Splenic Syndrome due to Sickle Cell Trait amongst Indian Soldiers Serving in Kashmir

Col MM Arora*, Lt Col JK Bhatia[†], Lt Col V Khanna[‡], Wg Cdr P Jaiswal^{††}, Col VD Charan⁺⁺

Abstract

Background: Heterozygous transmission of gene for Haemoglobin S leads to sickle cell trait. Mostly the trait remains silent with no additional morbidity or mortality. When these persons migrate to higher altitudes, in times of high oxygen demand, some of them develop splenic infarction. This is a rare phenomenon and only 47 such cases had been reported till 2005.

Methods: This study was conducted at an Indian military hospital serving the troops deployed in Kashmir valley at altitudes ranging from 5500 ft to 13000 ft. When two consecutive splenectomies for splenic abscesses, turned out to be sickling induced infarction histopathologically, we reviewed splenectomy specimens received in last six years for evidence of sickling.

Result: Out of 33 splenectomies performed during the period of study, 22 were due to trauma (gun shot injury 11; splinter injury one and blunt injury 10). Of the rest eleven, who presented without any history of trauma, seven had evidence of vascular occlusion with aggregates of sickled red blood cells. In none, Gram stain or Periodic Acid Schiff stain revealed any bacterial or fungal colonies. One patient of splenic syndrome was found to have unrecognised sickle cell trait and he was managed conservatively.

Conclusion : Sickle cell trait should be excluded before considering splenectomy in ethnically vulnerable patients presenting with splenic syndrome. An uncomplicated splenic infarction can be managed conservatively.

MJAFI 2008; 64 : 123-126

Key Words : Sickle cell trait; Splenic infarction; Splenic syndrome

Introduction

Molecular biology was born when Ingram demonstrated that haemoglobin in sickled red corpuscles differs from normal in amino acid sequence at sixth position in beta chain where glutamate is replaced by valate [1]. In most of the individuals the trait remains silent with no additional morbidity or mortality. However when these bearers of the trait leave their native place and migrate to higher altitudes, in times of high oxygen demand they become vulnerable to a plethora of complications one of them being splenic infarction which more often than not is misdiagnosed [2]. We came across a series of such patients. Internet search and review of literature revealed that only 47 cases have been reported till 2005 [3] and our experience of eight patients is higher than highest six reported till date. Sickle cell trait being a global phenomenon and being equally prevalent in Central India [1,4] the same is being reported.

Methods

This study was conducted at an Indian military hospital located at an altitude of 5500 feet and serving as a Zonal hospital for the troops deployed in mountainous terrain of

Kashmir valley at altitudes ranging from 5500 ft to 13000 ft. After receiving two consecutive splenectomy specimen (Table 1; Case No 4 & 5), in whom the diagnosis was revised from splenic abscess to splenic infarction with sickle cell trait after finding evidence of infarction and vaso-occlusion by aggregated sickled red blood cells (RBCs), without evidence of infection. Thereafter we reviewed all splenectomy specimens received in the hospital laboratory in last six years for evidence of sickling and infection. Hospital records for three found positive for sickling were reviewed and their diagnosis was revised (Table 1; Case No 1, 2 & 3). The awareness lead to better index of suspicion and thereafter preoperative diagnosis of unrecognised sickle cell trait complicating as splenic syndrome was made in three patients (Table 1; Case No 6, 7 & 8) and one of them managed conservatively.

Results

A total of 33 splenectomies were performed during the period of study, 22 of them due to trauma (Gun shot injury 11; Splinter injury 01; Blunt injury 10). Out of the 11 who presented without any history of trauma one each was diagnosed as Hodgkin's disease, spontaneous rupture of malarial spleen, splenic sequestration syndrome in sickle cell disease and spontaneous rupture cause unknown. Rest seven had evidence of vascular occlusion with aggregates of sickled

*Professor & Head (Dept of Biochemistry); [†]Reader (Dept of Radiodiagnosis) Armed Forces Medical College, Pune. [‡]Graded Specialist (Pathology), Military Hospital, Mathura (UP). ^{††}Graded Specialist (Surgery), Command Hospital (Southern Command), Pune. ⁺⁺ Classified Specialist (Medicine & Clinical Haematologist), Command Hospital (Northern Command), C/o 56 APO.

