Acute appendicitis in patients with sickle cell disease

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ABSTRACT

Objective: Patients with sickle cell disease (SCD) often present with abdominal pain, usually attributed to vaso-occlusive crisis, but not rarely, it may be caused by other surgical conditions. Acute appendicitis although common in patients with SCD, it is rare and has a rapid course with a high incidence of perforation.

Methods: Over a period of 7 years from 1995 to 2001, only 8 patients with SCD out of 1563 (0.5%) patients with acute appendicitis underwent operation at Qatif Central Hospital, Qatif, Kingdom of Saudi Arabia. Their histological slides were reviewed and the findings were compared to those with sickle cell trait (9 patients) and control group (28 patients).

Results: All patients with SCD and in spite of a short duration of symptoms had a moderate to severe inflammation and the vessels were packed with sickle red blood cells (RBCs) except one who had an intact mucosa, extensive transmural hemorrhage and congested blood vessels with sickled RBCs without inflammatory cell infiltrate. The mucosa was intact in only one patient with SCD when compared to 5 (55.6%) in those with sickle cell trait and 6 (21.4%) in the control group and in the majority (87.5%) of those with SCD there were moderate to severe mucosal ulcerations when compared to those with sickle cell trait (44.4%) or controls (64.3%).

Conclusion: In patients with SCD, acute appendicitis is rare, and these appendicular changes were a sequelae of blockage of appendiceal vessels by sickled RBCs leading to congestion, edema, and ischemia with subsequent mucosal ulceration and marked inflammatory cell infiltrate.

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Patients with sickle cell disease (SCD), often present with abdominal pain, usually attributable to SCD vaso-occlusive crisis, but not rarely, it may be caused by other surgical conditions such as cholelithiasis, peptic ulcer disease, and acute appendicitis.[1-3] Acute appendicitis remains the most common cause of acute abdomen requiring emergency abdominal operation. This however may not be the case in patients with SCD, where acute appendicitis is reported not only to be rare, but also has a rapid course with a high incidence of perforation.[4,5] This is a pathological study comparing acute appendicitis in normal patients to those with a sickle cell trait and SCD.

Methods. Over a 7 years period from 1995 to 2001, 1563 patients had appendicectomy at Qatif Central Hospital, Qatif, Kingdom of Saudi Arabia (KSA). Eight of them (0.5%) had SCD. One pathologist reviewed their histological slides, and the findings were compared to those with a sickle cell trait (9 patients); and a control group (28 patients) of normal patients with acute appendicitis randomly selected. In all the 3 groups, the appendices were studied including length, diameter, lumen, and histological evaluation of mucosa, muscles, serosa, blood vessels and fat. The diagnosis of SCD was established by a positive sickling test and hemoglobin

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(Hb) electrophoresis (Helena Laboratories Super Z electrophoresis kit).

Results. ***Sickle cell disease patients.*** The average appendix length was 7.5cm (4-13 cm), and the average appendix width was 1.05 cm (0.5-2.5cm). The appendix lumen was full of pus in 3, hemorrhage in one, pus and hemorrhage in 2, and pus and fecal material in one. The mucosa was intact in one (**Figure 1**), moderately ulcerated in 3 and severely ulcerated in 4 (**Figure 2**). The muscles were congested in one, moderately inflamed in 2 and severely inflamed in 5 (**Figure 3**). There was no fat in one patient, moderately inflamed in one, severely inflamed in 5, and one patient had hemorrhage. In all of them the blood vessels were packed with sickled red blood cells (RBCs) (**Figure 4**). One of our patients, although clinically and intraoperatively labeled as acutely inflamed appendix, histologically the mucosa was intact and did not show any acute inflammatory cell infiltrate, but there was a marked of transmural hemorrhage and the blood vessels were packed with sickled RBCs (**Figure 5**). In all patients, the duration of symptoms ranged from 12-48 hours (mean 19.5 hours).

Sickle cell trait patients. The average appendix length was 7.4 cm (5-10 cm), and the average appendix width was 0.85cm (0.4-1.2 cm). The appendix lumen was full of hemorrhage in 4, pus in 4, and contained pus and hemorrhage in one. The mucosa was intact in 5, moderately ulcerated in 2, and severely ulcerated in 2. The muscles were normal in 3, mildly inflamed in 2, moderately inflamed in 2, and severely inflamed in 2. The serosa was normal in 2, mildly inflamed in 2, moderately inflamed in one, severely inflamed in 3 and congested in one. The fat showed hemorrhage and congestion in 4, mild inflammation in one and severe inflammation in 4. The blood vessels were normal in 2 and packed with sickled RBCs in 7.

