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Autopsy findings of sickle cell disorders in cases of unknown cause of death.

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ABSTRACT
Sudden and unexpected death due to sickle cell crises is the commonest presentation in Sickle cell syndromes. In cases of deaths with no apparent cause and physical over activity medical officer must keep in mind the possibility of death due to vasoocclusive crisis in sickle cell disease while doing autopsy. To improve morbidity and mortality in sickle disease more precise analysis of causes of death is needed. This study carried out in the department of pathology, at tertiary care hospital overs the period from January 2018 to December 2019. The study was retrospective. The cases having history of sudden death were brought dead to the casualty were included in the present study. After post mortem examination, the specimens preserved and sent for histopathological examination.
we found 17 cases of sickle cell anaemia autopsy cases.Out of 17 cases 13 were males and 4 were females. The youngest person was 13-year female and oldest was 48 years male. In clinical history 3 cases had complains of chest pain (17.64%), 7 others had complained of breathlessness (41.17%), 3 had history of unconsciousness (17.64%) and ,2 had history of fever (11.76%) ,1 case had a history of fall and injury (5.88%) ,1 had pain in abdomen &vomiting (5.88%) ,1 brought dead (5.88%).
All organs microscopic examination was carried out. Wide spread congested blood vessels along with clogged of sickled RBC seen in all organ like lungs, liver, spleen, kidneys, heart and brain. The purpose of the study was to analyse and minimize future unexpected death due to complication and crisis of sickle cell disease
Keyword: Vaso occlusive crisis, sickle cell disorder,autopsy.

I. INTRODUCTION

A group of genetic blood disorders that affect the haemoglobin molecular structure and in some cases the association with haemoglobin synthesis is aSickle cell disease (SCD). In sickle cell anaemia, the Glutamic acid is replaced by Valine at the 6th position on the beta chain results in the synthesis of the abnormal haemoglobin called haemoglobin S (HbS) (1).The main causes of sudden deathare theacute chest syndromes, cerebrovascular events, splenic dysfunction or sequestration and aplastic crises.From above if one of these more serious complications when arises due to sickling can lead to death(2).High index of mortality in a patient with double heterozygosis to HbS and HBc was seen due to sickling crisis followed by bone marrow necrosis and fat embolism (3).

More than the 50 % of the world's sickle cell anaemia cases are in India. Sickle haemoglobinwith variable frequency ranging from 10-23% is highly prevalent among the tribal of central, southern and western India (4, 5). In the non-tribal communities of these areas increased prevalence is noted. Death is not uncommon in clinically asymptomatic patients with sickle cell disease or sickle cell trait. But, unfortunately less numbers of deaths were reported due to sickle cellanaemia despite of high prevalence, because of ignorance of autopsy surgeon in considering this disease as a cause of death.

The clinical features show remarkable heterogeneity. Someare totally asymptomatic while others show repeated episodes of admissions. Severity depends on various factors like climate, socioeconomic conditions, haemoglobin level and percentage of Hb F severity of disease depends (6,7).

It is common that sickle cell disease presenting as death in clinically asymptomatic patients.But unfortunately, due to sickle cell anaemia because of ignorance of autopsy surgeon in considering this disease as a cause of death, less numbers of deaths are reporteddespite of its high

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prevalence. Considering this medical officer must keep in mind the possibility of death due to sickle cell anaemia, while doing autopsy in cases with no apparent cause and history of physical over activity.

To evaluate and create awareness among the physicians and relatives / public and to minimize future unexpected death from complications or crisis from SCD. This study shows the importance of considering sickle cell disease along with sickle cell crisis is the most common cause of sudden death in cases with no apparent causes.

II. MATERIAL METHODS

Our study is a retrospective carried out in the department of pathology, at tertiary care hospital and overs the period of January 2018 to December 2019 in which 17 cases studied. These were the cases brought dead to the casualty with a history of sudden death. After that autopsy carried out andwe receive organs for histopathological examination. We received gross specimen of lungs, heart, liver, kidney, spleen and brain for histopathological examination. From the clinical recordthe age, gender, ethnic groups, clinical presentations and from police panchnama were gathered.Study based on gross andthehistopathologicalfindings. A total of 5226 autopsies were done in this 2 year.

III. RESULT

Out of our 17 cases 13 were males and 4 were females. The youngest person was 13-year female and oldest was 48years' male.

