CASE SERIES

Autopsy Diagnosis of Vaso-occlusive Crisis in Sickle cell Disease: A case Series Study from Northern Odisha

Das U,[1] Sahu P,[2] Bal AK,[3] Pati S.[4]

Associate Professor,[1-4]
1. Department of Pathology. JK MCH, Jajpur
2-3. Department of Pathology. PRM MCH, Baripada
4. Department of FMT, JK MCH, Jajpur

Abstract :

Sickle cell anemia is a qualitative genetic defect leading to abnormal HbS formation. During certain stressful conditions like infections, severe physical exertion, pregnancy, dehydration etc. complications may arise especially in subclinical sickle cell trait/ disease cases. Among all Sickle cell crises which include vaso-occlusive crisis, aplastic crisis, hemolytic crisis and sequestration crisis, vaso-occlusive crisis is the most commmon. Though many case reports were published on vaso-occlusive crisis in SCD, rarely we get series of cases. Here we present four cases of sickle cell crisis diagnosed during routine autopsy procedure. All the cases lost their life due to vaso-occlusive crisis involving different organs. First case was a sudden death of a pregnant lady presenting with respiratory infection and renal failure. During autopsy, all the organs were congested. Spleen was fibrotic and atrophied. Microscopic examination revealed sickled red cells with classical Gamna-Gandy body with thick fibrous bands. An HPLC report was of sickle cell disease (SCD). Case 2 was a 26 year female died suddenly in her post-partum period with features of cardiomyopathy. Spleen had Gamna-Gandy bodies. The coagulation factors and liver enzymes were deranged. HPLC study showed HbS & HbA2 only. Third case was an elderly male, a known case of sickle cell trait presented to emergency with left side hemiplegia. During the hospital stay of 7 days, he developed generalized anasarca and died because of multiorgan failure. Microsections from all viscera demonstrated sickled RBCs. Last case was a 26 year young lady who had sudden collapse while working in rice field. Histopathology examination of heart demonstrated features of acute myocardial infarction because of sickle cell crisis. HPLC confirmed the case as SCD. Sickle cell disease has complications involving many organs. Vaso-occlusion can lead to ischemic crisis of heart, brain, lungs, kidney & liver causing acute myocardial infarction, CVA, ARDS, renal failure and many more. Clinicians must have eyesight of these complications in an undiagnosed hemoglobinopathy case. Initiation of prompt treatment may reduce mortality & morbidity.

Keywords: Sickle cell disease; HPLC; Gamna-Gandy body; Autopsy.

Introduction :

Sickle cell disease is a genetic disorder due to point mutation at the 6th position of β chain of hemoglobin. Valine amino acid replaces Glutamic acid and an abnormal hemoglobin (HbS) results. Homozygous and heterozygous states are classified depending on the HbS percentage. The geographic distribution in India covers the tribal belt of states like Odisha, Maharashtra and Madhya Pradesh.[1,2] Sickle cell trait cases may lead a near normal life except in stressful conditions like dehydration, major surgery, infection and severe physical exertion.[3] Complications observed in sickle cell disease (SCD) are vaso-occlusive, aplastic, hemolytic and sequestration crisis. In hypoxic state, deoxygenated HbS polymerizes into long strand which is initially reversible. Repeated episodes lead to irreversible sickle shape of red cells and cause membrane damage. Due to inflammation, chemical mediators are formed and express adhesion molecule on endothelial cells. This leads to stagnation of blood flow and sickle shaped red cells get trapped in the microcirculation causing vaso-occlusive crisis. Again increase in blood viscosity and adhesion of these deformed red cells to the endothelial cells result in continuous damage to the visceral organs.[4] Infarction involving multiple organs may cause death.[5,6] Presence of other abnormal hemoglobin like HbSC, HbSD, HbS- β thal modify the pathogenesis and the clinical manifestations.[7] Here we present four cases with vaso-occlusive crisis involving different organs.