Normal patients. The average appendix length was 7.7 cm (5-12 cm), and the average width was 1.1 (0.5-2 cm). The appendix lumen contained pus in 10, hemorrhage in 11, pus and hemorrhage in 6 and pus, hemorrhage and fecal material in one. The mucosa was intact in 6, mildly ulcerated in 4, moderately ulcerated in 6 and severely ulcerated in 12. The muscles were mildly inflamed in 6, moderately inflamed in 10 and severely inflamed in 12. The serosa was mildly inflamed in 6, moderately inflamed in 9, severely inflamed in 12 and showed congestion and hemorrhage in one. The fat was normal in 2, mildly inflamed in 8, moderately inflamed in 6, severely inflamed in 7 and 5 showed only hemorrhage and congestion. The blood vessels were normal in 7 and packed with normal RBCs in 21.

A comparative analysis of mucosal ulceration in the 3 groups is shown in **Table 1**, and a comparison according to the degree of inflammation is shown in **Table 2.**

Discussion. Patients with SCD often present with abdominal pain, which is frequently attributable to vaso-occlusive crisis. In a retrospective study involving 53 patients with SCD who had abdominal pain, vaso-occlusive crises were responsible for the pain in 57%, and based on this, conservative therapy was advocated in the large majority of patients with SCD who present with acute abdominal pain.[2] However, this does not exclude the possibility of other common surgical conditions; namely, acute cholecystitis and acute appendicitis, which may be difficult to differentiate clinically from a simple vaso-occlusive crisis.[1,2,6] Acute appendicitis in patients with SCD has been reported not only to be rare, but also different.[4,5] Antal et al[5] in a 17-year review of 200 patients with SCD found only 2 patients with pathologically proven acute appendicitis, an incidence of 5.7 cases per 10000 patient-years and among 3765 patients with SCD enrolled in the cooperative study of SCD and followed for a mean of 5.3 years, a maximum of 9 cases of acute appendicitis were identified, yielding an incidence rate of 4.5 cases per 10000 patient-years. Based on this, they advocated limiting surgical exploration to those with clear evidence of potential surgical pathology or progressive findings during a period of observation.

In the Eastern province of KSA, SCD is common, and in certain areas, approximately 20-25% of the population have sickle cell trait, and approximately 2% have SCD.[7-9] Our hospital is the main Central hospital in Qatif, an area of Saudi Arabia, well known to have a high prevalence of hemoglobinopathies, mainly SCD. In spite of this high prevalence of SCD, we encountered only 8 cases of acute appendicitis in patients with SCD among 1563 patients who had appendicectomy at our hospital, which comprised only 0.5% of total appendicectomies performed over a 7-year period. The reason for this low incidence of acute appendicitis in patients with SCD is not exactly known. The exact pathogenesis of acute appendicitis is not known, and inflammation is often said to be precipitated by obstruction, but in most acutely inflamed appendices, there was no evidence of luminal obstruction.[10] Approximately 15-25% of appendices removed from patients with suspected appendicitis appears normal on histologic examination.[11] This however may not be the case always as new distinct pathological entities have now emerged in those with clinically suspected acute appendicitis but normally looking appendix at the time of surgery. These include neurogenic appendicopathy, a disease caused by proliferation of nerve fibers and hyperplasia of endocrine cells in the submucosa of the appendix,[12] and pathological changes of the epithelium and lymphatic tissue of the appendix.[13] This may explain the dramatic symptomatic relief following appendicectomy in those with clinically diagnosed acute appendicitis but negative appendicectomy.

In patients with SCD, and due to its difficulties in distinguishing painful abdominal vaso-occlusive crisis, which is common from other surgical conditions; namely, acute appendicitis, it is expected to find a high rate of negative (normally looking appendix) appendicectomy. This was not the case in our hospital.

