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ORIGINAL ARTICLE

# Prevalence of abdominal ultrasonographic abnormalities in patients with sickle cell disease

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PURPOSE
The aim of this study was to evaluate the type and prevalence of abdominal ultrasonographic abnormalities in patients with sickle cell disease.

MATERIALS AND METHODS
A total of 102 patients with sickle cell disease at the Center of Hemoglobinopathy of the Antakya State Hospital were screened for intra-abdominal abnormalities by abdominal ultrasonography (US). Eighty-four patients were homozygous for sickle-cell disease (S/S), and 18 patients were compound heterozygotes for sickle cell-ß thalassemia (S/$ß^{thal}$). At the time of examination, 15.7% (16/102) of patients had undergone splenectomy, and 18.6% (19/102) of patients had undergone cholecystectomy.

RESULTS
The most frequent US findings (expressed as percentages of all patients) were hepatomegaly (71.6%), renal enlargement (30.4%), autosplenectomy (33.3%), cholelithiasis (30.4%) and splenomegaly (17.4%). A bright liver was identified in 6 patients (5.9%), an echogenic pancreas in 4 patients (3.9%), and pancreatic punctate echogenic foci were identified in 5 patients (4.9%). Medullary or diffusely increased renal echogenicity was observed in 16 patients (15.7%). Sonographic findings typical of renal papillary necrosis were observed in one patient with S/S. Periportal lymphadenopathy was detected in 10 (11.9%) of 84 patients of the S/S group, and 2 (11.1%) of 18 patients of S/$ß^{thal}$ group.

CONCLUSION
Abdominal ultrasonographic imaging of patients with sickle cell disease revealed a high prevalence of abdominal abnormalities, especially in solid organs.

*Key words:* • *sickle cell disease* • *ultrasonography* • *abdomen* • *liver* • *kidney*

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Sickle cell disease (SCD) is an inherited disease caused by production of abnormal hemoglobin chains within the red blood cell, which cause rigid sickling of the cell, leading to vascular occlusion and ischemia in multiple organs.

The normal human hemoglobin molecule is composed of four globin chains (two α and two ß). SCD results from the inheritance of either two sickle ß globin genes (hemoglobin S/S, sickle cell anemia) or one sickle ß globin gene (heterozygote form of SCD). Sickle cell-*ß* thalassemia (S/$ß^{thal}$) is one of the heterozygote forms of SCD. Patients with S/$ß^{thal}$ have clinical features more similar to those of SCD than to those of thalassemia. Homozygous SCD, with no normal ß globin chain, is usually more severe than sickle cell-*ß* thalassemia.

Repeated vaso-occlusion accounts for the majority of the clinical manifestations of the disease (1, 2). The most common abdominal manifestations include hepatomegaly, splenomegaly, autosplenectomy, cholelithiasis, renal enlargement, and increased renal echogenicity (2, 3). According to the findings of Turkish Hemoglobinopathy Working Group, most of the SCD patients in Turkey live in the province of Hatay (56.7%) (4). The aim of this study was to evaluate the type and prevalence of abdominal ultrasonographic abnormalities in SCD patients living in Hatay.

## Materials and methods

A total of 102 patients with SCD at the Center of Hemoglobinopathy of the Antakya State Hospital were screened for any intra-abdominal abnormalities by abdominal ultrasonography (US). Their ages ranged from 3 to 46 years (mean age, 19.7 ± 8.5). Eighty-four patients were homozygous for sickle cell disease (S/S), and 18 patients had sickle cell-*ß* thalassemia (S/$ß^{thal}$). Demographic data of the patients are summarized in Table 1. None of the patients had any clinical evidence of acute sickle crisis at the time of ultrasonographic examination. At the time of examination, 15.7% of patients (16/102) had undergone splenectomy and 18.6% of patients (19/102) had undergone cholecystectomy.

Informed consent was obtained from all patients (or parents of minor patients), and the study protocol was approved by the ethics committee of our institution.

All patients were examined by B-mode US with an Acuson Antares™ US scanner (Siemens Medical Systems, Mountain View, California, USA) with a variable frequency probe at 1–4 MHz or 4–9 MHz. After the patient fasted overnight, the examination was performed with the patient in the supine, right side, or left side position to obtain an optimal view of the abdominal viscera.

