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Case Report

Sudden Death due to Acute Splenic Sequestration Crisis in Sickle Cell Disease: A Case Report with Active Post-Mortem Follow up.

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Abstract

Background: Sickle cell disease (SCD) is an autosomal recessive monogenic disorder that is common among individuals in many countries. In India, SCD is particularly prevalent in the western states. Sudden death in asymptomatic young adults with sickle cell trait, although uncommon, is usually due to infection and acute chest syndrome. Acute splenic sequestration crisis (ASSC) is an uncommon presentation among such patients. Clinically, cause of sudden deaths in SCD cases remain elusive and requires further research and reporting. **Case presentation:** In this report, we present the case of a previously asymptomatic 25-year-old male with ASSC. After complaining of fever and backache for three days, he was brought dead to the casualty of a tertiary care hospital. Apart from yellowish tinge of skin, on autopsy, we noted an enlarged spleen (weight=2010 grams) with chalky white calcified deposits on the surface. Histopathology of the spleen revealed sickled RBCs leading to ASSC and presence of Gamna Gandy Bodies. Bone marrow aspirate revealed erythroid hyperplasia. The final cause of death was opined to be splenic sequestration crisis. **Conclusion:** Sudden death due to sickle cell disease in an asymptomatic person warrants a stronger genetic vigilance. More focus on prenatal diagnosis of inheritable diseases is needed along with follow-up, guidance and counselling. In the present case, the decedent's family was followed up post-mortem, counselled for undergoing genetic screening, and was finally referred to the Sickle Cell Society of India for further guidance.

1. Introduction

In 1910, Herrick was the first to report peculiarly elongated and sickle-shaped RBCs in a dental student who suffered from severe anemia and pulmonary symptoms.[1] Since then, various *in vitro*, as well as *in vivo* experiments were conducted[2], and the phenomenon of sickling was attributed to hypoxia, or an increased concentration of carbon dioxide in blood. In 1960s, the sickle cell disease (SCD) was further described as "a disease of the childhood," with high mortality

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rates, and reported only a few survivors reaching adulthood, regardless of best medical care available at the time.[3]

SCD may manifest in homozygous or heterozygous forms, the latter usually presenting in combination with other genetic defects such as thalassemia, spherocytosis, etc. In the homozygous form, the condition is termed as sickle cell anemia (SCA). Here, the β-hemoglobin gene in Chromosome 11 undergoes a glu-6-val (substitution of amino acid glutamate by valine) mutation, leading to an abnormal polymerization of deoxygenated hemoglobin. This polymer is rope-like and forms bundle with others, thereby distorting the RBCs into crescentic, 'sickle' forms.[4] SCA has a high mortality rate and very few survive until adulthood.[3]

Heterozygous form or the *sickle cell trait* has a milder clinical manifestation, showing features of the disease only in case of extreme conditions like severe dehydration, intense exercise, high altitudes, poor physical conditioning, concurrent febrile illness [5–7], which may in turn prove to be fatal. Such adults are usually asymptomatic. In some previously undiagnosed cases, they die of acute sickle crises with painful episodes or due to acute chest syndrome.[3,8,9]

Acute splenic sequestration crisis (ASSC) is an uncommon, sudden, unexpected and life threatening entity among adult sickle cell disease patients. It is characterized by rapidly progressive anemia, circulatory compromise in setting of sudden splenic enlargement. Details regarding the fatalities in acutely-ill SCD cases remain elusive and requires further research and reporting for better understanding and prevention of sickle cell crises.[3] Herein, we discuss a case of an adult male brought dead to tertiary care center, where autopsy revealed SCD with splenic sequestration crisis.

2. Case Report

A 25-year-old manual laborer, previously healthy and no known ailments, complains of fever and backache for a span of three days. He had approached a primary health center, where his family physician prescribed symptomatic treatment with analgesics and antipyretics, with an advice to follow up. However, on third day of his treatment, he collapsed at home, and was brought to the emergency room of a Tertiary Care Centre, where he was declared dead by the medical officer.

At autopsy, it was noted that the skin and conjunctiva showed yellowish discoloration. Externally, no injuries were detected on the surface of the body. Internally, it was noted that the lungs, liver, pancreas, and kidneys congested. Spleen was grossly enlarged, measuring 18cms in length and 24cms in width, and the same weighed 2010 grams. On examination, the spleen was firm, and chalky white calcified lesions covered the surface of the organ **(Fig 1)**. Lungs, liver, kidney, pancreas, spleen and piece of sternum were sent for histopathological examination.

Fig 1: Enlarged spleen with chalky-white calcified lesions on the surface.

