CASE REPORT

Homozygous HbS in A Malay Patient: A Rare Variant of Sickle Cell Disease in Malaysia

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ABSTRACT

Sickle cell disease in Malay ethnicity is uncommon, with few cases been reported only in Malaysian Indians. Detecting sickle haemoglobin in patients with osteoarticular manifestation is not as simple as those with haemolysis crisis, due to its extremely low incidence in this country. We hereby report a case of a 19-year-old Malay female who presented with a long-standing history of disabling movement of both hip joints, intermittent painful swollen right elbow, and chronic back pain. Imaging investigations revealed features of chronic osteomyelitis and avascular necrosis while blood investigations demonstrated features of mild normochromic normocytic anaemia and extravascular haemolysis. Further blood smear and haemoglobin analysis eventually confirmed the presence of homozygous sickle haemoglobin manifesting as sickle cell anaemia. Our case has highlighted the importance of prompt identification and thorough evaluation of the cause of anaemia in a patient with disabling chronic osteoarticular problem.

Keywords: Sickle cell anaemia, homozygous HbS, osteoarticular, Malay, Malaysia

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INTRODUCTION

Sickle haemoglobin (HbS) is a structural variant of normal adult haemoglobin resulting from a single nucleotide mutation of the β-globin chain. Sickle cell disease (SCD) is a group of disorders referring to genetic disorders with this mutated form of haemoglobin e.g., homozygous HbS or sickle cell anaemia (SCA), heterogenous HbS, or sickle cell trait, sickle-beta thalassemia, haemoglobin SC disease, etc. The incidence of homozygous HbS in Malaysia is uncommon with isolated cases being reported among Indian ethnic. We hereby report a rare case of homozygous HbS in Malaysia affecting the Malay ethnic.

CASE REPORT

A 19-year-old Malay female presented with recurrent bilateral thigh pain predominantly on the left, as well as intermittent swelling and pain over the right arm. She also had been having chronic back pain since her childhood. She had neither constitutional symptoms nor history of contact with a tuberculosis patient. On examination, her right elbow appeared swollen and tender. The range of movement of both hip joints was markedly reduced due to pain. Examination of other systems was unremarkable.

Plain radiograph revealed multiple mixed lytic and sclerotic lesions involving multiple bones. Further magnetic resonance imaging (MRI) of the pelvis revealed features of avascular necrosis affecting both hip joints (Fig.1). A core biopsy was taken from the right humeral bone and the histopathological examination showed features of necrotic bony foci which likely to be due to chronic osteomyelitis. She was initially managed by the orthopaedic team and was empirically treated for bacterial osteomyelitis.

Her baseline haemoglobin level has been low since at first presentation, ranging from 9 to 10 g/dL and it was normochromic normocytic anaemia. Of note, she had no prior medical illness and was not aware of any blood-related problem in the past. Anaemia was persistent over a period of time that eventually became noticeable as a significant medical issue, which had triggered the managing team to seek an expert clinical haematological opinion.

Full blood count revealed normochromic normocytic anaemia (Hb 9.8 g/dL, MCV 82.4 fL, MCH 29.3 pg),

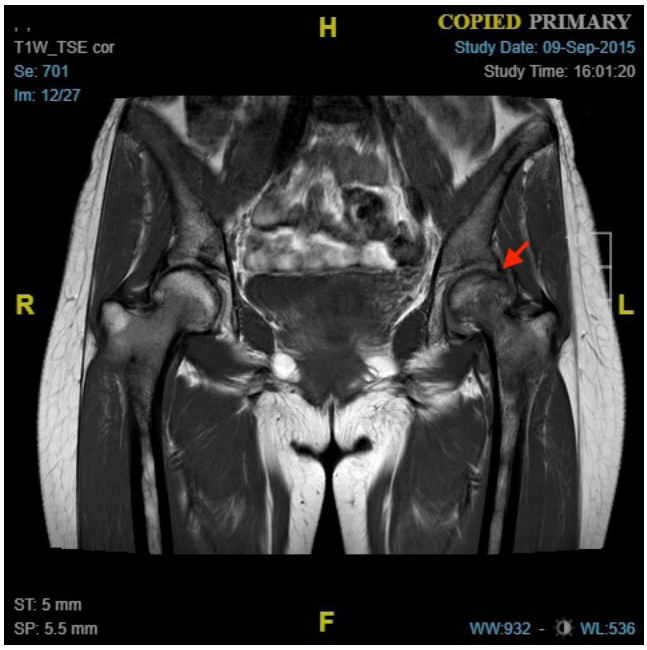

Figure 1: T1 weighted image of MRI which shows focal area of hyperintense with hypointense rim at the left head of femur.