Measurements of the liver, spleen, and kidneys were performed in all patients as follows: long axis of the right lobe of the liver; long axis

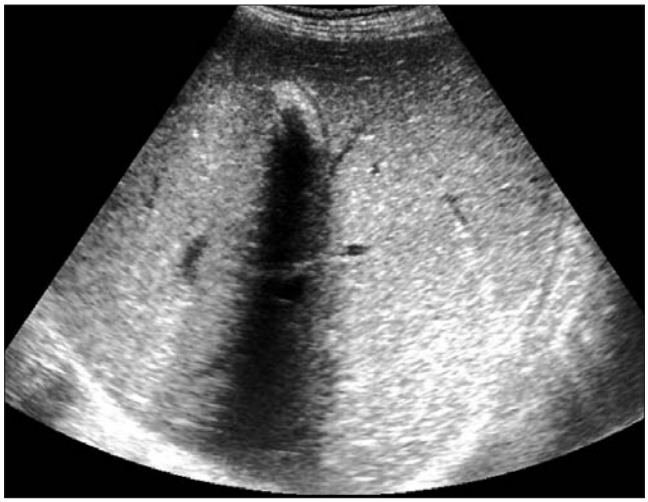

**Figure 1.** US image shows small stones within the contracted gallbladder with distal acoustic shadowing and bright liver in a 13-year-old male patient with sickle cell S/S.

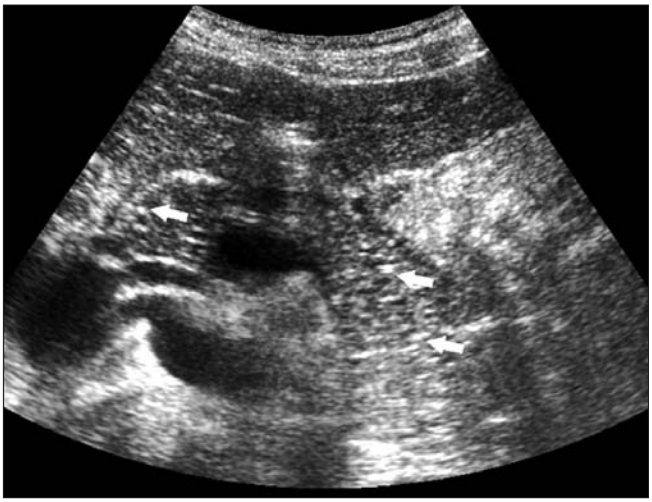

**Figure 2.** US image shows multiple millimetric echogenic foci *(arrows)* in pancreas in a 19-year-old male patient with sickle cell S/S.

of the spleen at the level of the hilum; and long axis of each kidney. The organ sizes were compared to published data obtained from a healthy Turkish population of normal distribution for age and height for infants and children (5). For adult patients, hepatomegaly and splenomegaly were defined as the long axis of the organs longer than 155 mm and 130 mm, respectively (6). The upper limits for normal right and left kidneys were accepted as 128 mm and 130 mm, respectively (7). Hepatomegaly and splenomegaly were defined as "mild" if the two measurements exceeded the upper limit of normal by less than 10%; "moderate" when the measurement was 10% to 20% greater, and "marked" when it exceeded the upper limit of normal by more than 20%.

The parenchyma of the kidneys and liver was evaluated by two radiologists, and the ultrasonographic appearance of the organs was described by consensus. An increase in reflectivity throughout the kidney and poor cortico-medullary differentiation were defined as diffusely increased renal echogenicity. A high reflective renal medulla with a normal renal cortex was defined as medullary hyperechogenicity. A diffuse increase in liver echogenicity was defined as "bright liver". B-mode parameters such as frequency, focus, gain, and tissue harmonics application were optimized by the radiologist on a case-by-case basis. Image analysis was performed visually and qualitatively. All patients were also evaluated for biliary tract and pancreatic abnormalities, intraabdominal fluid collections, masses, and enlarged lymph nodes.

## Results

The most frequent US findings (expressed as percentage of all patients) were hepatomegaly (71.6%), renal enlargement (30.4%), autosplenectomy (33.3%), cholelithiasis (30.4%), and splenomegaly (17.4%). Bright liver was identified in 6 (5.9%) patients (Fig. 1). One case in the S/S group had the ultrasonographic findings of cirrhotic liver. A hepatic hemangioma was observed in 1 patient of the S/$ß^{thal}$ group.