Corresponding Author
Dr. Upasana Das
Email: drupasana80@gmail.com
Mobile No.: 9437261223

Article History
DOR : 25.05.2024; DOA : 02.08.2024

Case 1:

A 19 year old primigravida of Northern belt of Odisha with 14th week of gestation was received with alleged history of sudden death after complaining of cough and dyspnea for last 2 days. The deceased had not visited hospital and was treated locally for her chest symptoms.

On autopsy examination, the uterus was of 14 weeks size. The viscera like kidney, liver and lungs were congested. There was an emboli lodged in pulmonary artery. Spleen was reduced in size weighing 120 grams. The external surface showed multiple white nodules. Cut section revealed severe congested areas with firm consistency.

Uterus, cervix with bilateral tubes and ovaries, both the kidneys, a

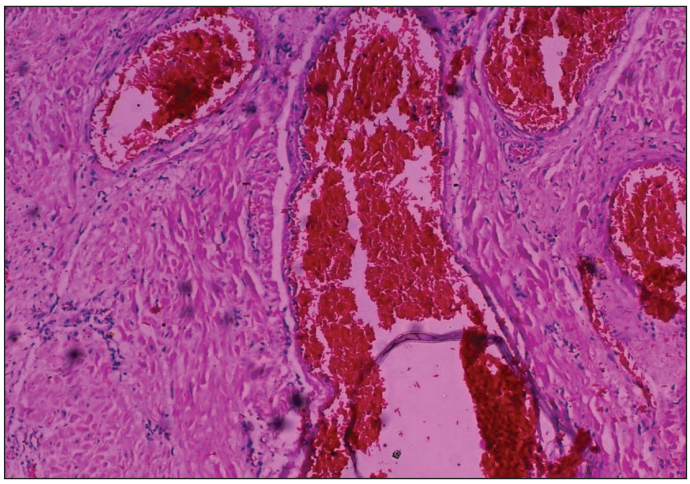


Figure 1. Myometrial blood vessels show congestion by sickle shaped red cells. H&E 200X

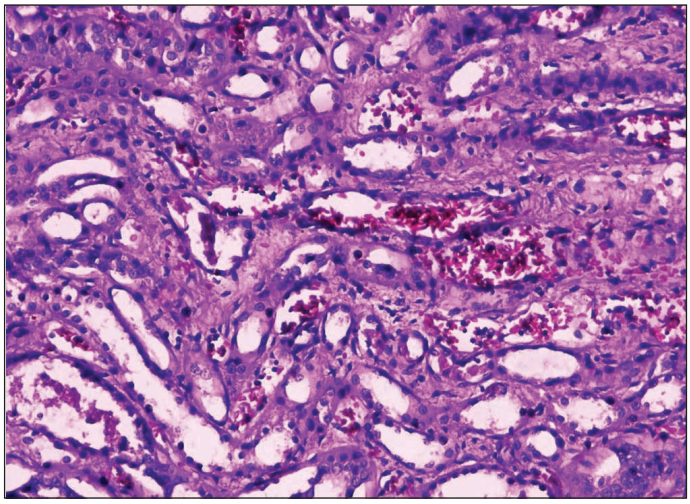


Figure 2. Section from kidney shows congestion of interstitial blood vessels. H&E 200X

piece of liver and spleen were sent for histological examination. Uterus, cervix with appendages measured around 15x9x12 cm. Cervix was effaced and dilated. Endometrial cavity content was brownish black friable material. On microscopy, endometrium showed decidualized stroma and fibrinohemorrhagic material containing villi. There were dilated and congested blood vessels in the myometrium filled with sickled red cells [Fig-1]. Cervix also revealed sickled RBCs within blood vessels. In both the kidney sections, glomerular capillaries and interstitial blood vessels were filled up with sickled red cells [Fig-2]. Proximal tubules had features of acute tubular necrosis. Liver sinusoid also demonstrated microvascular occlusive features.