Regarding haemoglobinopathy no much previous details available except in 5 cases. In clinical history 3 cases had complains of chest pain, 7 others had complained of breathlessness, 3 had history of unconsciousness and ,2 had history of fever ,1 case had a history of fall and injury ,1 had pain in abdomen & vomiting ,1 brought dead.

On gross in 2 cases splenomegaly was seen with congestion. Three case showed hepatomegaly and two case had cardiomegaly. Microscopicallyfive cases of lung showed changes of pulmonary enema, there were single case of CVC and pneumonia& pulmonaryhaemorrhages. In rest of the cases lungs showed congestion. In heart 2 cases showed myocardialfibre hypertrophy along with thrombus in coronary artery in one case. Also blood vessels clogged with sickle cell RBC'S (Fig 1). In 2 cases Liver shows Fatty changes ,along with sickled RBC's in blood vessels (Fig 2) & in other 2 showed CVC. Spleen showing gamma gandy bodies (Fig 3) in one case & fibrosis in other case. One of the case showed ischemic scars in kidney. One case showed viral meningitis. Thirteen cases including 2 postpartum females showed blood vessels of all organs clogged with sickle RBC's i.e. vasoocclusive crisis.

Table 1 showing detail of all cases gross and microscopic findings.

Case no	Age	Sex	Presentation	H/O hemoglobinopathy	Gross examination	Histopathological examination
1	13	F	Breathlessness	K/C/O Sickle cell anaemia	hepatomegaly Splenomegaly	Lung-blood vessels showsickled RBC'S, Liver sinusoids&spleen congested with sickled RBC'S Diagnosis-Sickle cell vaso-occlusive crisis
2	48	M	Fall and injury	Not known	Hepatomegaly	Lung-shows sickled RBCs, Intra-alveolar polymorphs- pneumonia Myocardium,liver, Spleen, kidney& Meninges blood vessels shows sickled RBCs.Liver also shows fatty change. Diagnosis-Sickle cell vaso-occlusive crisis with pneumonia.

3	23	F	Postpartu mbreathles sness	Not known	Lung,liver, heart &Meninges of brain show congestion. Spleen shows diffuse scarring .	Lung, myocardium, Liver, cerebrum&cerebellum blood vessels shows sickled RBCs. Spleen blood vessels congested with Sickled RBCs, fibrosis&Gamma Gandy bodies. placentalintervillous blood vessels show sickled RBCS. Fallopian Tubes&Ovaries show blood vessels withsickled RBC'S. Diagnosis-Sickle cell disease with vaso-occlusive crisis
4	28	M	H/O Sudden unconscio us ness	Not known	Lung, Heart, liver, spleen, kidney&me ninges of brain show congestion.	Lung ,Heart, Liver, spleen, kidney & meninges show blood vessels congested with sickled RBCs. Sickle cell vaso-occlusive crisis.
5	26	M	Breathless ness	Not known	Heart-left&right ventricular hypertrophy.	Heart-myocardium shows hypertrophy of myocytes & blood vessels congested with sickled RBCs. Lung,liver, Spleen,kidney & meninges show blood vessels congested with sickled RBCs&lymphoplasmacytic infiltrate. -Viral meningitis. Diagnosis-Sickle cell disease with cardiomegaly &viral meningitis.
6	20	F	Postpartu m breathlessn ess	K/C/O Sickle cell anaemia	Lung,heart, liver, spleen, kidney, meninges of brainshowco ngestion. Uterus - postpartum changes&co ngestion.	Lung,myocardium,liver, spleen, kidney, meninges of brain & uterine myometrium show blood vessels congested with sickled RBC'S. Diagnosis-Postpartum vaso-occlusive crisis.
7	45	M	Chest pain	Not known	Lung,Heart,l iver,spleen,k idney,menin ges of cerebrum &cerebellu mshow congestion.	Lung,myocardium, liver,spleen,kidney,cerebrum &cerebellum show blood vessels congested with sickled RBC'S. Diagnosis-Sickle cell disease, vaso-occlusive crisis

