

Ischemic Duodenal Ulcer, an Unusual Presentation of Sickle Cell Disease

Rahul N. Julka, MD; Farshad Aduli, MD; Laura W. Lamps, MD; and Kevin W. Olden, MD

Sickle cell disease is caused by molecular abnormalities in the formation of hemoglobin, leading to pain crisis from recurrent vascular occlusion by sickled hemoglobin. Impaired flow in the microvasculature can lead to ischemia, tissue infarction and ulceration. Abdominal pain, a common complaint in sickle cell disease, can be due to an uncommon etiology, ischemic duodenal ulceration. This is due to primary mucosal infarction caused by sickling, leading to poor healing of infarcted areas. Prompt endoscopic and/or urgent surgical intervention should be considered, particularly if anticoagulation is an issue, as proton pump inhibitor use is ineffective in healing this type of ulcer.

Key words: sickle cell anemia ■ intestines ■ ulcers

© 2008. From the Division of Gastroenterology (Julka, fellow; Aduli, assistant professor of medicine; Olden, Jerome S. Levy Professor of Medicine, division director), Division of Pathology (Lamps, professor and vice chair of diagnostic labs), University of Arkansas for Medical Sciences, Fayette, AR. Send correspondence and reprint requests for *J Natl Med Assoc*. 2008;100:339–341 to: Dr. Kevin W. Olden; phone: (501) 686-5126; fax: (501) 686-6248; e-mail: kwolden@uams.edu

INTRODUCTION

Sickle cell disease (SCD) is an autosomal recessive genetic disorder caused by a mutation in the hemoglobin-beta gene (located on the short arm of chromosome 11), which creates abnormalities in the formation of the structure of hemoglobin. It is most common in people of African descent, resulting in chronic hemolytic anemia. It often presents with sickle cell crisis (SCC), due to recurrent vascular occlusion by sickled hemoglobin molecules. These occlusions can lead to impaired flow in microvasculature, causing ischemia and tissue infarction.¹ We report the case of a 35-year-old African-American female with duodenal ulceration secondary to SCD. This case emphasizes that ischemic duodenal ulceration as part of a SSC is a potential cause of abdominal pain and morbidity in patients with SCD and must be investigated early in the course of patient care. This entity does not respond to usual treatment measures for peptic ulcer disease, such

as proton pump inhibition, due to the underlying pathogenic mechanism in SCC. Early endoscopic or surgical intervention should be considered for this condition.

CASE REPORT

A 35-year-old African-American woman with SCD presented to the hospital with a SCC involving her lower extremities (typical symptoms for her) and abdominal pain (an atypical symptom for her). The patient was started on intravenous pain medications, intravenous fluids, oxygen therapy and deep venous thrombosis (DVT) prophylaxis. Her leg pains improved, while her abdominal pain continued unchanged. The patient began to have nausea and vomiting with several episodes of hematemesis and a drop in her hemoglobin. She was started on a proton pump inhibitor and received two units of red blood cells. DVT prophylaxis was stopped, despite the patient's risk factors, including cigarette smoking, oral contraceptive use and being bedridden. An esophagogastroduodenoscopy was performed, revealing duodenal edema, severe hemorrhagic duodenitis, and a 1-cm ulcer in the bulb. The ulcer had a small adherent clot but no active bleeding. Biopsies of the ulcer revealed patchy crypt withering and lamina propria fibrosis. The mucosal capillaries were congested with sickled red blood cells (Figure 1). Biopsies in the antrum were negative for *Helicobacter pylori*. Overall, the changes were consistent with ischemic ulceration. Proton pump inhibitor therapy was continued. The patient continued to require high doses of narcotics for pain.

On hospital day 4, she developed shortness of breath. Her oxygen saturation decreased from 97% to 89%. Computed tomography of the chest was consistent with a diagnosis of bilateral pulmonary emboli. The patient developed pulmonary edema and supraventricular tachycardia. Enoxaparin and warfarin were restarted. Despite attempted anticoagulation and medical management, the patient's condition worsened, and she died on day 5 of admission due to cardiac arrest.

