegaly (greater than 2 cm from the steady-state level) or sudden enlargement of a preexisting splenomegaly in association with acute anemia, evidence of active bone marrow, and regression of splenomegaly after blood transfusion. It is the result of rapid sequestration of RBCs in the spleen, which alters its functioning. ASSC is divided into major and minor [6, 7, 8]. Minor ASSC refers to the moderate increase in splenic size and the decrease in Hb level of 2 to 3 g/dL; sometimes reaching a level as low as 2 to 3 g/dL, the spleen size regresses after blood transfusion, and there is evidence of active bone marrow.

Minor ASSC is referred as a moderate increase in splenic size and a decrease in Hb level of 2 to 3 g/dL; the spleen size regresses after blood transfusion, and there is evidence of active bone marrow.

Splenomegaly is the enlargement of the spleen. However, an enlarged or palpable spleen is not necessarily of clinical significance. Moreover, certain individuals with broadly splayed costal margins have readily palpable but small spleens. A spleen weight of 400–500 g indicates splenomegaly, and some authors consider spleens weighing more than 1000 g to have massive splenomegaly. Spleens that are prominent below the costal margin typically weigh 750–1000 g. Poulin et al. defined splenomegaly as moderate if the largest dimension is 11–20 cm and severe if the largest dimension is greater than 20 cm [9]. Hypersplenism refers to splenomegaly and any combination of anemia, leucopenia, and thrombocytopenia, with compensatory bone marrow hyperplasia and tendency to normalization of blood parameters after splenectomy [10, 11]. Hyposplenism is defined as an acquired disorder caused by several hematological and immunological diseases and characterized by absent or reduced splenic function impairment [12]. The most common condition associated with hyposplenism is sickle cell anemia, but it is also usually due to surgical removal, congenital aplasia, tumor metastasis, splenic vascular accident, alcoholic liver disease, celiac disease, bone marrow transplantation, and inflammatory bowel disease [13]. RBC abnormalities, including the presence of inclusions, nucleated RBC, and target cells, are commonly present. Patients with hyposplenism are at increased risk of bacterial sepsis, especially due to infection by *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenza* type b. Massive splenic infarction (MSI) is the infarction involv-

ing more than 50% of the spleen size. MSI is extremely rare in children with SCA. It can develop spontaneously or be precipitated by other factors, namely, high altitude, acute chest syndrome, and severe stress in the form of septicemia or severe vasoocclusive crisis [6, 14].

Epidemiology
 ASSC is a serious and the earliest life-threatening complication seen in patients with SCA [15]. It may occur during the first weeks of life, and it could be the first symptom of the disease. Up to 75% of first cases occur before 2 years. ASSC is considered the second leading cause of death after infection in the first decade of life in these patients. These crises are usually seen in infants and young children commonly between 5 months and 2 years of age. Mortality is up to 3% in children and 10% of adults who die from hypovolemic shock given the lack of early transfusion. Other reports show mortality rates of 15%–44% [16, 17]. Early neonatal screening and early parental education diminishes mortality rate up to 0.53% [4]. Between 10% and 30% of homozygous children have suffered a crisis of splenic sequestration before 3 years of age, and all patients with SCA and no fibrosis spleen are susceptible to ASSC. In homozygous patients, it usually occurs between 3 months and 3 years old, but it can occur at older ages in those treated early with hydroxyurea, delayed autosplenectomy, and also in double heterozygotes SC and S-thalassemia, in which it can occur even in adulthood. There is a recurrence in the 50% of those who survive a first episode of splenic sequestration [11].

In the study of Brousse and colleagues [18], 190 children with SCA diagnosed at birth with SS or Sbeta0 were followed during a study period of 9 years. Among these 190 children are 111 boys and 79 girls (sex ratio, 1:4). They found 437 episodes of ASSC (0.06/patient-year); the median age at the first episode was 1.4 years (0.1–7), and 67% of patients had more than one episode. This study showed that the risk of recurrence was lower when the first episode occurred after 2 years and was higher when the first episode appeared before 1 year of age. In the same study, it was found that patients may experience several episodes, including more than 5; also, the prevalence of ASSC among children with SCA was 12.6%. ASSC incidence was 0.06/patient-year. The lifelong prevalence of acute splenic sequestration ranges from 7% to 30% according to studies [5, 15, 16].

