

Effect of Sickle Cell Disease on Cardiovascular System: A 4.5 Years Autopsy Study Conducted in a Tertiary Care Center of Central India

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Abstract

Background: In Central India, the sickle cell gene is distributed mainly in Madhya Pradesh, Chhattisgarh, Maharashtra, Orissa and Jharkhand and in Chhattisgarh prevalence is nearly 10%. It has variable clinical presentation and most patients remain asymptomatic for longer period. SCA is ignored by autopsy surgeon to be considered as cause of death despite of its high prevalence. While doing autopsy in cases of death with no apparent cause, autopsy surgeon must keep in mind the possibility of death due to vaso-occlusive crisis in SCD.

Materials & Methods: A cross sectional study of duration 4.5 years from January 2012 to May 2016 was conducted in Central India Tertiary care center. Total no. of whole heart autopsy specimen received within this duration was 427 out of which 12 cases were found to have sickle cell disease. Clinical and history detail were collected then thorough gross and microscopic examinations were performed.

Results: History of chest pain was present in 5/12 cases i.e 41.67%. On Histopathological examination, congestion of vessel with Sickle shaped Red Blood Cells was present in 100% cases, MI without atherosclerosis in 41.66%, MI with atherosclerosis in 33.33%, medial calcification in 16.66%, and myocardial hypertrophy in 8.33% of cases.

Conclusion: Sickle cell disease should be considered as one of the cause in case of unexplained and sudden death.

Key Words: Autopsy, Autosomal Recessive, Myocardial Infarction, Prevalence, Sickle Cell Disease.

INTRODUCTION

Sickle cell anemia (SCA) is the most common inherited hematological disorder worldwide.^{1,2} It is an autosomal recessive genetic disorder characterized by single point mutation at codon 6 of the globin gene on chromosome 11 resulting in replacement of valine for glutamic acid and thus formation of hemoglobin S.³ SCA was first described, in 1910, by Herrik.⁴ SCA is a common health problem in Chhattisgarh. Out of 26 million populations, about 27% of population is suffering with heterozygous hemoglobin

trait and 2.5% of population with fatal homozygous hemoglobin disease.⁵

Sickle cell disease (SCD) is highly prevalent among the triable of central, southern, and western India with frequency ranging from 10% to 23%.^{6,7} There is also increasing prevalence in nontribal communities in the above-mentioned region. Among all states, higher prevalence of this disease is found in Maharashtra, Madhya Pradesh, Chhattisgarh, and Tamil Nadu.⁸ The prevalence of SCA in Madhya Pradesh including Chhattisgarh is 1-40%.⁹ Central India region is a focus of sickle cell disorder.¹⁰ This disease has variable clinical presentation, and many of the Indian patients remain asymptomatic for a longer duration due to higher levels of HbF.

SCD produces considerable morbidity and mortality worldwide and also SCD presenting as death in clinically asymptomatic patients is not uncommon.⁸ However, only

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very few numbers of deaths were reported due to SCA because of ignorance of autopsy surgeon in considering this disease as one of the causes of unexpected or sudden death despite its high prevalence in central India.⁸

MATERIALS AND METHODS

A cross-sectional study of duration 4.5 years from January 2012 to May 2016 was conducted in Central India Tertiary care center, in the Department of Pathology, Pt. Jawaharlal Nehru Memorial Medical College, Raipur, Chhattisgarh, India. Most of the autopsy specimens were received from primary health-care centers in peripheral districts and some from the Department of Forensic Medicine. Gross examinations were performed in all cases, and relevant findings were noted. After gross inspection for obvious lesions or scar formation, sections were taken from cardiac walls and coronaries. Standard hematoxylin and eosin staining were performed, and sections were examined under light microscope carefully, and results were noted.

RESULTS

Total autopsy specimens received during the above-mentioned study period were 544 cases, out of which, specimens of whole heart numbered 427. Total autopsied cases having SCDs on histopathological examinations were 12 in number, i.e., 12/427 cases (2.81%).

Age range found was 16-84 years with mean age of 39 years. Maximum number of cases lied between 25 and 49 years, i.e., 5/12 (41.66%) (Table 1).

Sex-wise distribution of cases showed male predominance. Out of 12 cases, 10 were male (83.3%) and remaining 2 (16.7%) were female with male: female ratio 5:1 (Table 2).

Maximum number of cases were found in the year 2016 from January to May 2016 (5 months), i.e., about

6/12 (50%). Two cases were found in each year 2012, 2014, and 2015, respectively. None of the cases was found in the year 2013 (Table 3).

Out of total 12 cases, only 1 of them was a known case of SCA. Rest of other cases came to notice having sickling as incidental autopsy finding. Most common presenting symptom was found to be chest pain which was present in 5/12 (41.67%) cases. Two of the cases had a history of hypertension, one of them also had H/O diabetes mellitus (Table 4).