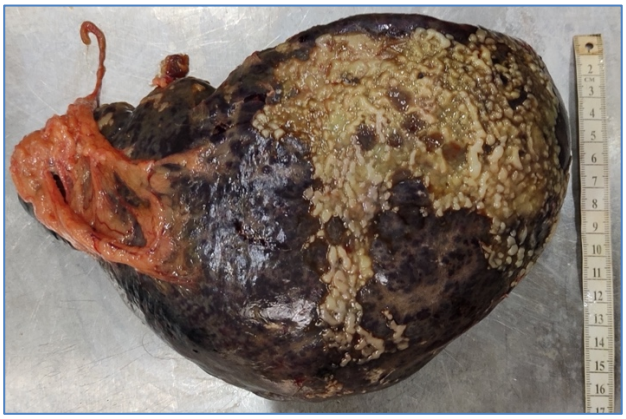


Fig 2: High power view of red pulp showing sequestrated RBCs.

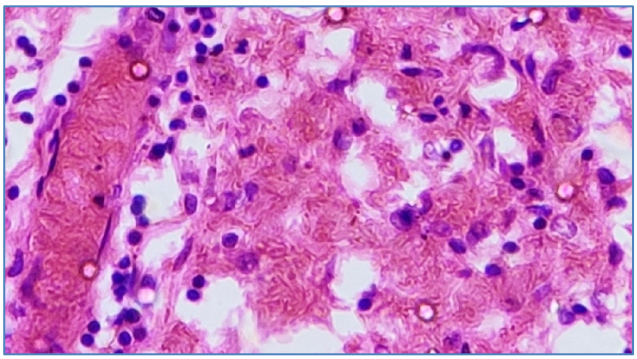
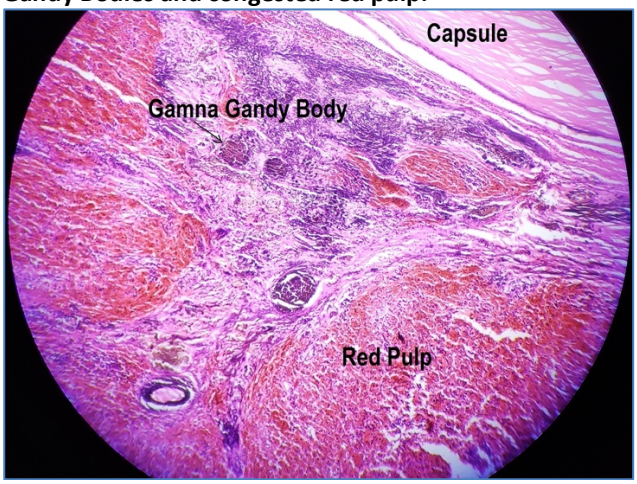


Fig 3: Low power view of spleen showing Capsule, Gamna Gandy Bodies and congested red pulp.



Histopathology confirmed the presence of sickled RBCs in the organs and bone marrow. Spleen showed marked congestion of the cords and sinuses by sickled RBCs **(Fig. 2)**, leading to ASSC. Presence of Gamna Gandy bodies were noted in spleen **(Fig. 3)**. Lungs, liver, kidneys and pancreas showed marked congestion with presence of sickled RBCs. Sections from the bone marrow (manubrium) revealed marked congestion with sickled RBCs, and presence of erythroid hyperplasia. The final cause of death was opined to be due to "splenic sequestration crisis in a person with sickle cell disease."

Furthermore, the decedent's family was followed up post-mortem, counselled for undergoing genetic screening, and was finally referred to the Sickle Cell Society of India (SCSI) for further guidance. This led to the discovery of similar deaths among other male members of his family and similar clinical manifestations in his younger brother. Finally, a diagnosis of sickle cell trait in the family tree was established and SCSI is actively following them up.

3. Discussion

SCD is an umbrella term that comprises of inherited disorders related to red blood cells, with at least one 'sickle gene' inherited in an autosomal recessive pattern. It encompasses a group of hemoglobinopathies resulting from the presence of hemoglobin S (HbS), either in the homozygous or in the heterozygous form with another abnormal hemoglobin such as HbC, HbE, fetal hemoglobins or beta–thalassemia (HbS/β-Th).[10] This could range from fatally severe clinical manifestations to asymptomatically mild ones. In the present case, the decedent had mild to almost no clinical symptoms the sickle cell condition was discovered only post-mortem.

In such asymptomatic cases with sickle cell traits, studies have shown relatively good life expectancy. About 85% of individuals with SCA and more than 95% of the individuals with SCD cross 20 years of age[3], with a projected life expectancy of 54 years.[11] Contrastingly, the decedent in the present case was only 25 years old, with lower life expectancy than expected.