Echogenic pancreas was identified in 4 patients (3.9%), and pancreatic punctate echogenic foci were identified in 5 patients (4.9%) (Fig. 2).

Medullary or diffusely increased renal echogenicity was observed in 16 (15.7%) patients (Figs. 3, 4). Sonographic findings typical of renal papillary necrosis, multiple round or triangular cystic spaces communicating with the collecting system in the medullary region without dilated renal pelvis, were observed in one patient with S/S (Fig. 5).

Periportal lymphadenopathy was detected in 10 (11.9%) of 84 patients of the S/S group and 2 (11.1%) of 18 patients of S/$ß^{thal}$ group. The prevalence and distribution of abdominal US findings according to the SCD phenotypes are summarized in Tables 2–5.

**Table 1.** Demographic data

| Hematologic genotype | Number of patients | Sex (M/F) | Mean age ± SD (years) |
|---|---|---|---|
| Sickle cell (S/S) | 84 | 39/45 | 20.0 ± 8.9 |
| Sickle cell-ß thalasemia (S/$ß^{thal}$) | 18 | 7/11 | 18.3 ± 6.3 |
| Total | 102 | 46/55 | 19.7 ± 8.5 |

M: male; F: female; SD: standard deviation

## Discussion

SCD is one of the most common inherited hemoglobinopathies worldwide (8). In the Eastern Mediterranean Region of Turkey, SCD is common, and constitutes a major challenge in ultrasonographic examinations. SCD manifests in a variety of abdominal problems, including hepatomegaly, splenomegaly, autosplenectomy, biliary tract abnormalities, renal enlargement, and increased renal and pancreatic echogenicity (2, 3). US is a simple, rapid, non-invasive, and non-ionizing tool for assessing the abdominal manifestations of SCD.

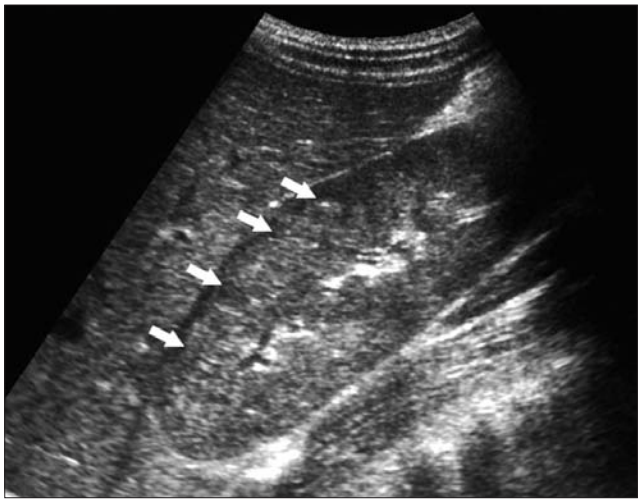

**Figure 3.** US image shows increased renal medullary echogenicity in a 26-year-old male patient with sickle cell S/S. Renal cortex may be differentiated from renal medulla *(arrows)*.

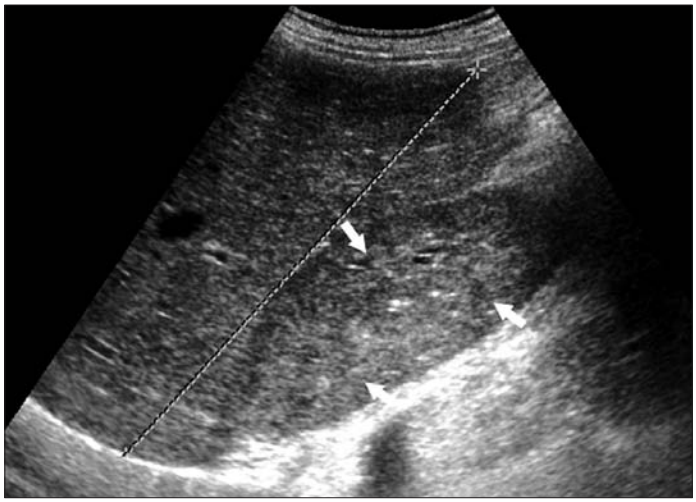

**Figure 4.** US image shows diffuse increase in renal echogenicity, similar to that of the adjacent liver *(arrows)*, in a 33-year-old female patient with sickle cell S/S. Corticomedullary differentiation is poor *(arrows)*.