Spleen had congested red pulp with widespread thick fibrous bands [Fig-3]. There were presence of yellowish-brown pigments and flecks within the parenchyma. These classical Gamna-Gandy bodies were noted along with giant cell reaction at places [Fig-4]. The blood vessels were congested with sickled red cells [Fig- 5] and dilated with proliferation of tunica media at places. The blood sample was sent for HPLC and it showed HbS & HbA2 bands. After careful autopsy and histopathological observation, the cause of death was reported as vaso-occlusive crisis leading to

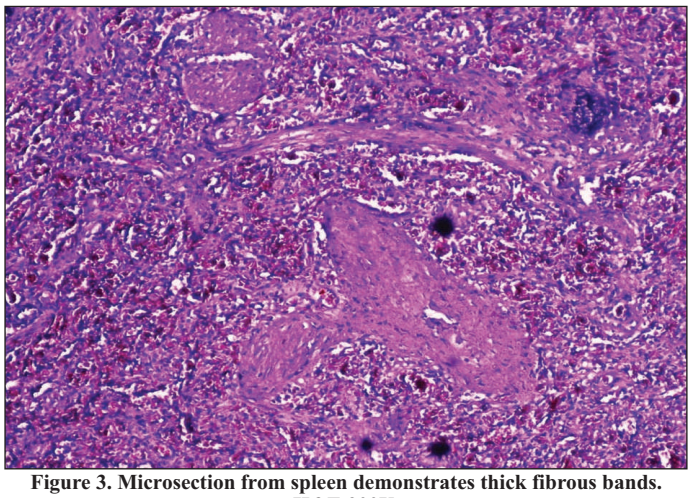


Figure 3. Microsection from spleen demonstrates thick fibrous bands. H&E 200X.

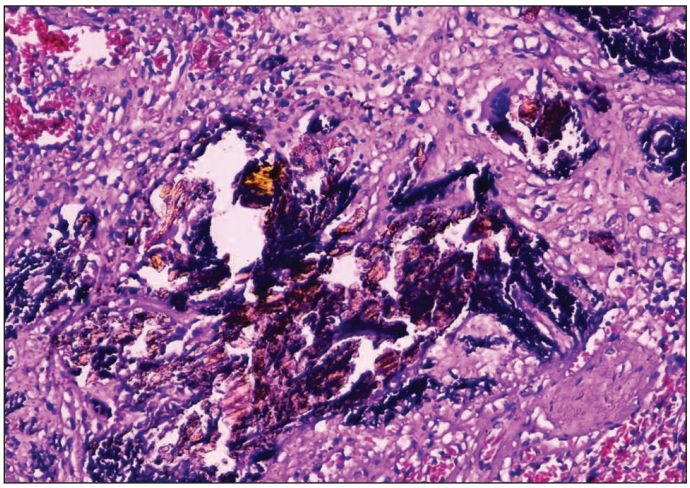


Figure 4. Microsection from spleen demonstrates Gamna-Gandy bodies as yellowish-brown flakes and pigments. H&E 400X

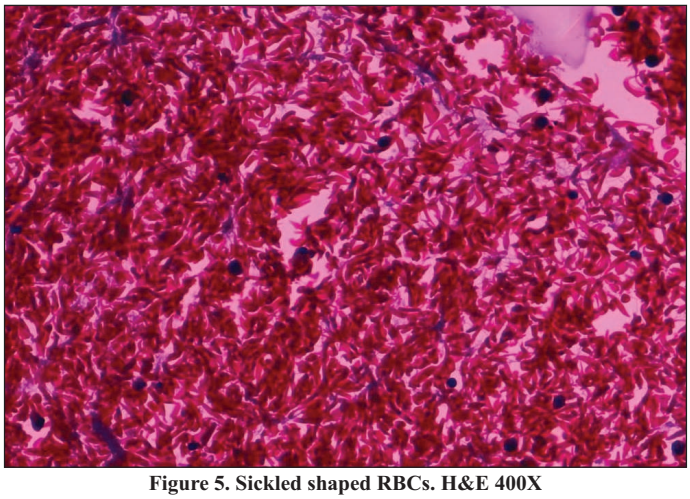


Figure 5. Sickled shaped RBCs. H&E 400X

multiorgan failure in an undiagnosed sickle cell disease.