On microscopic examination, in all the cases, i.e., 12/12 cases showed congestion of small and medium-sized vessels with sickle-shaped red blood cells (RBCs) suggestive of microvascular occlusion (Figure 1a and b). In some of the cases, coronaries were also congested with sickle-shaped RBCs (Figure 2a and b). Second most common finding observed was features of myocardial infarction (MI) without evidence of atherosclerosis (Figure 3) which was seen in 5/12 cases (41.66%) followed by MIs with atherosclerotic changes in coronaries in 4/12 (33.33%) of cases. Medial calcification was present in two of the cases. One case of myocardial hypertrophy and one case with features of atherosclerosis alone were also found. 2 of the 12 case showed no

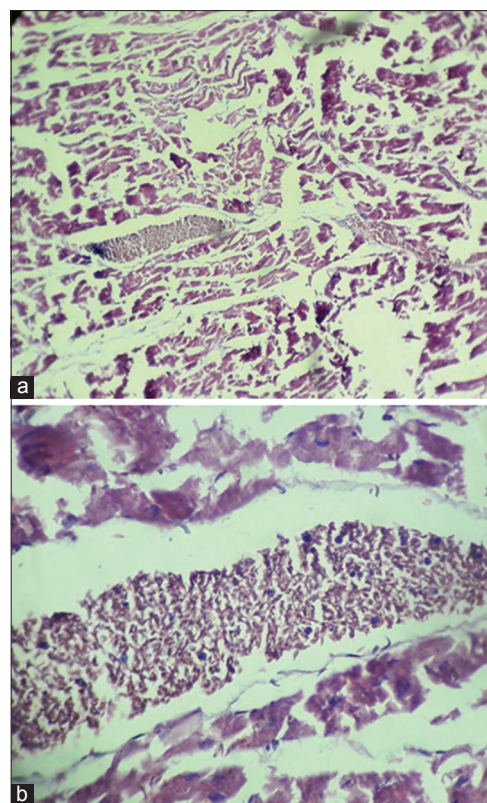


Figure 1: (a) Myocardial infarction and small vessels congested with sickle-shaped red blood cells (RBCs) (x4). (b) Small vessels congested with sickle-shaped RBCs (x10)

Table 1: Age-wise distribution of cases

Age groups (in years)	Number of cases	Percentage
<25	3	25
25-49	5	41.7
50-75	3	25
>75	1	8.3
Mean age=39 years	Total=12	100

Table 2: Sex-wise distribution of cases

Sex	Number of cases	Percentage
Male	10	83.3
Female	2	16.7
Male:female ratio=5:1	Total=12	100

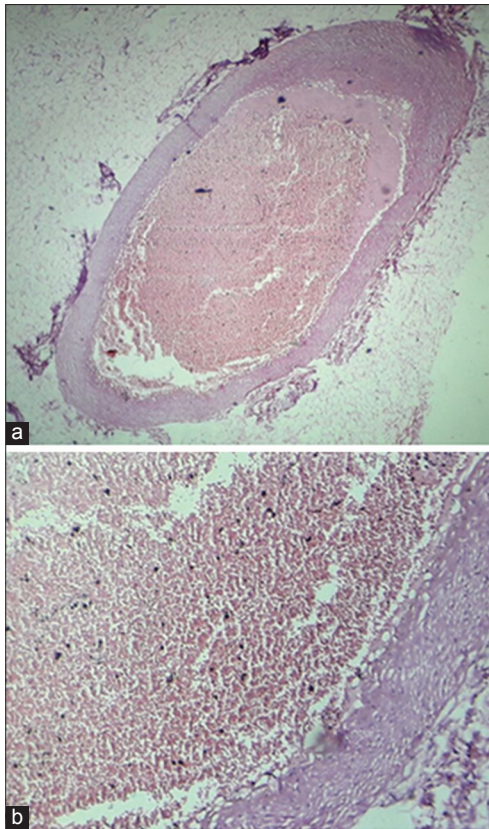


Figure 2: (a) Coronary artery filled with sickle-shaped red blood cells (RBCs) (x4). (b) Coronary artery filled with sickle-shaped RBCs (x10)

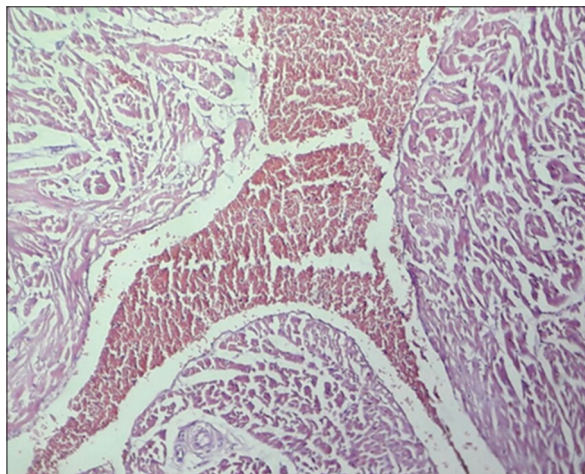


Figure 3: Myocardial infarction with medium-sized vessel congested with sickle-shaped red blood cells (x10)

specific pathology except for vessel congestion with sickle RBCs (Table 5).