Table 1**Patients' profile**

District(State)	Clinical presentation	Investigations	Imaging diagnosis	Splenic pathology
1. Nagpur (Maharashtra)	36 y, Male, Pain Lt upper abdomen Splenic infarction, Splenectomy on 10 Aug 99	Hb 11.6g/dl; TLC 10,600/cmm; DLC P63L32M1E4; Sickling test, Smear, and HB Electrophoresis not done	Splenic infarction	Weight 190g, Size 9x5x5cm, Old infarction with vaso-occlusion by aggregates of sickled RBCs. No bacterial/fungal colonies
2. Srikakulam (Andhra Pradesh)	30 y, Male, Pain Lt upper abdomen at High Altitude; Splenic infarction, Splenectomy on 25 Jul 03	Hb 12.8g/dl; TLC 11,400/cmm; DLC P73L21M1E5; Sickling test, Smear, and HB Electrophoresis not done	Splenic infarction	Wt 390g, Size 10x9x6cm, Recent haemorrhagic infarction with vaso-occlusion by sickled RBCs. No bacterial/fungal colonies
3. Bargar (West Bengal)	23 y, Male, Pain Lt upper abdomen, fever, Splenic Abscess; Splenectomy on 14 Nov 03	Hb 14.8g/dl; TLC 7,300/cmm; DLC P61L34M2E3; Sickling test, Smear, and HB Electrophoresis not done	Splenic Abscess	Wt 150g, Size 6.5x5x5cm, Hematoma on cut surface 4x3.5cm Old infarction with fibrosis & vasoocclusion by sickled RBCs. No bacterial /fungal colonies
4. Visakapatnam (Andhra Pradesh)	44 y, Male, Pain Lt upper abdomen, fever, Splenic abscess, Splenectomy on 09 Jul 05	Hb 12.4g/dl; TLC 9,300/cmm; DLC P58L36M2E4; Smear-No abnormality Sickling test Positive HB Electrophoresis A2- 1.9%; S- 41.6%; F- 1.0%; A- 55.5%	Splenic abscess/ hematoma	Wt 160g, Size 8x6x3cm, Hematoma, recent haemorrhagic infarction vasoocclusion by sickled RBCs. No bacterial/fungal colonies
5. Yawatmal (Maharashtra)	27 y, Male, Pain Lt upper abdomen, fever, Splenic abscess Splenectomy on 15 Sep 05	Hb 11.2g/dl; TLC 8,900/cmm; DLC P58L36M2E4; Smear No abnormality Sickling test Positive HB Electrophoresis A2- 3.2%; S- 44.1%; F- 0.3%; A- 52.4%	Splenic abscess with splenomegaly	Wt 250g, Size 9x8.5x2.3cm and 2.5x2x1cm, recent haemorrhagic & old fibrotic infarction, vasoocclusion by sickled RBCs. No bacterial/fungal colonies
6. Srikakulam (Andhra Pradesh)	23 y, Male, Pain Lt upper abdomen, low grade fever, Tender Splenomegaly, Icterus, Pleural effusion, Splenic hematoma / abscess, Splenectomy on 11 Jul 06	Hb 13.3g/dl; TLC 9,700/cmm; DLC P69L26M2E3; Smear No abnormality Sickling test Positive HB Electrophoresis A2- 1.2%; S- 39.4%; F- 0.5%; A- 58.9%	Splenic pseudocyst	Wt 170g (without hematoma), Size 14x6x1cm and 9x6x3cm Subcapsular & parenchymal hematoma, haemorrhagic infarction vaso-occlusion by sickled RBCs, No bacterial/fungal colonies
7. Akola (Maharashtra)	33 y, Male, Pain Lt Abdomen at high altitude, no fever, Sub capsular hematoma, Managed conservatively; 29 Jun 05	Hb 11.1g/dl; TLC 6,800/cmm; DLC P74L18M2E6; Smear No abnormality Sickling test Positive HB Electrophoresis A2- 2.7%; S- 39.5%; F- 0.3%; A- 57.5%	Sub capsular hematoma	NA
8. Katni (Madhya Pradesh)	42 y, Male, Pain Lt Abdomen, fever, Splenic abscess with pleural effusion, Splenectomy on 08 Aug 06	Hb 11.4g/dl; TLC 10,400/cmm; DLC P73L17M2E8; Smear No abnormality Sickling test Positive HB Electrophoresis A2- 2.3%; S- 40.8%; F- 0.9%; A- 56%	Sub capsular hematoma	Wt 475g, Size 13x10x5 hematoma, Recent haemorrhagic infarction vaso-occlusion by sickled RBCs, No bacterial/fungal colonies