8	32	M	Chest pain	Not known	Lung,spleen, kidney,cerebrum & cerebellum, meninges show congestion.	Lung, spleen, kidney, meninges, cerebrum&cerebellum show blood vessels congested with sickled RBC'S. Diagnosis -Sickle cell disease with, vaso-occlusive crisis
9	29	F	fever	Not known	Hepatomegaly	Liver, spleen, kidney show blood vessels congested with sickled RBC s. Diagnosis-Sickle cell vaso-occlusive crisis
10	23	M	Chest pain&breathlessness	K/C/O Sickle cell anaemia	Heart show Left ventricular and Right ventricular mild hypertrophy	Lung , liver, spleen, kidney & meninges show blood vessels congested with sickled RBC s. Diagnosis: Sickle cell anaemia with vaso-occlusive crisis. Pulmonary haemorrhage.
11	20	M	Breathlessness	K/C/O Sickle cell anaemia	Lung,liver,brain shows congestion, spleen enlarged &enlargedkidney	Lung, myocardium, Liver, spleen, kidney, meninges, cerebrum&cerebellum show blood vessels congested with sickled RBCs. Diagnosis-Sickle cell vaso-occlusive crisis.
12	28	M	Unconsciousness	Not known	Spleen - shrunken(5x4x2cm)&capsule wrinkled.	Lung, myocardium, liver, spleen, kidney &meninges show blood vessels congested with sickled RBC s Spleenalso show fibrosis. Diagnosis-Sickle cell disease with vaso-occlusive crisis.
13	25	M	Brought dead	Not known	Heart-Left circumflex coronary - thrombus.kidney-corticomedullary differentiation not possible.	Lung,myocardium,Liver, spleen, kidney, meninges show blood vessels congested with sickled RBC s. Heart-left circumflex coronary show thrombus. Diagnosis-Sickle cell disease with vaso-occlusive crisis.
14	28	M	Unconsciousness	Not known	Lung show pulmonary oedema,kidney-corticomedullary differentiation partly	Lung-pulmonary oedema& myocardium,Liver, spleen, kidney, meninges show blood vessels congested with sickled RBC s. Diagnosis-Sickle cell vaso-occlusive crisis.

					possible	
15	35	M	Pain in abdomen& vomiting	Not known	Heart-Left anterior descending &right coronary -atherosclerosis with 50% narrowing of lumen,Liver -nutmeg appearance.	Lung,myocardium,Liver, spleen, kidney, meninges show blood vessels congested with sickled RBCs.Liver-chronic passive venous congestion &sickled RBCs in blood vessels. Left anterior descending&right coronary -atherosclerosis with 50% narrowing of lumen. Diagnosis-Sickle cell vaso-occlusive crisis with Chronic passive venous congestion of liver.
16	29	M	fever	K/C/O Sickle cell anaemia	Lung,Heart,liver,spleen,kidney,brain congestion.	Lung, myocardium, liver, spleen, kidney, meninges show blood vessels congested with sickled RBC s. Diagnosis Sickle cell disease, vaso-occlusive crisis
17	33	M	Breathlessness	Not known	Lung,Heart,liver,spleen,kidney,brain congestion.	Lung, myocardium, Liver, spleen, kidney, meninges show blood vessels congested with sickled RBCs.Liver shows fatty liver. Diagnosis-Sickle cell vaso-occlusive crisis

IV. DISCUSSION

In certain states like Madhya Pradesh, Orissa, Chhattisgarh, Jharkhand, Gujarat and Maharashtra it forms a major public health problem. (8)

Our patients were residents of Maharashtra. Only meagre histories were available for these patients. Most of the patients were virtually asymptomatic and were apparently never diagnosed as having SCD except five.

Precipitating factor for sickle cell crisisare infection, fever, anxiety, abrupt changes in the body temperature or hypertonic dyes. (9) But, in many cases no cause is obvious. (10) The factor precipitating sickle cell crisis in the first case was physical exertion while in the second case anxiety associated with the vehicular accident may be the triggering cause.

Acute chest syndromes, cerebrovascular events, splenic dysfunction or sequestration, and aplastic crises are the main causes of sudden death highlighted in several studies, although any presentation of sickling can lead to death if one of these more serious complications then arises. (11)

In the sickle cell disease include acute events as a painful vasooclusive crisis, infarctive stroke, acute chest syndrome, priapism, aplastic crises, splenic sequestration, haemolytic crises, & infections. (12) The trait patients are mostly asymptomatic but the patient is exposed to extreme hypoxic conditionsthen the sickle cell crisis. (12)

Grossly Cardiomegaly, hepatomegaly, evidence of infections and splenic findings suggestive of haemolytic anaemia are classical features of the disease. (13) Recurrent infarctions of the spleen due to occlusion of the splenic

vasculature by non-deforming sickled RBCs lead to auto splenectomy as observed in the first case.