Case 2:

26 year female of North Odisha was brought to casualty with sudden loss of consciousness. On examination, pulse was feeble, blood pressure was 100/60 mmHg and respiration was 32/minute.

 DOI : 10.48165/jiafm.2024.46.2(Suppl).22

Past history revealed similar type of attacks. On systemic examination, cardiovascular functions were normal. Blood tests revealed mild anaemia, elevated liver enzymes and creatinine kinase. ECG had tall T wave with normal ST segment. HPLC was performed on the basis of doubt as her brother was a known case of sickle cell anemia. The report came out to be sickle cell trait. Unfortunately we lost the patient. Autopsy examination revealed cardiomegaly. Right ventricle was dilated. Aorta had small fatty streaks. Spleen showed mild atrophy. There was a thrombus detected in right renal vein. Lungs were heavy weighing 255 grams and external surface showed patchy hemorrhages. Cut surface of other viscera like liver & uterus were unremarkable. On microscopic examination of heart, cardiac myocytes had box shaped nuclei. There was derangement in myocardial fibers. The intervening blood vessels were filled with sickle shaped red cells. Kidney had congestion with acute tubular necrosis. Sections from lung revealed alveolar hemorrhage, hyaline membrane & pulmonary edema along with acute inflammatory cell infiltration [Fig- 6]. The cause of death was due to vaso-occlusive crisis leading to multi organ failure.

Case 3:

An elderly male of 53 years of age, a known case of sickle cell trait presented to emergency department with left side hemiplegia and respiratory distress. Hb was 6.8g% and total leucocyte count was 24,500 with neutrophilia. CT scan of brain revealed ischaemic lesion of lacunar type in the internal capsule. Peripheral smear showed schistocytes and reticulocytosis. After 3 days of hospitalization, patient developed generalized anasarca. Due to massive pulmonary infection, the patient succumbed. Autopsy findings showed there was cardiomegaly with dilated right chamber and a thrombus detected in left anterior descending artery. Right lung showed a consolidated focus in lower lobe and left lung was congested. The final diagnosis was death due to ischemia leading to CVA and multiorgan failure.

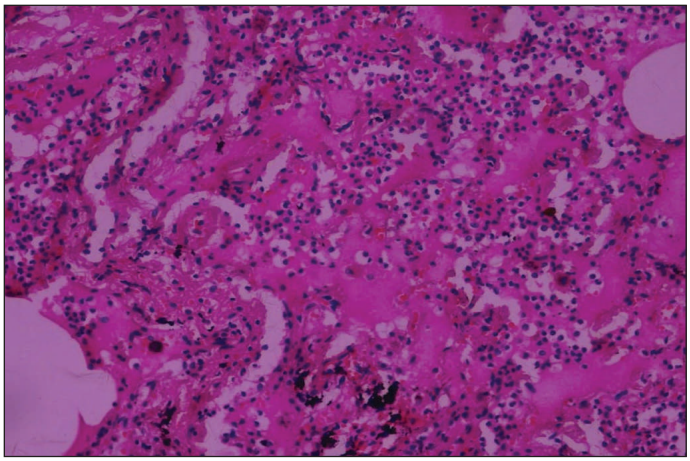


Figure 6. Lung alveoli show proteinaceous exudate with interstitial edema and acute inflammatory cell infiltration. H&E 200X

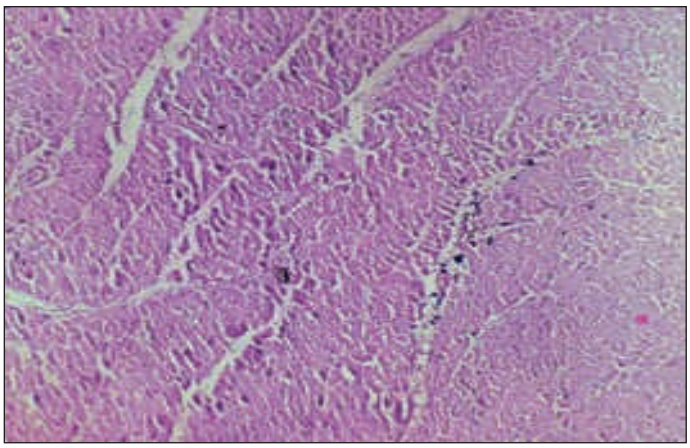


Figure 7. Waviness of myocardial fibers & contraction band necrosis.