RBCs and haemorrhagic infarction. In none of them Gram stain or Periodic acid Schiff stain revealed any bacterial or fungal colonies. These were diagnosed as cases of sickle cell trait. One additional patient of splenic syndrome was diagnosed as sickle cell trait but no splenectomy was performed; he remains asymptomatic at low altitude for last 15 months. These eight patients harbouring sickle cell trait were male and not native to Kashmir. All belonged to defined geographical areas for sickling trait, however in none of them

trait was recognised before they suffered splenic syndrome in this zone. In last five patients of the series, haemoglobin electrophoresis revealed presence of Haemoglobin S less than haemoglobin A. In first three, the diagnosis of trait was only histopathological.

Discussion

Sickle cell trait is a global phenomenon with prevalence as high as 45% in some African populations

[5]. Central India and Eastern province of Saudi Arabia share a common sickle cell mutation which is different from those prevalent in Africa [5]. In a mass survey in the school children of Bardoli in India, 24 out of 130 (18%) were found positive for sickling test. In the same zone, prevalence amongst hospital admissions was 1.74%, confirming largely asymptomatic natural history of sickling syndrome [4]. Growth and development, pregnancy outcome, infection risk, overall mortality and life expectancy is same as that of general population [5]. Altitude hypoxia increases the extent of sickling observed with sickle cell trait from 2% at 4,050 ft. to 8.5% at 13,123 ft, however no haemolysis was observed in uncomplicated sickle cell trait on hypoxic exposures in hypobaric chamber simulating an altitude of 10,000 to 25,000 ft [6]. Splenic syndrome in sickle cell trait at high altitude is rare. The published literature was reviewed by Sheikha [3] in 2005 and is summarised in Table 2. Only 47 patients had been reported till 2005, of which one was Indian. It is mostly limited to visitors and is uncommon in native sicklers [7,8].

When persons with haemoglobin S are exposed

Table 2

Literature Review: Splenic syndrome in Sickle cell trait at high altitude

Year	Authors	Patients	Remarks
1985	Lane and Githens	29	Literature review with 6 new patients
1982	Callis et al	1	White boy
1984	Nussbaum and Rice	1	
1985	Goldberg et al	2	Father and son
1988	Shalev et al	1	White Jewish family
1989	Kopp et al	2	
1990	Sugarman et al	1	With pulmonary embolism
1999	Franklin et al	4	First female patient reported
1999	Tiernan et al	2	White men
2005	Sheikha	4	One each from Yemen, Saudi Arabia, Eritrea, and India
2006	Present study	8	First report from India

Modified from Sheikha [3]

acutely to high altitude hypoxia, the spleen is the organ most consistently injured by micro-vascular obstruction. Splenic infarction with sickle cell trait is usually self-

Fig. 1 : Vascular occlusion by aggregated sickled RBCs (H&E; 40x)

Fig. 3 : Margin of infarct (H&E; 40x)

Fig. 2 : Fibrosis in old infarct (H&E; 10x)

Fig. 4 : Positive sickling test (40x)

limited, resolving in 10 to 21 days and rarely requiring surgical intervention. Splenic infarction from sickle cell trait is more common with exercise at high altitude but has occurred with altitude exposure at rest or with exercise at sea level [9]. Acute splenic sequestration crisis, hypersplenism, and massive splenomegaly are surgical complications of sickle cell trait as well as disease [10]. Splenic abscess may complicate an infarct and may lead to septicemia and rupture, more so with sickle cell disease [11-15]. All the spleens removed from our patients revealed vascular occlusion by aggregates of sickled red blood cells with evidence of infarction. There was no gross scarring or fibrosis and no siderofibrotic bodies in any of the removed spleens. With these histopathological findings, one can conclude that these patients were harbouring sickle cell trait and none of them had sickle cell disease [9]. Though acute inflammatory infiltration was seen along the margins of infarct in some of our patients, none of them revealed microbiological evidence of infection.

Other complications associated with sickle cell trait include isosthenuria with loss of maximal renal concentrating ability; hematuria secondary to renal papillary necrosis; fatal exertional heat illness or sudden idiopathic death with exercise; Glaucoma or recurrent hyphema; bacteruria in women with or without pregnancy; renal medullary carcinoma in young people; and early onset of end stage renal disease from autosomal dominant polycystic kidney disease [9]. Isolated cases of hypertension, pulmonary embolism and haemolytic anaemia are also reported [16-18]. None of these were observed in our patients.