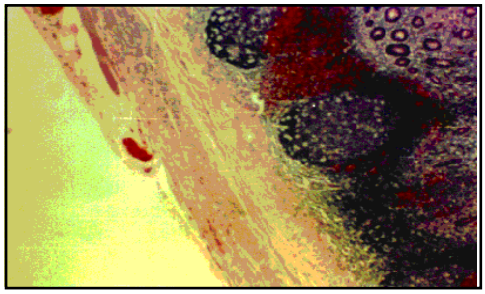

Figure 1 - Photomicrograph showing intact mucosa, rich lymphoid follicles with hemorrhage. Serosa demonstrates blood vessels packed with red blood cells. (Hematoxylin & Eosin x 10).

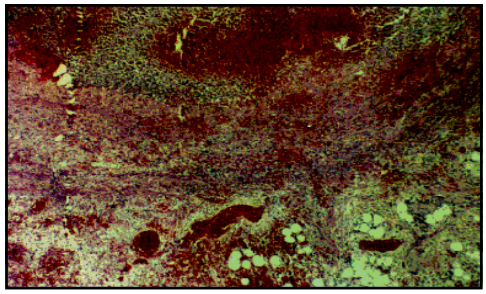

Figure 2 - Photomicrograph showing severe mucosal ulceration, congestion and acute inflammation involving the serosa as well. (Hematoxylin & Eosin x 10).

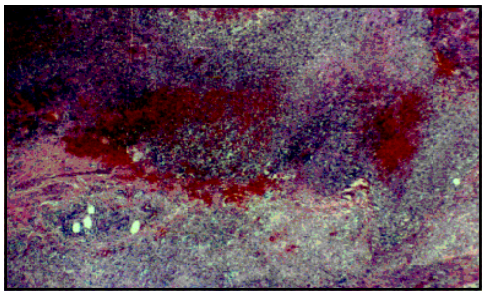

Figure 3 - Photomicrograph showing severe acute inflammatory cell infiltrate of the appendix wall with mucosal ulceration and hemorrhage. (Hematoxylin & Eosin x 10).

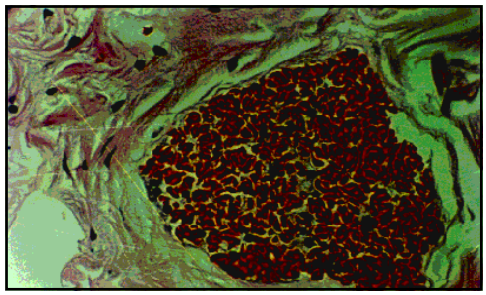

Figure 4 - Photomicrograph showing blood vessels packed with sickled red blood cells. (Hematoxylin & Eosin x 25).

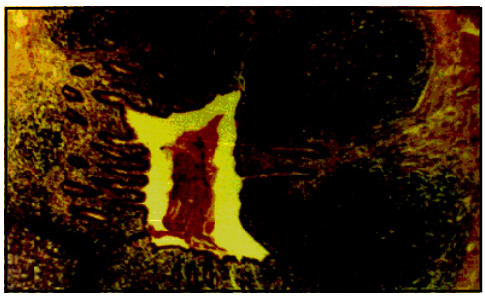

Figure 5 - Photomicrograph showing transmural hemorrhage of the appendix and intact mucosa. (Hematoxylin & Eosin x 10).

Table 1 - Comparison according to the degree of mucosal ulceration.

Patient control	Intact (%)	Mild ulceration (%)	Moderate ulceration (%)	Severe ulceration (%)
Sickle cell disease (n=8)	1 (12.5)	-	3 (37.5)	4 (50)
Sickle cell trait (n=9)	5 (55.6)	-	2 (22.2)	2 (22.2)
Normal patients (n=28)	6 (21.4)	4 (14.3)	6 (21.4)	12 (42.9)

Table 2 - Comparison according to the degree of inflammation.