The distorted shape of the RBCs *in vivo* usually results in complications like hemolytic anemia, vaso-occlusive crisis and ischemic changes that lead to reperfusion tissue damage and infarctions.[12-14] The leading causes of death in SCD are infection, chronic organ damage, renal diseases, pain episodes consequent to sickle cell crises, acute chest syndrome and stroke.[3,8,12,15,16]

The manifestation of hemolytic anemia is moderately severe in nature, with hematocrit ranging from 18% to 30%, further associated with reticulocytosis, hyperbilirubinemia, and the presence of irreversibly sickled cells.[10] In the present case, hemolytic anemia was marked by jaundice and the presence of sickled cells in histopathological sections of all organs. Erythroid hyperplasia of the bone marrow was also observed.

Until recently, there was a misconception that origin of vaso-occlusive crises were attributed purely to physical entrapment of deformed erythrocytes within microvascular network. In reality, it is a multi-factorial process, with prolongation of erythrocyte transit time in microvasculature, reduction in delay time to polymerization and other miscellaneous modulators like free-radical release and coagulation activation with pro-adhesive thrombin formation.[4]

Chronic erythrostasis in spleen can lead to splenic infarction, fibrosis and shrinkage of the organ, leading to functional asplenia and dubbed as autosplenectomy in young individuals. Autosplenectomy is fairly common (55.4%) in Nigerian individuals with sickle cell anemia.[17]Due to the intermittent nature and chronicity, splenomegaly can also be seen in such cases. In the present case, there was a massive splenomegaly, associated with areas of infarct and fibrosis. Mineral deposition following vaso-occlusion, periarteriolar hemorrhages and hemolysis within the central arteriole of the white pulp of the spleen as a chronic event is characterized by the presence of Gamna Gandy Bodies[18], which was noted in this case.

This further leads to infections, which is by far the most common cause of death in young individuals with SCD. Higher mortality rates are noted in cases with a low level of fetal hemoglobin, or total hemoglobin, and increased level of white blood cell count.[3]In the present case, acute splenic sequestration crisis without any underlying infection was noted to be the cause of death. Acute enlargement of spleen consequent to a classic sickle cell crisis, when associated with about 20% fall in the hemoglobin level (at least 20 g/l) from baseline level and increase in basal reticulocyte count, is termed as splenic sequestration crisis.[15]

A robust screening and follow-up system is the answer to reducing deaths in sickle cell anemia. In

California, HPLC is used as an initial screening method for all newborns, followed by a confirmatory lab report. Positive babies are followed up actively and enrolled into treatment systems, which includes routine Penicillin prophylaxis.[19] Contrastingly, most Indian institutions lack such screening measures, and the same is prescribed only by request, clinical suspicion or an accidental discovery following a transfusion reaction. This leads to missed diagnosis in patients with sickle cell trait, leading to sudden death in later years, as seen in the present case. This is after not taking into account the maternal deaths (1.9%).[20] Even then, autopsy reports of splenic sequestration crisis is lacking in Indian literature, which necessitated this case report.

If a diagnosis is established after autopsy, family members should be directed to a genetic center for screening and diagnosis. In this instance, the decedent's family was followed up post-mortem, counseled for genetic screening, and directed to the SCSI. Soon, the decedent's sibling was identified with sickle cell trait after genetic testing and pedigree research. Few other paternal family members who died of unexplained "natural cause" after a painful episode ultimately received a closure for their deaths.

4. Conclusion

Sudden death due to SCD is uncommon in young adults, especially where the disease is mild and clinically asymptomatic. ASSC is a rare presentation among such individuals, which is sudden, unexpected and fatal. Multiple factors are responsible for this vaso-occlusive crisis, which until recently was believed to be caused due to micro-circulatory obstruction by deformed RBCs. However, recent literature point out that the mechanism is much more complicated and multi-factorial.

Such unexpected and sudden death due to undiagnosed sickle cell disease in an asymptomatic person warrants a stronger genetic vigilance. More focus on prenatal diagnosis of inheritable diseases is needed along with follow-up, guidance and counselling. If diagnosis is made during autopsy, the information should be passed on to the family members with due diligence, explaining the details of the disease and referring them to the local genetic center for diagnosis and follow-up, as it was done in the present case. This case reinforces that forensic pathology is the study of dead that helps to serve the living better.

Conflict of interest: None

List of Abbreviations

1. ASSC: Acute splenic sequestration crisis
2. SCA: Sickle Cell Anemia
3. SCD: Sickle Cell Disease
4. SCSI: Sickle Cell Society of India

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