Pathophysiology
 The spleen is a lymphoid organ dedicated to the clearance of blood cells and pathogens. It links innate and adaptive immune responses. The spleen filters approximately 5% of the cardiac output every minute [19]. At present, the pathophysiology of ASSC is not completely understood. In normal conditions, the blood enters to the spleen through the splenic artery and then is distributed through the trabecular arteries that branch throughout the parenchyma to a terminating arteriole called the central arteriole. Splenic arterioles may drain into the venous sinuses or within the parenchyma and thus relieve their blood in the cords of red pulp. The spleen contains specialized macrophages, which are in close contact with blood cells and circulating bacteria, producing phagocytosis of some pathogens [20, 21]. Ten percent of the blood flowing through the spleen passes through filtration beds slowly. There is additional resistance due to the dynamic properties of both endothelial cells, and specialized fibroblasts [22] may play an important role in regulating blood filtration and possibly be dysfunctional in pathological conditions like SCA. The white pulp selectively clears lymphocytes and accessory cells from the blood and allows the spleen to initiate an adaptive immune response. The marginal zone of the spleen produces immunoglobulin M (IgM) that is essential for the

phagocytosis of encapsulated bacteria such as *S. pneumoniae* and *H. influenza* type b (Hib). The marginal area is responsible for the generation of IgM by memory B cells. Macrophages in the filtration beds exert functions as erythrophagocytosis and recycling iron [23]. The main clinical consequences of defective spleen function derive from the alteration of both the filtering and immune functions, leading to increased susceptibility to bacterial infection, increased risks of vascular complications and autoimmunity [18].

In SCA, RBCs are not deformable enough. The Hb S chain, with valine at the sixth position, has an unusual propensity to bind with other Hb S chains when deoxygenated. This polymerization results in rigid molecules of hemoglobin, which are joined to each other and thus it is produced larger polymers that trigger a variety of elongated erythrocytes with decreased deformability. Polymerization in SCA is a process that occurs by factors that lead to deoxygenation such as high altitudes, infections, decreased pH, and low temperatures [24]. Polymerization is responsible for the sickled or banana shape of RBCs in SCA, which causes a nonselective increase in membrane cation permeability to sodium, potassium, magnesium, and calcium. When these cations enter the RBC (down their concentration gradient), several cell membrane transport systems are activated, with the important cumulative effect being the egress of water. The polymerization causes erythrocytes with a banana-shaped form that leads to an increase in the permeability of sodium, potassium, magnesium, and calcium. These cations will produce an activation of several transportation systems in the red cell membrane, which leads to dehydration of these cells. When the red cell has had several episodes of polymerization and dehydration, it becomes irreversibly deformed cell, which leads to vasoocclusion [25] (see Figure 1). The normal red blood cell can deform as it passes through small vessels. Dehydrated cells increase their viscosity, leading to a decreased deformability [26].

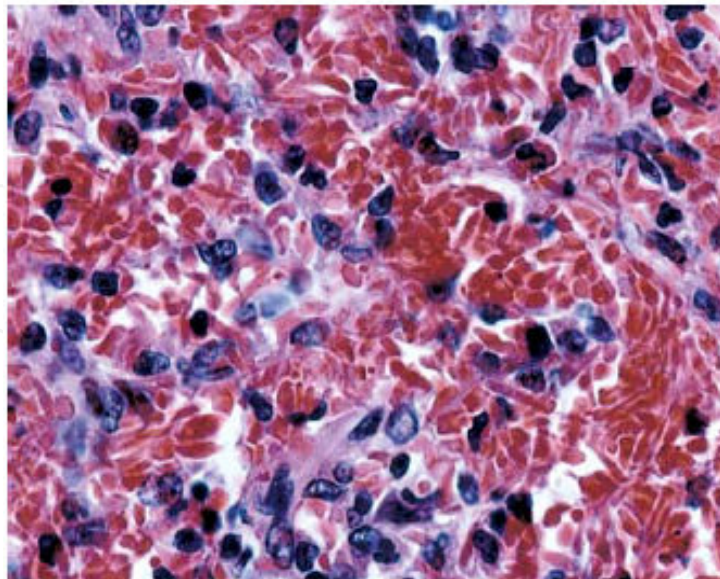


Figure 1. Vascular sinus congestion with Hb SS BCs. Medium-power photomicrograph (original magnification, $\times 40$; hematoxylin–eosin stain) of a spleen tissue sample shows congestion of the vascular sinuses with Hb SS RBCs. (Adopted from Gael J. Sick cell anemia. RadioGraphics, 2001; 21:971–994.)