In all cases histopathological sections of all organs show disseminated intravascular sickling suggestive of vasoocclusive crisis leading to multiorgan failure and death. The vaso-occlusive crisis which is manifests as multiorgan failure and acute chest syndrome is an important cause of death in sickle cell patients. (14)But, interpretation of histopathological findings should be cautious as death itself involves hypoxia, hypo- perfusion and other processes that could initiate sickling.

In the sickle cell anaemia hypoxia due to exertion induces a chain of events in a person, that causes sickling of RBC leading to vascular occlusion, potentiating hypoxia and culminating in sudden death. Also for sickle cell crisis infection, fever, anxiety, abrupt changes in the body temperature or hypertonic dyes are precipitating factor. (15) but, in many cases no cause is obvious. The factor precipitating sickle cell crisis was dehydration may be the triggering cause. Hence, the gross and histopathological findings must be considered sickle cell disease related deaths circumstances. (16)

Suddendeath was defined as an unexpected death occurring in relatively healthy patient who suddenly died either at home or in the hospital. Most of the cases presented with sudden death. Similarly, our patient presented with complains of fever, not feeling well, body ache (which may be joint pain) this preceding symptoms were not taken seriously. Extensive clinical studies by Kar BC et al too noted that attack of pain, fever and anaemia were the predominant presenting features. (17) According to Kate SL et al anaemia, intermittent Jaundice, severe Joint pain, recurrent infection where the common symptoms. Three Patients who were admitted in our hospital showed the same presenting symptoms.

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LEGENDS

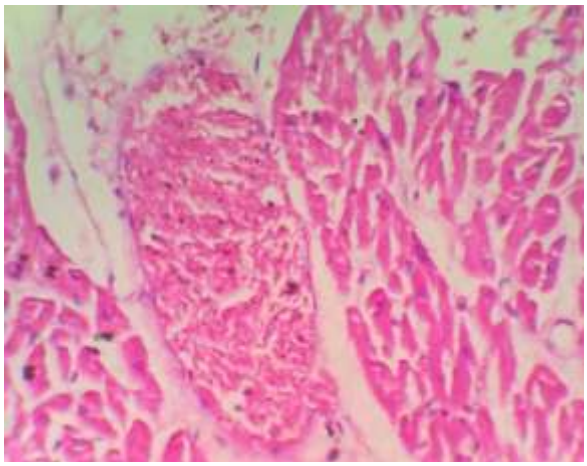

Figure 1: H and E 40X microphotograph of heart myocardial fibers and vessels containing sickled RBCs.

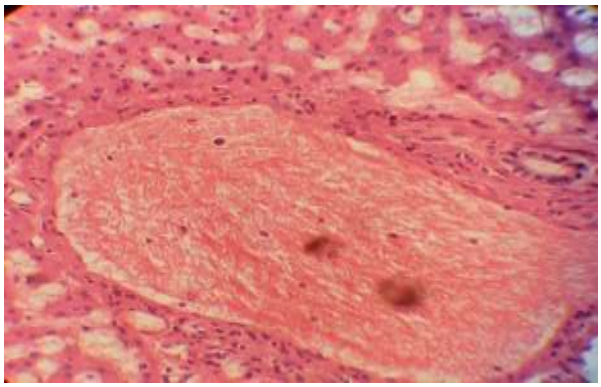

Figure 2: H and E 40X microphotograph of Liver showing sickled RBCs.

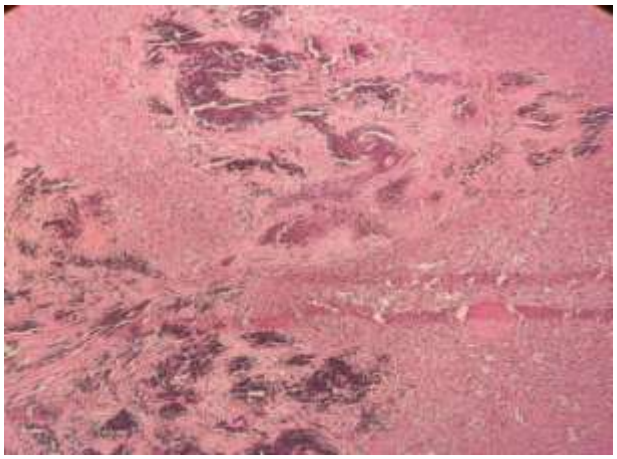

Figure 3: H and E 40X microphotograph of spleencongested showing Gamma gandy bodies.