WBC 22.83 x 10^9/L and platelet 339 x 10^9/L. Reticulocyte count was elevated (7.79%) as well as total bilirubin (51 mmol/L; direct 12 mmol/L, indirect 39 mmol/L) and lactate dehydrogenase (3296 U/L). Peripheral blood smear (Fig. 2) demonstrated reticulocytosis with sickle cells, nucleated red blood cells and Howell-Jolly bodies (HJB). The presence of HJB in the smear is pathognomonic of splenic dysfunction. This DNA-containing inclusion is commonly seen not only in post-splenectomy but also in any functional hyposplenism such as SCD.

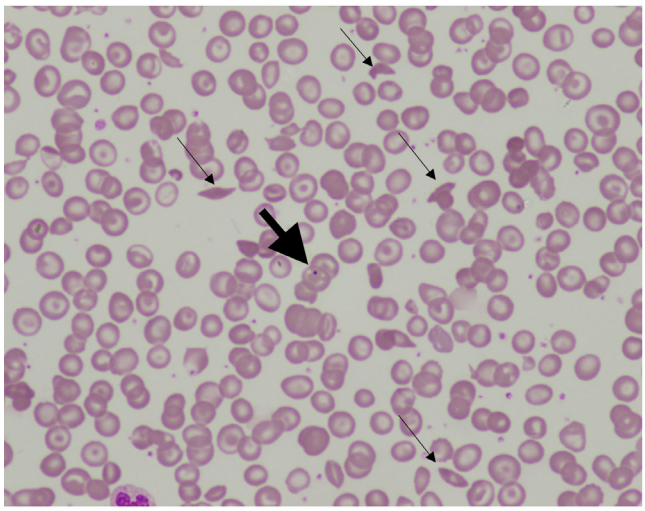

Figure 2: Blood film (under magnification 40x) shows few sickle cells (thin arrow) in crescent-shape and boat-shape. Occasional Howell-Jolly bodies (thick arrow) and some target cells were seen.

High performance liquid chromatography (HPLC) showed HbS 81.7%, HbF 13.8% and HbA2 2.4% (Fig. 3). Haemoglobin electrophoresis at alkaline and acidic pH showed the presence of HbS and HbF bands only.

Peak Name	Calibrated Area %	Area %	Retention Time (min)	Peak Area
P1	---	0.0	0.83	766
F	13.8*	---	1.14	235858
Unknown	---	0.8	2.15	14136
Ao	---	1.9	2.29	35565
A2	2.4	---	3.61	50642
S-window	---	81.7	4.36	1501160

Total Area: 1,838,12

F Concentration = 13.8* %
A2 Concentration = 2.4 %

*Values outside of expected ranges

Analysis comments:

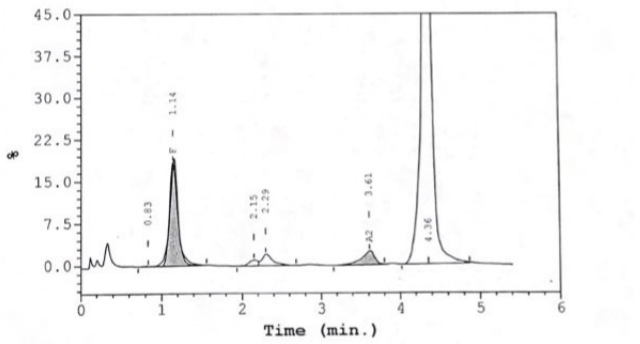

Figure 3: This Bio-Rad Variant HPLC chromatogram shows elevated HbS (81.7%) at the retention time of 4.36 min and HbF (13.8%) at the retention time of 1.14 min.

Thus, the haemoglobin analysis was consistent with homozygous HbS.