2. Etiology

Precipitating factors have been described such as bacterial–viral infections (parvovirus B19) or acute chest syndrome or exposure to high altitudes. Febrile events in SS infants may trigger or promote ASSC [27]. Increased inflammation during a febrile condition or vasoocclusive crisis may promote the trapping of blood within the spleen by increasing blood cellularity, blood viscosity, and erythrocyte rigidity [28]. Other precipitating factors (genetic or environmental) need to be sought in the hope that factors predicting ASSC will eventually be identified. Of note, none of the studied children in some studies had concomitant or secondary acute chest syndrome [16, 29].

3. Diagnosis

As defined previously, the ASSC is a decrease of at least 2 g/dL in Hb concentration from baseline (or fall by 20% hematocrit) and increased reticulocytosis and splenomegaly >2 cm compared to baseline. It can also have thrombocytopenia. The clinical manifestations, laboratory studies, and radiological features may raise the suspect about this condition.

The differentiation of ASSC from similar conditions is imperative. Transient aplastic crisis due to parvovirus B19 infection occurs in older children with SCA and typically manifests as worsening anemia with reticulocytopenia and no splenomegaly [30]. Malaria and SCA could be present concomitantly and may exacerbate each other, so it is crucial to rule out coinfections [31].

3.1. Clinical presentation

ASSC manifests clinically as the sudden onset of asthenia, adynamia, pain and abdominal distension, pallor, tachycardia, tachypnea, splenomegaly, thirstiness, decreased activity, decreased oral intake, and increased fussiness, and children could quickly manifest signs and symptoms of hypovolemic shock in severe cases. These crises are transient and usually may last from 3 to 4 h until 1 day. Mallouh et al. [28] found that two-thirds of the patients had a fever or infection at the time of the first ASSC.

The older patients may complain of left-sided abdominal pain. Infants with acute splenic sequestration can have sudden, rapid, massive enlargement of the spleen. The hemoglobin may fall by half of its baseline value within a few hours of onset of the sequestration crisis.

It is important to recognize that the spleen is moderately to markedly enlarged, and sometimes very painful. Diffuse abdominal tenderness may increase the suspect of splenic sequestration.

3.2. Laboratory

All patients should promptly have minimum laboratory studies, such as CBC with differential, reticulocyte, and platelet count, and chemistry profile, including electrolytes, AST, ALT, bilirubin, alkaline phosphatase, LDH, BUN, creatinine, and urinalysis.

As mentioned before thrombocytopenia, leukopenia and elevated reticulocyte count can also be seen in these children and can be useful in the diagnosis. It is necessary to take into account that hepatic sequestration can occur in patients with SCA, and this condition could have a clinical presentation with abdominal pain and hepatomegaly. Findings may include mild to moderate elevation of liver transaminases.

There is no exact functional evaluation of the spleen, but blood markers, such as Howell–Jolly bodies (HJB) or pitted cells (PIT), could assess the filtering function of the spleen [4].

Howell–Jolly bodies are nuclear remnants in circulating mature red cells, which are, in physiological conditions, groomed or pitted by the spleen. The circulating number of HJB can be counted on blood smears or by flow cytometry [32] and has therefore been used as a marker of splenic dysfunction.

3.3. Imaging

Clinical signs make the diagnosis. Imaging is therefore not essential and, if performed, should be planned after treatment has started. Suspicion of splenic abscess in children with SCA, who have fever, abdominal pain, and an enlarged spleen, must be corroborated by ultrasound.

When loss of splenic function is present, the uptake of ^{99m}Tc sulfur colloid diminishes and may entirely disappear. Areas with loss of function could appear as rounded masses of hypoechoic tissue at ultrasound (US) and computed tomography (CT) and may have an attenuation similar to that of normal spleen (see Figure 2A) [33].

The spleen with several ASSC becomes small and calcified. This fibrotic spleen has low signal intensity. These calcifications may be visible at radiography and CT (as shown in Figure 2B).