Case 4:

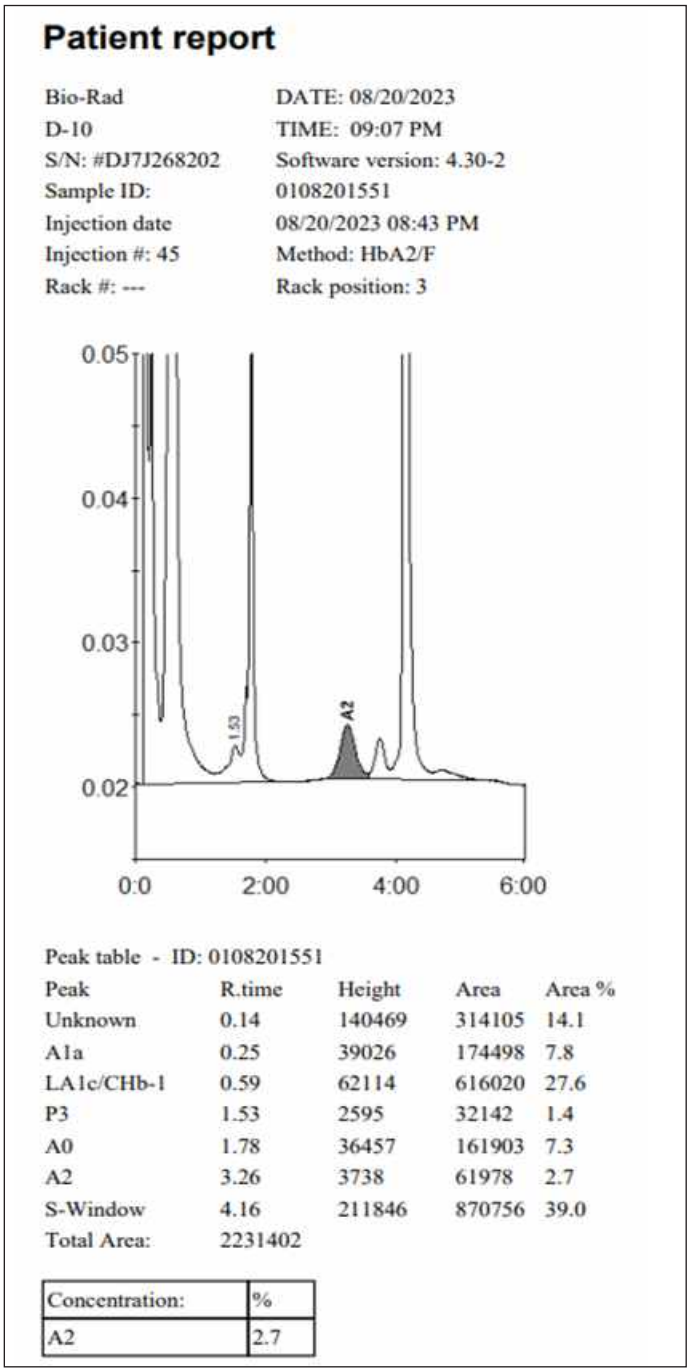
A young 25 year female was brought dead with sudden collapse while working in the rice field. There was no similar past history. Autopsy was performed. There was cardiomegaly with a whitish patch near the apex region. Aorta was normal. A white fibrotic patch was present in myocardium of left ventricle. Left anterior descending artery cross section showed a clot. Microscopic examination showed congestion and acute inflammation of lungs. Cardiac blood vessels were blocked with sickle shaped red cells. There was waviness of myocardial fibers, contraction band necrosis and neutrophilic infiltration [Fig- 7]. The lumen of left anterior descending artery was completely obstructed. HPLC confirmed sickle cell disease [Fig- 8]. The death was due to acute myocardial infarction as a consequence of sickle cell crisis.