Patient control	Intact (%)	Mild ulceration (%)	Moderate ulceration (%)	Severe ulceration (%)
Sickle cell disease (n=8)	1 (12.5)	-	2 (25)	5 (62.5)
Sickle cell trait (n=9)	3 (33.3)	2 (22.2)	2 (22.2)	2 (22.2)
Normal patients (n=28)	-	6 (21.4)	10 (35.7)	12 (42.9)

None of our patients with SCD had appendicectomy for a normal appendix. Most of them and in spite of a short duration of symptoms had moderate to severe inflammation of the appendix with a high incidence of perforation. Acute appendicitis in patients with SCD is not only rare but also tends to have a rapid course with a high incidence of perforation.[4,5] All our patients and in spite of a short duration of symptoms had moderate to severe inflammation except for one who did not show any acute inflammatory cell infiltrate. This patient had clinically acute appendicitis, and intraoperatively was found to have an enlarged, congested and acutely inflamed appendix. Histologically, there was no evidence of acute inflammatory cell infiltrate. The mucosa was intact, but there was extensive transmural hemorrhage, and the blood vessels were also congested and packed with sickled RBCs. We considered these changes were attributed to SCD, and have this progressed further, there will be evidence of mucosal ulceration and acute inflammatory cell infiltrate. This was evident in the remaining 7 patients with SCD where and in spite of a short duration of symptoms, there was a markedly severe inflammatory reaction when compared to those with sickle cell trait and controls, and one of them showed mild inflammation only. The mucosa was intact in only one of those with SCD when compared to 5 (55.6%) in those with sickle cell trait and 6 (21.4%) in the control group. In most of those with SCD (87.5%), there was moderate to severe mucosal ulceration when compared to those with sickle cell trait (44.4%) or controls (64.3%). The changes in blood vessels in patients with SCD are most probably primary and not a sequelae of surgically induced hypoxia as was seen in those with sickle cell trait. This is supported by the marked pathological changes and high incidence of perforation in spite of short duration of symptoms, as complicated appendicitis is primarily associated with a longer delay before first medical consultation.

In conclusion, acute appendicitis in patients with SCD is rare and we think it is a sequelae of blockage of appendiceal vessels by sickled RBCs leading to congestion, edema, ischemia with mucosal ulceration and marked inflammatory cell infiltrate. Our patients are however, small, but these findings emphasize the need for further studies in this regard.

References

1. Ariyan S, Shenel FS, Pickett LK. Cholecystitis and cholelithiasis masking an abdominal crisis in sickle cell disease. ***Pediatrics*** 1976; 58: 252-258.
2. Baumgartner F, Klein S. The presentation and management of the acute abdomen in sickle cell anemia. ***Am Surg*** 1989; 55: 660-664.
3. Bandio WA. Clinical features of abdominal painful crisis in sickle cell anemia. ***J Pediatr Surg*** 1990; 25: 301-302.
4. Al-Salem AH, Qureshi ZS, Qaisarudin S, Varma KK. Is acute appendicitis different in patients with sickle cell disease? ***Pediatr Surg Int*** 1998; 13: 265-267.
5. Antal P, Gauderer M, Koshy M, Berman B. Is the incidence of appendicitis reduced in patients with sickle cell disease? ***Pediatrics*** 1998; 101: E7.
6. Kudsk KA, Tranbaugh RF, Sheldon GF. Acute surgical illness in patients with sickle cell anemia. ***Am J Surg*** 1981; 142: 113-117.
7. Al-Awamy BH. Sickle cell anemia, its clinical manifestations and their management. ***Saudi Med J*** 1987; 8: 533-562.
8. Al-Awamy BH, Niazi GA, El-Mouzan MH, Altorki MT, Naeem MA. Newborn screening for sickle cell hemoglobinopathies and other inherited erythrocyte disorders in the Eastern Province of Saudi Arabia. ***Saudi Med J*** 1987; 7: 502-509.
9. Perrine RP, Pembrey ME, John P, Perrine S, Shoup F. Natural history of sickle cell anemia in Saudi Arabia. ***Ann Intern Med*** 1987; 88: 1-6.
10. Chang AR. An analysis of the pathology of 3003 appendices. ***Aust N Z J Surg*** 1981; 51: 169-178.
11. Dymock RB. Pathological changes in the appendix: a review of 1000 cases. ***Pathology*** 1977; 9: 331-339.
12. DiSebastiano P, Fink T, DiMola FF, Weihe E, Innocenti P, Friess H et al. Neuroimmune appendicitis. ***Lancet*** 1999; 354: 461-466.
13. Ring-Mrozik E, Hecker WC, Wiebecke B, Hansmann A, Trammer A. New morphological findings in so-called negative appendicectomies. ***Eur J Pediatr Surg*** 1993; 3: 79-82.