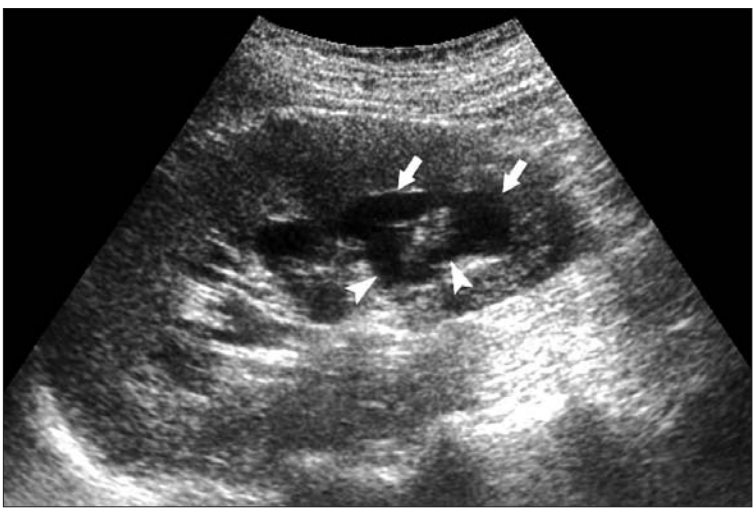

**Figure 5.** US image shows triangular fluid-filled cavities *(arrows)* with narrow infundibuli *(arrowheads)* placed on renal papilla that communicate with the collecting system *(arrowheads)*, in a 26-year-old male patient with sickle cell S/S. Renal pelvis was not dilated.

Vascular occlusion, viral hepatitis, iron overload, and drug reactions may contribute to SCD-related liver disease (8). In one study, the sonographic appearance of the liver in SCD and thalassemia intermedia has been described in 105 patients. Hepatomegaly was demonstrated in 70.5%, and bright liver in 3.8% of these patients (3). An autopsy series reported a 91% prevalence of hepatomegaly in patients with SCD (9). Hepatomegaly was the most common pathologic finding in the current study, its frequency being 72.6% in S/S group and 66.7% in S/$ß^{thal}$ group. However, hepatomegaly is a common clinical finding with various causes. Infectious, infiltrative, and granulomatous disease, malignancy, and other hematologic diseases may cause hepatomegaly (6). Blood-transfusion-related viral infections such as hepatitis B and C may also cause hepatomegaly in SCD. However, only a few study patients were positive for hepatitis B or C. The prevalence of bright liver was 6% in each group. The liver of one patient of the S/S group had the sonographic appearance of cirrhosis. Several features of liver histology in patients with SCD may contribute to the bright liver. These include hemosiderin pigment, periportal fibrosis, and distension of sinusoids with sickle cells (8). One case of hepatic hemangioma was demonstrated in a patient with S/$ß^{thal}$.

The chronic hemolysis of SCD predisposes patients to cholelithiasis, the prevalence of which by ultrasonographic examination has been reported to be 11–55% in patients with SCD (10–12). Prevalence varies with age, gender, and method of examination (8). In our series, cholelithiasis was observed in 27 (32.1%) of 84 patients of the S/S group, and 4 (22.2%) of 18 patients of S/$ß^{thal}$ group. The prevalence of biliary sludge was 3.6% and 5.6% in the S/S group and S/$ß^{thal}$ group, respectively. This observation is in accordance with other studies (3, 13). It is well known that majority of SCD patients with biliary sludge eventually develops gall stones (13). At the time of examination, 15 (17.9%) patients in the S/S group and 4 (22.2%) patients in the S/$ß^{thal}$ group had undergone cholecystectomy for gallstones. Therefore, the prevalence of cholelithiasis was higher than the above-mentioned rates.