Discussion:

Sickle cell disease in a homozygous state usually presents with complications at an early age. In review of literature, it was observed that many case reports were on sickle cell disease patients with sudden death due to heavy exercise, bacterial infection, viral illness, dehydration and high altitude.[8] Infections by encapsulated bacteria like Streptococcus pneumoniae may cause collapse and sudden death. SCD patients are easy prey for

Table 1.

Case	Age	Sex	Clinical details	Organs involved	Hemo-globin	Cause of death	Other findings (Autopsy & Microscopic)
1	19	F	14 weeks pregnancy	Uterus, liver, lung, spleen, kidney	HbS, HbA2, HbF	Acute Respiratory Distress Syndrome (ARDS), Renal failure	Gamna-gandy body in spleen
2	26	F	Had delivered a full term baby and was in Lactation period	Heart, spleen, uterus	HbS, HbA2, HbF	Cardiomyopathy, ARDS with diffuse alveolar damage	Aorta with fatty streak Spleen showed Gamna-gandy body
3	53	M	CVA causing left hemiplegia	Lung, liver, spleen. Kidney	HbA, HbS, HbA2	Multi organ failure	Generalized anasarca
4	25	F	Sudden cardiac death	Lung, heart	HbS, HbA2, HbF	Acute Myocardial Infarction	Lungs showed interstitial thickening of septa and inflammation



Patient report

Bio-Rad DATE: 08/20/2023
D-10 TIME: 09:07 PM
S/N: #DJ7J268202 Software version: 4.30-2
Sample ID: 0108201551
Injection date 08/20/2023 08:43 PM
Injection #: 45 Method: HbA2/F
Rack #: --- Rack position: 3

Peak table - ID: 0108201551

Peak	R.time	Height	Area	Area %
Unknown	0.14	140469	314105	14.1
A1a	0.25	39026	174498	7.8
LA1c/CHb-1	0.59	62114	616020	27.6
P3	1.53	2595	32142	1.4
A0	1.78	36457	161903	7.3
A2	3.26	3738	61978	2.7
S-Window	4.16	211846	870756	39.0
Total Area:	2231402			

Concentration:	%
A2	2.7

Figure 8. HPLC report demonstrates presence of HbA2, HbF and HbS.

infection due to splenic infarction since childhood. Some authors also cited that lazy leucocyte syndrome is one of the important contributors causing infection.[9] Case No 1 & case no 2 of present study had lost their life due to severe respiratory infection and development of ARDS.

Pregnancy in SCD has many medical complications both for the mother and fetus. Physiological changes in pregnancy like increase in metabolic demands, blood viscosity and the hypercoagulable states are aggravated in SCD.[10] Due to recurrent vaso-occlusion, placental tissue may be infarcted leading to decreased utero-placental circulation and chronic fetal hypoxia. Spontaneous abortion is not uncommon.[11] Special medical care may decrease maternal mortality as well fetal loss.[12]

Preeclampsia and eclampsia like complications are usually seen in mid and late trimester. Pregnancy in SCD present with these complications with higher percentage of incidence than general population.[13] In our study, one deceased had recent delivery and other one is in her 4th gestational month. Both the cases were not diagnosed cases of hemoglobinopathy.

Due to obstetric complications, there was spontaneous abortion followed by infection. Poor general health condition and lack of medical awareness were additive risk factors. Due to septicemia, there was development of acute respiratory distress syndrome (ARDS) and the deceased had history of dyspnea and cough. ARDS can also result due to pulmonary embolism and warrant LMWH. A study by Deepti et al,[8] reported that heavy physical exertion resulted in sudden collapse and death in a sickle cell trait case. In our case, presence of fatty streaks on aorta predisposed more pathological favorable platform for the sickle cell crisis.