DISCUSSION

In SCD, abdominal pain is common and can be generalized or localized to the right upper quadrant of the

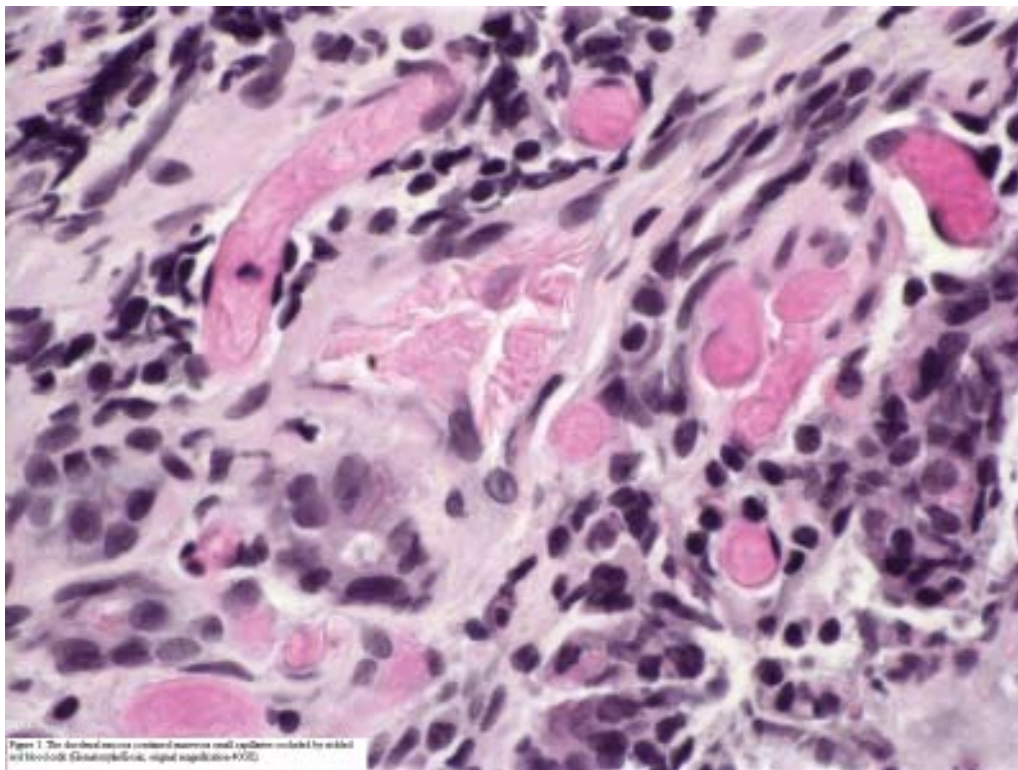
abdomen. Possible etiologies for abdominal pain in SCC include splenic sequestration, acute chest syndrome, ischemic colitis, hepatobiliary pathology, acute pancreatitis or appendicitis.^{1,2} Another consideration with symptoms of prominent epigastric pain, prandial or postprandial pain, or pain relief with antacids is SCD-induced ischemic ulceration of the duodenal mucosa. In 1973, Serjeant et al. reported a study of 353 SCD patients from Jamaica, looking at the occurrence of duodenal ulceration.³ Twenty-seven of 353 patients were noted to have duodenal ulceration. None of the patients with duodenal ulceration were age <14; at least one-third of the patients had onset of their ulcer in the second decade of life.³

The use of nonsteroidal anti-inflammatory drugs, decreased mucosal resistance and *H. pylori* infection are the three major reasons for development of duodenal ulceration in the general population.² In 1989, a study by Lee et al. looked at peak acid output during augmented histamine tests, which is usually elevated in normal patients with duodenal ulceration.⁴ When comparing SCD patients with duodenal ulceration to controls of SCD patients without ulceration, Lee et al. found there was no difference in peak acid output between the two groups. Additionally, the peak acid output was significantly ($p < 0.05$) lower in SCD patients with duodenal ulceration compared to controls of normal patients with duodenal ulceration.⁴ These findings supported the

hypothesis that duodenal ulceration in SCD patients is not caused by increased acid production. Furthermore, Wosornu et al. in 1971 investigated 115 patients from Ghana with duodenal ulceration, including 45 with concomitant SCD, in regards to their gastric acid response to the augmented histamine test.⁵ Their results showed that patients without SCD but with duodenal ulceration secreted significantly ($p < 0.05$) more acid than those with SCD. In fact, the gastric acid responses in SCD patients were found to be normal.⁵ These studies indicate that the major pathology behind duodenal ulceration in SCD patients without *H. pylori* infection is ischemia.