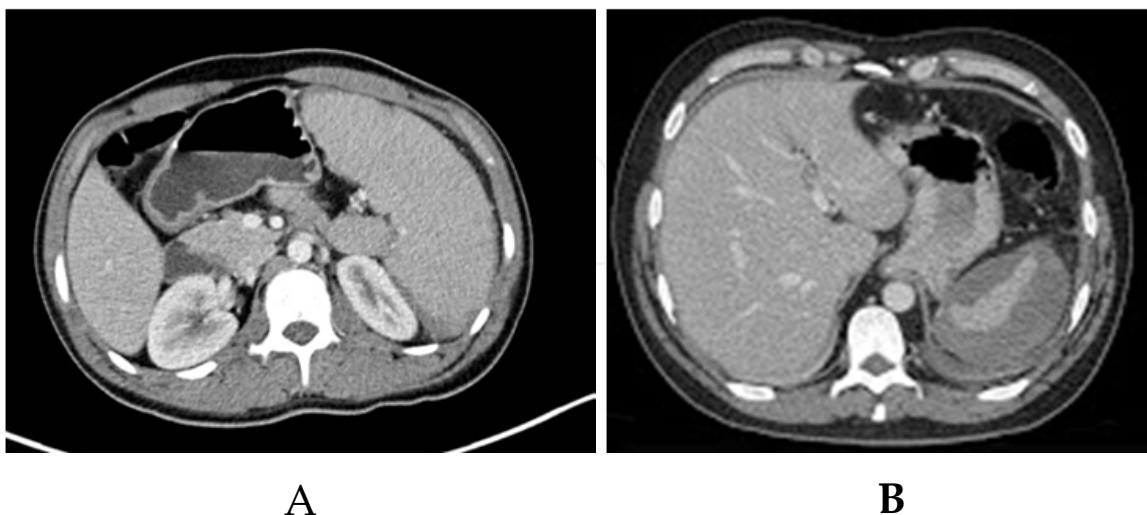


Figure 2. (A) Enlarged spleen with subcapsular infarction in the posterior pole, suggestive of ASSC. (B) Enlarged spleen that enhances heterogeneously with calcifications, suggestive of ASSC in fibrotic phase. (Courtesy of Lina Marcela Cadavid Alvarez, MD, Radiologist.)

4. Treatment

Management is supportive, including the restoration of intravascular volume by packed red blood cell transfusion. The spleen usually decreases its size after a few days or weeks, also resolving thrombocytopenia and leucopenia.

Other support measures include intravenous (IV) fluids such as volume expanders as Ringer lactate or saline solution 0.9%. Transfuse patients with packed RBCs who have acute splenic sequestration and severe anemia to raise the hemoglobin to a stable level. Keep in mind that sequestered red blood cells in the spleen are mobilized after transfusion, so that the level of Hb may increase more than expected.

Do not expect to know the results of additional tests if the suspicion diagnostic request is clear and very urgent transfusion even without cross in case there is evidence of hemodynamic instability. It is recommended to proceed with partial exchange transfusion for signs of respiratory distress [34].

Children younger than 2 years should to ingress in a program of chronic transfusion to maintain HbS <30% until consider splenectomy after that age [35]. Discard malaria in patients recently arrived from endemic countries, including PCR by low parasitemia usual [31].

It is important to address the performance and timing of splenectomy in patients with recurrent acute splenic sequestration or symptomatic hypersplenism (see Algorithm 1).

Splenectomy is an essential part of the management of splenic sequestration crisis. Most of the authors recommend splenectomy after the second episode of ASSC. Consider urgent splenectomy if the patient shows no clinical signs of improvement [36]. Splenectomy may be recommended after a first episode if life threatening is predicted.

Within the complications seen after splenectomy are an increased susceptibility to infections by encapsulated bacteria, but other authors have not found an increased incidence of bacteremia or mortality in children who underwent splenectomy. However, they could have more episodes of pain and acute chest syndrome [33].