Various authors have studied the natural history of splenic infarction [19, 20]. They observed that splenic infarction in young is most often associated with a haematological disorder, while patients older than 41 years most often had an embolic event. An uncomplicated splenic infarction can be managed safely with medical treatment with resolution of symptoms in 7 to 14 days. Early surgical intervention (splenectomy) is necessary to lower the mortality rate in complications of the infarct.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Col MM Arora

Drafting & Manuscript Revision : Col MM Arora, Lt Col JK Bhatia

Statistical Analysis : Col MM Arora, Lt Col JK Bhatia, Lt Col V Khanna

Technical Support : Col MM Arora, Lt Col JK Bhatia, Lt Col V Khanna, Wg Cdr P Jaiswal, Col VD Charan

Study Supervision : Col MM Arora

References

1. Lukens JN. The abnormal hemoglobins: General principles. In: Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, editors. Wintrobe's clinical hematology, 10th edition. New York: Lippincott Williams & Wilkins 1999; 1329-45.
2. Franklin QJ, Compeggie M. Splenic syndrome in sickle cell trait: four case presentations and a review of the literature. *Mil Med* 1999;164:230-3.
3. Sheikh A. Splenic syndrome in patients at high altitude with unrecognized sickle cell trait: splenectomy is often unnecessary. *Can J Surg* 2005;48:377-81.
4. Iyer SR, Iyer RR, Oza GD, Rane RM, Khandwala RM, Desai PK, Desai SD. Sickle cell syndromes in and around Bardoli. *J Assoc Physicians India*. 1994; 42:885-7.
5. Wang WC, Lukens JN. Sickle cell anemia and other sickling syndromes. In: Lee GR, Foerster J, Lukens J, Paraskevas F, Greer JP, Rodgers GM, editors. Wintrobe's clinical hematology, 10th edition. New York: Lippincott Williams & Wilkins 1999; 1346-98.
6. Kark JA, Ward FT. Exercise and hemoglobin S. *Semin Hematol* 1994; 31:181-225.
7. Addae S, Adzaku F, Mohammed S, Annobil S. Sickle cell disease in permanent residents of mountain and low altitudes in Saudi Arabia. *Trop Geogr Med* 1990; 42:342-8.
8. Addae S, Adzaku F, Mohammed S, Annobil S. Survival of patients with sickle cell anemia living at high altitude [letter]. *South Med J* 1990;83: 487.
9. Kark J. Sickle cell trait. Howard University School of Medicine Centre for Sickle Cell Disease. 2121 Georgia Avenue, Washington, D.C. 20059. Article on internet.
10. al-Salem AH, Qaisaruddin S, Nasserallah Z, al Dabbous I, al Jam'a A. Splenectomy in patients with sickle-cell disease. *Am J Surg* 1996; 172:254-8.
11. Al-Salem AH, Qaisaruddin S, Al Jama A, Al-Kalaf J, El-Bashier AM. Splenic abscess and sickle cell disease. *Am J Hematol* 1998; 58:100-4.
12. Kapur A, Vasudeva R, Howden CW. Candida splenic abscess in the absence of obvious immunodeficiency. *Am J Gastroenterol* 1997; 92:509-12.
13. Hibler BA, Jochimsen PR. Splenic abscess in a patient with sickle trait. *Iowa Med* 1984; 74:429-31.
14. Gangahar DM, Delany HM. Intrasplenic abscess: two case reports and review of the literature. *Am Surg* 1981; 47:488-91.
15. Sarma PS. Klebsiella ozaenae splenic abscess following odontogenic infection in a girl with sickle cell disease. *Int J Infect Dis* 2006; Apr 28 (e-pub ahead of print).
16. Narasimhan C, George T, George JT, Pulimood BM. Hypertension in sickle cell disease. *J Assoc Physicians India* 1990; 38:435-6.
17. Sugarman J, Samuelson WM, Wilkinson RH Jr, Rosse WF. Pulmonary embolism and splenic infarction in a patient with sickle cell trait. *Am J Hematol* 1990; 33:279-81.
18. Nussbaum RL, Rice L. Morbidity of sickle cell trait at high altitude. *South Med J*. 1984; 77:1049-50.
19. Jaroch MT, Broughan TA, Hermann RE. The natural history of splenic infarction. *Surgery* 1986; 100:743-50.
20. Norens M, Phillips EH, Morgenstern L, Hiatt JR. The clinical spectrum of splenic infarction. *Am Surg* 1998; 64:182-8.