Histopathological examination revealed irreversible sickle shaped red cells completely obstructing the glomerular capillaries and interstitial blood vessels of kidney leading to decreased glomerular filtration rate (GFR) and proximal tubular necrosis and subsequently acute renal failure. As HbS polymers are repeatedly formed, the red cell membrane gets damaged resulting in release of procoagulants. Ultimately derangement of liver enzyme occurs and renal failure ensues. Classical Gamna-Gandy bodies in spleen along with thick fibrotic strands were due to autoinfarction. We got these classical bodies in two cases. Though Gamna-Gandy bodies are not confined to sickle cell disease only, their presence signifies repeated hemorrhage and deposition of iron pigments and calcium salts.[14] These bodies are usually seen around central arteriole of the white pulp.

Infarctive crisis is more common than hemolytic, aplastic and sequestration crisis. Autosplenectomy results by the age of adolescence. Autopsy finding in our case was reduced but not fibrotic and small spleen which could be due to other associated hemoglobinopathies like HbSD, HbS- β thal, HbSC, where splenomegaly results due to extramedullary hematopoiesis.[15] Cerebral vasculature blocked by sickled red cells, results in cerebro-vascular accidents. Many authors reported that ischemic strokes were more common than hemorrhagic one.[16,17]

Sickle cell homozygous cases are more prone for stroke than trait cases.[18] Tumaj et al reported a 21 year old SCD patient presenting with frontal lobe infarction.[19] In our case, the 53 year sickle cell trait case succumbed to death due to multiorgan involvement and failure. John et al study highlighted diffuse ischemic stroke in a HBSC patient precipitated due to infection by Babesia and disseminated Anaplasmosis.[20]

Kark et al study review highlighted the sudden unexplained death risk was 30 times more common associated with sickle cell trait than normal individuals.[21] SCD patients may present with coronary syndrome at an earlier age as in our 4th case. Sickled RBCs had blocked the left anterior descending artery along with histological changes of infarction in cardiac myocytes.

Conclusion:

Many literatures had demonstrated on sickle cell disease causing vaso-occlusion as a complication even leading to death in some cases. Pregnancy in SCD patients' needs extra medical support and care, both during pregnancy and delivery. About patients from known hemoglobinpathy belt zones like Northern-Odisha need awareness, knowledge and high index of suspicion of clinicians which can prevent a crisis to develop and progress.

References :