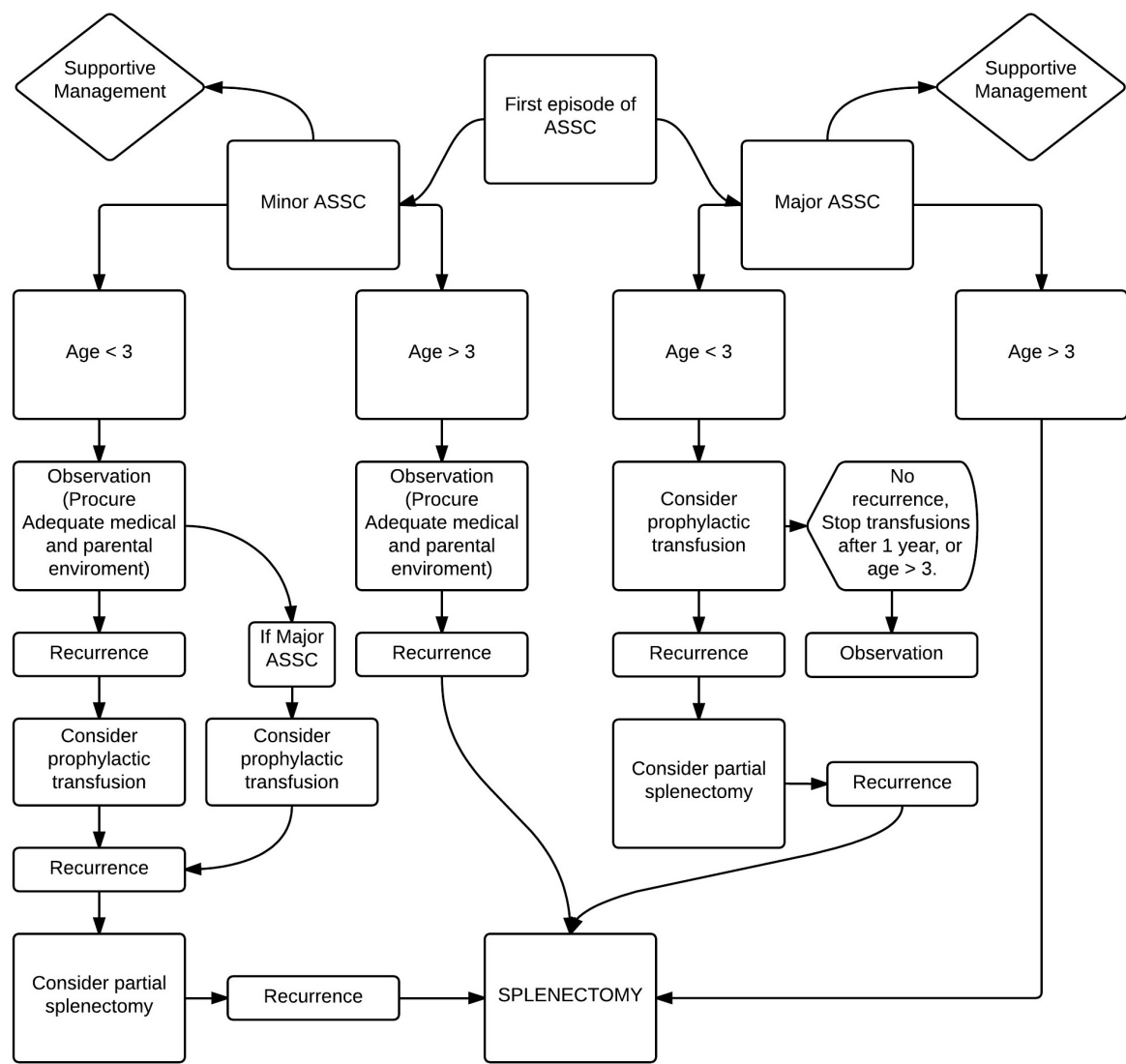
Total splenectomy prevents the recurrence of splenic sequestration, but there are no clinical trials comparing the efficacy of splenectomy compared to chronic transfusion regimes in patients with SCA.

Total splenectomy in SCA is related to a high risk of fulminant sepsis and increased incidence of other events, which have not been reported in patients with partial splenectomy. Gutiérrez et al. examined 54 patients with SCA, who underwent partial splenectomy and compared the clinical and laboratory results with nonsplenectomized patients. They found that partial splenectomy was a safe procedure in patients with sickle cell disease. There were no differences in the clinical picture in children splenectomized and nonsplenectomized except the greater frequency of hepatic sequestration crisis in the first group [37].

Some authors recommend chronic red cell transfusion to prevent recurrent crises, but this can lead to risks such as hepatitis, HIV, parvovirus, and allosensitization. In addition, many patients developed ASSC when red cell transfusion was stopped [38].

SCA conditions that may require splenectomy are as follows:

- a. Recurrent splenic sequestration crisis
- b. Discomfort and deterioration in quality of life secondary to hypersplenism and splenomegaly
- c. Splenic abscess
- d. Massive splenic infarction
- e. Splenomegaly with nonfunctioning spleen



Algorithm 1. Peña and Londoño. Proposed management of ASSC.

5. Follow-up

Patients must be followed periodically, clinically, and with laboratory tests. It is also important to teach the family to palpate the spleen from the diagnosis, warning the need to go quickly to a hospital in case of decay, fever, pallor, and splenomegaly.

Therefore, patients who experience their first ASSC in their first year should be monitored carefully.

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