Another common abdominal manifestation of SCD is splenomegaly, which is particularly common in patients with hemoglobin S/C and S/$ß^{thal}$ (2); however, repetitive sickling of red cells in the splenic microcirculation leads to splenic infarction, which progresses over time to autosplenectomy. The necrotic tissue is replaced by fibrosis, with deposition of calcium and hemosiderin. Finally, the spleen becomes small, shrunken, and calcified (1). In the present study, splenomegaly was detected in 15 patients with S/S (17.9%), and 3 patients with S/$ß^{thal}$ (16.7%). Other diseases that cause splenomegaly include infectious or granulomatous disease,

malignancy, congestive conditions, and other hematologic diseases (6). A common cause of splenomegaly in SCD is acute splenic sequestration (2). However, none of the study patients had any clinical evidence of splenic sequestration at the time of examination.

**Table 2.** US findings in the liver: distribution according to sickle cell disease genotype

| US findings | | S/S group | S/ß$^{thal}$ group |
|---|---|---|---|
| Hepatomegaly, mild | | 24 (28.6%) | 4 (22.2%) |
| | moderate | 22 (26.2%) | 6 (33.3%) |
| | marked | 15 (17.9%) | 2 (11.1%) |
| Bright liver | | 5 (6.0%) | 1 (6.0%) |
| Focal parenchymal lesions | | 0 | 1 (6.0%) |

**Table 3.** US findings in the biliary tract: distribution according to sickle cell disease genotype

| US findings | | S/S group | S/ß$^{thal}$ group |
|---|---|---|---|
| Cholelithiasis, overall | | 42 (50%) | 8 (44.4%) |
| | US positive | 27 (32.1%) | 4 (22.2%) |
| | cholecystectomy* | 15 (17.9%) | 4 (22.2%) |
| Biliary sludge | | 3 (3.6%) | 1 (5.6%) |

* All patients with cholecystectomy had surgery for gall stones.

**Table 4.** US findings in the spleen: distribution according to sickle cell disease genotype

| US findings | | S/S group | S/ß$^{thal}$ group |
|---|---|---|---|
| Splenomegaly, overall | | 27 (32.1%) | 7 (38.9%) |
| | mild | 3 (3.6%) | 1 (5.6%) |
| | moderate | 3 (3.6%) | 0 |
| | marked | 9 (10.7%) | 2 (11.1%) |
| | splenectomy* | 12 (14.3%) | 4 (22.2%) |
| Shrunken spleen | | 5 (6.0%) | 0 |
| Autosplenectomy | | 36 (42.9%) | 2 (11.1%) |
| Hypoechoic parenchymal lesions | | 5 (6.0%) | 2 (11.1%) |
| Multiple punctate echogenic foci | | 1 (1.2%) | 0 |

* All patients with splenectomy had been treated for splenomegaly.

**Table 5.** US findings in the kidneys: distribution according to sickle cell disease genotype

| US findings | | S/S group | S/ß$^{thal}$ group |
|---|---|---|---|
| Renal enlargement | | 26 (30.1%) | 5 (27.8%) |
| Renal cysts | | 1 (1.2%) | 0 |
| Increased renal echogenicity | Focal | 6 (7.1%) | 0 |
| | Diffuse | 8 (9.5%) | 2 (11%) |

Shrunken spleen was observed in 5 (6%) of 84 patients of the S/S group, but not in any of 18 patients of the S/ß$^{thal}$ group. At the time of examination, 36 patients with S/S (42.9%) and 2 with S/ß$^{thal}$ (11.1%) were noted to have autosplenectomy. One S/S patient had multiple punctate echogenic foci in the spleen. Splenic echogenic foci have been noted previously in SCD. These changes are generally benign and may represent micro-infarcts (14). Hypoechoic focal parenchymal lesions were observed in 5 S/S patients (6%) and 2 S/ß$^{thal}$ patients (11.1%). Splenic infarcts usually appear as wedge-shaped or rounded hypoechoic areas on US (6). Rests of preserved splenic tissue or regrowth of splenic tissue occasionally may also be seen as hypoechoic areas in patients with SCD (1). Accessory spleen was observed in 3 of 102 patients (2.9%). At the time of examination, 15 (17.9%) patients in S/S group and 4 (22.2%) patients in S/ß$^{thal}$ group had undergone splenectomy because of splenomegaly. Therefore, the prevalence of splenomegaly was higher than the above-mentioned rates in our series.