Ischemia in SCD patients is likely related to primary mucosal lesions due to infarction from the sickling phenomenon. At low oxygen tension, hemoglobin S tends to polymerize, causing a distorted erythrocyte with decreased deformability leading to vascular occlusion and injury.⁶ These arteriolar occlusions will lead to decreased healing of the infarcted areas.² The 1989 study by Lee et al. also looked at hematological indices between duodenal ulcer patients with SCD and those SCD patients without ulceration. The study found that total and fetal hemoglobin levels were significantly ($p < 0.05$) lower in the SCD duodenal ulceration group. This would indicate further evidence of the likely primary role of infarction causing disruption of mucosal integrity, putting a patient at risk for duodenal ulceration.⁴

Figure 1. The duodenal mucosa contained numerous small capillaries occluded by sickled red blood cells (hematoxylin & eosin, original magnification 400X)



Ischemic ulcers can be fatal in a SCD patient if not properly diagnosed and appropriately treated. A study by Thomas et al. looked at the cause of death in 276 patients with SCD; of the 276 deaths, three were attributed to gastrointestinal hemorrhage and perforation.⁷ Narcotic administration to SCD patients may hide the continuance of an ischemic ulcer, as it did in our patient. Other standard treatment measures such as oxygen administration and intravenous fluids will not provide resolution of the patient's symptoms either, and other etiologies for abdominal pain must be entertained. It was only at endoscopy that our patient's ulcer was detected. In our patient, there was no history of nonsteroidal anti-inflammatory use or *H. pylori* infection, and the biopsies of the ulcer revealed the histological findings implicating SCD as the cause of the ischemic ulceration.

Our case illustrates an important point that ischemic ulcers of the upper gastrointestinal tract due to SCD must be included in the differential diagnosis of abdominal pain in SCD patients. The studies quoted above show significant findings re: lower peak acid output in SCD patients with duodenal ulcer compared to controls with duodenal ulcer, and higher amounts of acid secreted by controls with duodenal ulcer compared to SCD patients with duodenal ulcer. Also, there was no difference in peak acid output between SCD patients with and those without duodenal ulcers. The gastric acid response was found to be normal in SCD patients with or without duodenal ulcer. Therefore, acid secretion is at a physiologic level in SCD patients with duodenal ulcer.

There are three defense mechanisms employed by the gastroduodenal mucosa against acid: pre-epithelial, epithelial and postepithelial.⁸ Without abnormally heightened acid secretion, the first two mechanisms are not the primary derangement. The third mechanism, post-epithelial, relates to mucosal blood flow, which happens to be markedly abnormal in SCD. This prevents maintenance of epithelial cell integrity and weakens protective epithelial cell functions (mucus production, bicarbonate secretion). The blood flow also removes any acid diffusion through the impaired mucosa.⁸ Therefore, a primary disruption of the postepithelial defense leads to potential secondary disturbances of the pre-epithelial and epi-

thelial defenses. This suggests that proton pump inhibitor therapy will not treat the penultimate cause and will thereby be an unsuccessful treatment long term.

CONCLUSION

Ulceration secondary to SSC-induced mucosal ischemia must be thought of in any SCD patient with atypical or persistent abdominal pain during SSC. Prompt endoscopic evaluation and/or urgent surgical intervention needs to be considered as the basic approach for this entity. In our case, the ischemic duodenal ulcer caused a complication not necessarily due to blood loss itself, but by creating an inability or fear to start anticoagulation in a patient at high risk for pulmonary embolism. In our case, if definitive treatment of the ulcer by endoscopy or surgery was done, anticoagulation could have been started with much lower risk of gastrointestinal hemorrhage, potentially preventing the fatal pulmonary embolism in this patient. It therefore follows that the use of anticoagulants needs to be balanced between the risks of pulmonary embolism and gastrointestinal bleeding.

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