The final diagnosis concluded was SCA with recurrent episodes of vaso-occlusive crisis leading to bilateral hips avascular necrosis and chronic osteomyelitis. She was started on oral hydroxyurea, which subsequently led to lesser episodes of acute painful crisis. She successfully underwent an operation for left hip prosthetic implant after a few months, with future planning for the right-side prosthetic implant.

Of note, she is the third out of 6 siblings. Her parents were divorced and there was no interracial marriage involving previous generations in the family. An effort to screen all of her first-degree relatives for HbS was very difficult in view of parenteral and sibling's separation. It is notable to highlight that she had one elder brother who passed away at age of 19 due to sudden cardiac arrest and a younger brother who has been tested having HbS trait (Fig. 4).

DISCUSSION

Homozygous HbS with SCA manifestation is the least prevalent hemoglobinopathy in Southeast Asia. The incidence of SCA affecting Malaysian population is very uncommon as there are only a few case reports highlighting such rarity affecting immigrants and Malaysian Indians (1,2).

The occurrence of SCA among Malay ethnic, in

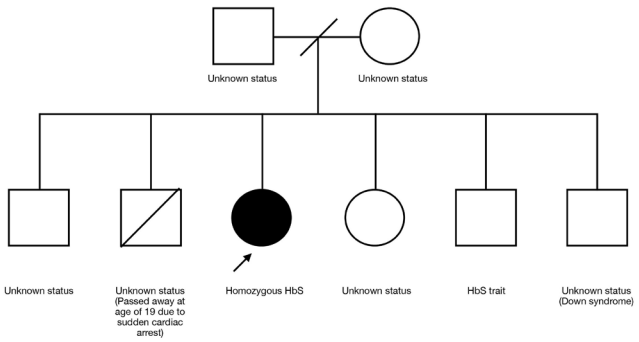

Figure 4: Patient's pedigree

particular, is extremely rare, although it is probably incompletely recognized and reported. Alauddin et al have described the detailed investigations performed on a 16-year-old female who presented with recurrent painful crisis of lower limbs, in which the affected patient was homozygous for HbS and the rest of the family members were heterozygous (3). Another case of homozygous HbS was described by Wee et al, who discovered a 14-year-old Malay female, who had jaundice since the age of 11 years with subsequent history of deep vein thrombosis and bilateral lower limb bone infarct (1). The incidence of SCA affecting Chinese ethnicity or people of Northeast Asian origin on the other hand is almost unheard of.

SCD is epidemiologically linked to people of African, Middle Eastern, Indian and Mediterranean descent. The isolated incidence of HbS in a Malay patient could be explained by the genetic architectures in the Malays who might be influenced by a diversified entity of multiple ancestries represented by Austronesian, Proto-Malay, East Asian, and South Asian (4). The fact that our patient came from a broken family background has hindered the process of tracing further information of her ancestors.

Our patient shared similar demographic characteristics and clinical presentation with the two aforementioned cases in Malay patients. The osteoarticular involvement of SCA is characterised by osteonecrosis, osteomyelitis, and arthritis. Sickling and vascular occlusion occur more often in tissues with low blood flow i.e., long bones. Chronic infarction and secondary osteoarthritis may exhibit both lytic and sclerotic destructive lesions. These may raise suspicion of other bone-related disorders for example osteomyelitis, osteosarcoma, or haematological malignancy such as multiple myeloma (5).

There seems to be a delay in detecting SCA in our patient due to procrastination in investigating the cause of anaemia. While acute anaemia is not uncommon in any critical illness, the clinician should thoroughly identify and further investigate the aetiology of anaemia, and not merely focussing on the primary medical or surgical problem of interest. The delayed detection of SCA in a patient with long-standing osteoarticular manifestation further reflects the exceptional incidence of SCA in our local population.

CONCLUSION

Homozygous HbS is rare and not frequently reported among Malay ethnics. Diagnosing SCA in a patient with osteoarticular manifestation is not as obvious as one presenting with haemolytic crisis especially in a region with a low incidence of SCD. A disabling chronic osteoarticular problem, which is very common in certain haematological disorders like SCA and multiple myeloma, should trigger the managing clinician to explore other possible aetiology beyond respective clinical expertise.

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