SCD is associated with many structural and functional abnormalities of the kidney (15), which may progress to chronic renal failure and end-stage renal disease (16). Several studies have reported medullary or diffuse increase in reflectivity on renal sonography in patients with SCD (2, 17–19). The cause and significance of this entity is unknown; however, renal papillary necrosis, high concentrations of iron deposits within tubular epithelial cells, focal scarring and interstitial fibrosis in vasa recta system, glomerular hypertrophy, and renal sclerosis have been suggested as factors that may cause increased renal echogenicity. Walker and Serjeant reported increased medullary echogenicity in 5 of 179 patients with S/S (2.8%), and 17 of 25 patients with S/ß$^{thal}$ (68%) (17). In the same study, diffusely increased renal echogenicity was reported in 15 of 179 patients with S/S (8.4%), and none of 25 patients with S/ß$^{thal}$ (17). In one report, increased renal echogenicity was noted in 26 of 189 patients with SCD (13.8%) (19). In our series, medullary hyperechogenicity was observed in 6 of 84 patients of the S/S (7%) group and was not observed in any of 18 patients of S/ß$^{thal}$ group. The prevalence of diffusely

increased renal echogenicity was 10% in the S/S group, and 11% in the S/ß$^{thal}$ group. Medullary hyperechogenicity has been reported in many conditions including hypercalciuria, medullary sponge kidney, hyperparathyroidism, and papillary necrosis (20). A simple renal cyst was observed in one patient with S/S.

Renal enlargement has been reported in up to 50% of patients with SCD (16). In our study, the prevalence of renal enlargement was 30.1% in the S/S group, and 27.8% in the S/ß$^{thal}$ group. The etiology of renal enlargement in SCD is unknown. However, glomerular hypertrophy and increased renal blood volume have been suggested as likely contributors (16, 21). One patient of S/S group had typical sonographic findings of renal papillary necrosis, multiple round or triangular cystic spaces communicating with the collecting system in medullary region without dilated renal pelvis (22).

A few reports have described pancreatic hemosiderosis in patients with SCD or thalassemia syndromes (2, 23). It has been shown that iron deposits cause the pancreas to be echogenic on US in these patients. Papadaki et al. reported a prevalence of 3.8% for echogenic pancreas in patients with SCD and thalassemia intermedia (3). In our study, echogenic pancreas was observed in 3 of 84 patients of the S/S group (3.6%) and 1 of 18 patients of S/ß$^{thal}$ group (6%). We have also observed pancreatic punctate echogenic foci in both groups. However, multiple other factors such as aging, obesity, chronic pancreatitis, steroid therapy, viral infections, diabetes mellitus, obstruction of the pancreatic duct, cystic fibrosis or dietary deficiency may cause pancreatic fatty infiltration and consequently echogenic pancreas on US (24). We had not obtained biopsy or magnetic resonance imaging to confirm pancreatic hemosiderosis in any patients with an echogenic pancreas. Chronic pancreatitis, cystic fibrosis, hyperparathyroidism, islet cell tumors, or protein malnutrition may also cause pancreatic calcification (24).

To our knowledge, the prevalence of abdominal lymphadenopathy in SCD has not been described previously. In our series, periportal lymphadenopathy was detected in 10 of 84 patients of the S/S group (11.9%) and 2 of 18 patients of S/ß$^{thal}$ group (11.1%). Papakonstantinou et al. reported the prevalence of abdominal lymphadenopathy in patients with β-thalassemia major to be 32%, and demonstrated a correlation with severity of liver iron overload and activity of coexisting chronic hepatitis C (25). Two patients in our series were positive for hepatitis C, and one of them had periportal lymphadenopathy. The majority of patients with this condition have a history of multiple blood transfusions; however, iron deposition, periportal inflammation, and fibrosis due to sickled red cells in hepatic sinusoids also may explain the presence of periportal lymphadenopathy.

A major limitation of the current study is that several abdominal ultrasonographic findings including hepatomegaly, splenomegaly, increased renal echogenicity, and echogenic pancreas are non-specific. We did not perform biopsy or any other imaging methods to confirm the ultrasonographic findings in our study patients.

In conclusion, abdominal US imaging of patients with SCD showed a high incidence of abdominal abnormalities, especially in solid organs such as liver, kidney, and spleen. Repeated vascular occlusion, chronic hemolysis, anemia, and iron overload contribute to the pathogenesis of multiple abdominal manifestations of SCD.

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