1. Pillai LV, Husainy S, Gosavi S, Vaidya N. Sudden unexpected death in an undiagnosed sickle disease. Indian J Crit Care Med [Internet]. 2005;9(2):92–5. Available from: http://dx.doi.org/10.4103/0972-5229.17096
2. Colah R, Mukherjee M, Ghosh K. Sickle cell disease in India. Curr Opin Hematol [Internet]. 2014;21(3):215–23. Available from: http://dx.doi.org/10.1097/moh.0000000000000029
3. Thogmartin JR, Wilson CI, Palma NA, Ignacio SS, Shuman MJ, Flannagan LM. Sickle cell trait-associated deaths: a case series with a review of the literature: Sickle cell trait-associated deaths. J Forensic Sci [Internet]. 2011;56(5): 1352–60. Available from: http://dx.doi.org/10.1111/j.1556-4029.2011.01774.x
4. Eaton WA, Hofrichter J. Sickle cell hemoglobin polymerization. Adv Protein Chem [Internet]. 1990;40: 63–279. Available from: http://dx.doi.org/10.1016/s0065-3233(08)60287-9
5. Gaartman AE, Sayedi AK, Gerritsma JJ, de Back TR, van Tuijn CF, Tang MW, et al. Fluid overload due to intravenous fluid therapy for vaso-occlusive crisis in sickle cell disease: incidence and risk factors. Br J Haematol [Internet]. 2021;194(5):899–907. Available from: http://dx.doi.org/10.1111/bjh.17696
6. Kaul DK, Fabry ME, Nagel RL. Microvascular sites and characteristics of sickle cell adhesion to vascular endothelium in shear flow conditions: pathophysiological implications. Proc Natl Acad Sci U S A [Internet]. 1989;86(9):3356–60. Available from: http://dx.doi.org/10.1073/pnas.86.9.3356
7. Steinberg MH, Hebbel RP. Clinical diversity of sickle cell anemia: genetic and cellular modulation of disease severity. Am J Hematol [Internet]. 1983;14(4):405–16. Available from: http://dx.doi.org/10.1002/ajh.2830140412
8. Mutreja D, KBP, Tvsvgk T. Fatal sickling-associated microvascular occlusive crisis in a young with sickle cell trait. Autops Case Rep [Internet]. 2021;11:e2021297. Available from: http://dx.doi.org/10.4322/acr.2021.297
9. Olaniyi JA. Multiple complications in a sickle cell disease patient: a case report. Clin Med Case Rep [Internet]. 2008;1:97–100. Available from: http://dx.doi.org/10.4137/ccrep.s812
10. Thame MM, Singh-Minott I, Osmond C, Melbourne-Chambers RH, Serjeant GR. Pregnancy in sickle cell-haemoglobin C (SC) disease. A retrospective study of birth size and maternal weight gain. Eur J Obstet Gynecol Reprod Biol [Internet]. 2016;203:16–9. Available from: http://dx.doi.org/10.1016/j.ejogrb.2016.05.002
11. Thame MM, Osmond C, Serjeant GR. Fetal growth in women with homozygous sickle cell disease: an observational study. Eur J Obstet Gynecol Reprod Biol [Internet]. 2013;170(1): 62–6. Available from: http://dx.doi.org/10.1016/j.ejogrb.2013.04.013
12. Smith-Whitley K. Complications in pregnant women with sickle cell disease. Hematology Am Soc Hematol Educ Program [Internet]. 2019;2019(1):359–66. Available from: http://dx.doi.org/10.1182/hematology.2019000039
13. Lari NF, DeBaun MR, Oppong SA. The emerging challenge of optimal blood pressure management and hypertensive syndromes in pregnant women with sickle cell disease: a review. Expert Rev Hematol [Internet]. 2017;10(11):987–94. Available from: http://dx.doi.org/10.1080/17474086.2017.1379895
14. Piubelli MLM, Clemente LC, Duarte-Neto AN. Gamna-Gandy bodies of the spleen in sickle cell disease. Autops Case Rep [Internet]. 2019;9(2):e2018076. Available from: http://dx.doi.org/10.4322/acr.2018.076
15. Bhatia V, Juneja R, Juvekar V. The post-mortem diagnosis of vasocclusive crisis in sickle cell disease. Autops Case Rep. 2014 Sep 30;4(3):9-11. doi: 10.4322/acr.2014.023. PMID: 28573113; PMCID: PMC5444393.
16. Earley CJ, Kittner SJ, Feeser BR, Gardner, J, Epstein A, Wozniak MA (1998). Stroke in children and sickle-cell disease: Baltimore-Washington Cooperative Young Stroke Study. Neurology, 51(1), 169–176. https://doi.org/10.1212/wnl.51.1.169
17. Kwiatkowski JL, Zimmerman RA, Pollock AN, Seto W, Smith-Whitley K, Shults (2009). Silent infarcts in young children with sickle cell disease. British Journal of Haematology. 146(3); 300–305. https://doi.org/10.1111/j.1365-2141.2009.07753.x
18. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW (1998). Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood, 91(1): 288–294.
19. Hashemzehi T, Bertok S, Figaszewska MJ, Batura D. Diverse manifestations of a sickle cell crisis. BMJ Case Rep. 2021 Jan 28;14(1):e236743. doi: 10.1136/bcr-2020-236743. PMID: 33509861; PMCID: PMC7845707
20. Herbst J, Crissinger T, & Baldwin K. (2019). Diffuse ischemic strokes and sickle cell crisis induced by disseminated anaplasmosis: A case report. Case Reports in Neurology. 11(3); 271–276. https://doi.org/10.1159/000502567
21. Scoville SL, Gardner JW, Magill AJ, Potter RN, & Kark JA (2004). Nontraumatic deaths during U.S. Armed Forces basic training, 1977-2001. American Journal of Preventive Medicine. 26(3); 205–212. https://doi.org/10.1016/j.amepre.2003.12.003