DISCUSSION

SCA, the classical prototype of hereditary hemoglobinopathy, is an autosomal recessive disease manifesting in two forms

Table 3: Year-wise case distribution

Years of study	Number of cases studied (with SCD)	Total number of specimen of heart received (/year)
2012 (January-December)	02	101
2013 (January-December)	00	57
2014 (January-December)	02	110
2015 (January-December)	02	104
2016 (January-May)	06	55
Total number of years=4 years 5 months	Total=12	Total=427

SCD: Sickle cell disease

Table 4: Associated history

Associated history	Number of cases (%)
History of HTN	2 (16.67)
History of heart disease	1 (8.33)
History of poisoning	1 (8.33)
History of epilepsy	1 (8.33)
History of chronic alcoholism	1 (8.33)
History of chest pain	5 (41.67)
History of DM	1 (8.33)
Known case of SCD	1 (8.33)
Total	12 (100)

SCD: Sickle cell disease, DM: Diabetes mellitus, HTN: Hypertension

Table 5: Microscopic findings

Microscopic examination	Number of cases	Percentage of cases out of 12
MI with atherosclerosis	4	33.33
MI without atherosclerosis	5	41.66
Atherosclerosis only	1	8.33
Myocardial hypertrophy	1	8.33
Vessels other than coronaries congested with sickle-shaped red blood cells	12	100
Medial calcification	2	16.66
No specific pathology	2	16.66

MI: Myocardial infarction

heterozygous (sickle cell trait) or homozygous, SCD. The homozygous patients are symptomatic from an earlier age but heterozygous, i.e., trait patients are mostly asymptomatic and so ignorant about their disease and sickle cell crisis can occur in them with exposure to extreme hypoxic conditions.

Many studies have been done on various causes of deaths in SCA patients, but only a few studies focus on the effect of SCA on the cardiovascular system of the patient and causes of cardiac death in these patients.

Our study focused on the cardiovascular changes in these patients and tried to find out cardiac causes of death in them so that proper care or management could be provided to these vary group of patients to prevent morbidity and mortality among them. Our study found the mean age of death in patients with SCA was 39 years, ranging from 16

to 84 years. It is similar to the study by Fitzhugh *et al.* as they also reported the mean age of death in SCD patients being 39 years.¹¹ This is comparable with a study done by Darbari *et al.*,¹² who found mean age to be 36 years.

Out of 12/427, 10 were male and only 2 were females with male to female ratio 5:1. Our observation shows discordance with the study conducted by Mancini *et al.*,¹³ who found no significant differences in presentation among male and female. In their study, male: female ratio was 1:0.98 in patients with homozygous (SS) and 1:1.44 in the heterozygous state. Probable reason behind this could be due to less number of study population included in our study.

In our study, we found 12 patients having SCA among 427 patients undergoing autopsy, i.e., 2.8% cases. Out of these, only 1 patient was a known case of SCA and rest 11 cases were diagnosed incidentally after histopathological examination only.

In the present study, out of 12 patients, 5 of them had history of chest pain as presenting complaint, i.e., 41.66%. Martin *et al.* found chest pain in 6/72 patients, i.e., in 8.33% of cases,¹⁴ whereas Norris *et al.*¹⁵ found chest pain in 100% of cases out of total 19 cases he studied. This could be explained by various factors such as type of disease, i.e., trait or homozygous, associated health conditions and geographical differences.

On histopathological examination, 100% cases showed small and medium-sized vessel congestion with sickle-shaped RBCs. This could be cause of microvessel occlusion leading to cardiac changes and deaths in the study group.

5/12 cases (41.66%) had features of MI without any atherosclerotic changes followed by features of MI with atherosclerosis in 4/12 (33.33%) of cases. Mancini *et al.* found in their study that in 2.5% of homozygous (SS) cases the immediate cause of death was directly related to vaso-occlusion.¹³ Martin *et al.* in their study found MI in 7/72 (9.2%) patients with SCD.¹⁴

In two of the cases, no specific pathology was noted during autopsy examination apart from the congestion of vessels with sickled RBCs.

Varies cardiac changes could be due to abnormal blood rheology in this disease that may result in vaso-occlusion, myocardial ischemia, and infarction.¹⁶

MI in SCD has been previously described in various case reports and series. These all have suggested microvascular disease related to vaso-occlusion as the likely cause of myocardial ischemia and injury in these patients.^{14,15,17-28}

CONCLUSION

Clinical presentation of sickle cell patients in Central India is less severe as compared to African countries and is characterized by delayed presentation; patients are more asymptomatic, less incidence of vaso-occlusion, and low mortality due to which most of the patients remain undiagnosed. However, it is not uncommon in these patients presenting as death without any significant present or past history. Although many patients remain asymptomatic MI occurs in SCD and should be considered in differential diagnosis of patients with chest pain. Patients with SCD and chest pain who are suspected of having myocardial ischemia should be managed properly.

Furthermore, in case of unexplained death, during autopsy, it is important to keep in mind the possibility of SCD and so, proper histopathological examination along with hemoglobin electrophoresis, and molecular studies is needed to reach causes of death which would also be useful to their relatives to know the disease status in their family that could propel them to seek relevant management timely to prevent SCD related morbidity and mortality.

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