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## PSEUDOXANTHOMA ELASTICUM IN A PATIENT WITH SICKLE CELL DISEASE: CASE REPORT

A.M. ADAM and M.C. MARITIM

### SUMMARY

**An 18 year female sickler (HbSS) presented with repeated history of epistaxis and bleeding gums. Features consistent with *pseudoxanthoma elasticum* were observed, such as hyper-extensile redundant skin folds in the neck, axilla, inguinal areas and abdomen. The skin biopsy showed swollen, clumped and fragmented elastic fibres and calcium deposits in the deep and mid reticular dermis, consistent with *pseudoxanthoma elasticum*. This is a well recognised complication of sickle cell disease which has not been described in Kenya.**

### INTRODUCTION

Sickle cell haemoglobinopathy and *pseudoxanthoma elasticum* are both hereditary diseases. *pseudoxanthoma elasticum* (PXE) is a rare hereditary connective tissue disorder; characterised by generalised degeneration of the elastic fibers with a broad phenotypic expression. Its prevalence in the general population ranges between 1/70,000 and 1/160,000 (1). The age of onset is variable but averages 13 years. The clinical picture consists mainly of cutaneous, ocular, and vascular manifestations; skin histopathology reveals swollen, irregularly clumped and multiple fragmented elastic fibers in the middle and deep reticular dermis, with secondary calcium deposition (2).

The typical cutaneous lesions are small yellowish papules or larger coalescent plaques with an appearance similar to plucked chicken skin. More severely affected skin results in hanging redundant folds. Skin lesions develop mainly at areas of flexion, such as the neck, axillae, antecubital and popliteal fossae, inguinal areas and periumbilical region. Mucous membranes, mainly of the inner aspects of the lower lip may also be affected (1,2).

Angioid streaks are the characteristic ocular manifestations, occurring in 80% of patients with PXE (3). They are fundoscopic findings, caused by breaks of the elastic lamina of the Bruch membrane, with secondary changes of the retinal pigment epithelium and choriocapillaries. Angioid streaks

are initially seen during the third or fourth decade of life, usually later than the skin manifestations and occasionally without the typical cutaneous lesions. They appear as single or multiple, assymetrical, bilateral, dark, red, brown, or grey bands radiating from the optic disk (4).

Vascular manifestations in PXE are caused by degeneration of the elastic lamina of the arterial wall, often with calcium deposition. The gastrointestinal, cerebral, coronary, renal and extremity arteries are usually involved (5,6).

On the other hand, sickle cell anaemia is caused by a point mutation in the  $\beta$ -globin chain of haemoglobin, replacing the amino acid glutamic acid with the less polar amino acid valine at the sixth position of the  $\beta$ -chain. The association of two wild type  $\alpha$ -globin sub-units with two mutant  $\beta$ -globin subunits forms haemoglobin S, which polymerises under low oxygen conditions causing distortion of red blood cells and a tendency for them to lose their elasticity. The clinical manifestation and complications are due to this defect.

Erythrocytes are quite elastic, which allows the cells to deform to pass through capillaries. Often a cycle occurs because as the cells sickle, they cause a region of low oxygen concentration which causes more red blood cells to sickle. Repeated episodes of sickling causes loss of this elasticity and the cells fail to return to normal shape when oxygen concentration increases. This causes tissue hypoxia which causes

further sickling and the abnormal shaped erythrocytes are removed from circulation causing a haemolytic anaemia.

Therefore the natural history and complications include painful crisis, haemolytic crisis, sequestration crisis, aplastic crisis, priapism, gall stones, obstructive jaundice, stroke, osteomyelitis, auto-splenectomy, stunted growth and decreased life span.

A PXE-like syndrome with cutaneous, ocular and vascular manifestations has been described in patients with thalassaemia and sickle cell disease. It is an acquired condition and age-dependent with generally late onset in the second decade of life (7-9). Here a case of PXE in a sickle cell anaemia patient is reported.

### CASE REPORT

*History:* Patient JI was an 18 year old female, who at the age of two years manifested clinical features of sickle cell disease. She was followed up in haematology clinic of Kenyatta National Hospital (KNH).

She was readmitted to KNH on 16<sup>th</sup> March 2006, with complaints of left knee and back pain, yellowless of the eyes, chills, vomiting for five days, epistaxis and bleeding gums for one day on 16<sup>th</sup> March 2006. The knee pain was not associated with joint swelling. The stools were dark brown and urine dark yellow in colour. There was no pruritus initially but developed one week after admission. She had postprandial vomiting, but no epigastric nor right upper quadrant pain.

There was no history of haematemesis nor melena stools. No history of recent travel out of Nairobi. There was no visual disturbance and no history suggestive of intermittent claudication nor of angina pectoris. She had two previous admissions in KNH Paediatric ward in 1995 and subsequently in painful crisis related to the SCD, some of them with bleeding tendencies at the rate of 0 to 1 per year. She had been transfused about 12 units of blood and was on folic acid supplements with no known drug allergy.

She was first referred to KNH Paediatric dermatology clinic at nine years of age when during an admission an erythematous skin lesions confined to the neck, abdomen and few areas on the arms was observed. A dermatological opinion which was sought revealed a diagnosis of non-specific cutaneous syndrome. She has not yet attained menarche.

She is first born among two siblings from different fathers. Her mother who was a single parent died of malaria in 1993. She lived with her maternal grandfather and aunt in the suburbs of Nairobi. She left school in class eight due to lack of fees. Her sibling was 16 years and had already attained menarche.

There is no other family member with SCD, chronic liver disease or dermatological condition.

*Examination:* She was sick looking young girl, febrile with a temperature of 37.8°C, deep jaundiced, moderately dehydrated, pale but no lymphadenopathy, nor oral ulcers. She had good dental hygiene and dentition. Her pulse rate was 96b/min regular, normal character, respiratory rate of 18/min, BP-130/90mmHg. Her body weight was 39kg, height 1.64m, with body mass index of 14.5kg/m<sup>2</sup> (severely underweight). There was no bossing of the skull nor malar prominence. Her skin had multiple papules 1mm-4mm in diameter, a few coalesced to form plaques, all round the neck, axilla and groin. The skin was lax and redundant in the neck, axilla, anterior abdominal wall and groin. The surface was rough. There was no petechiae nor ecchymosis (Figures 1 and 2).

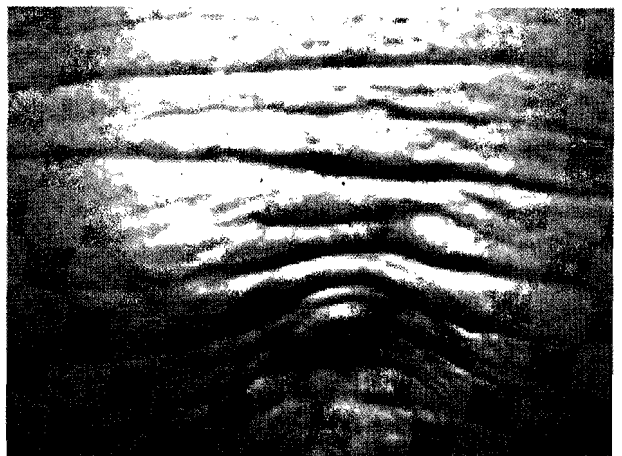
**Figure 1**

*Redundant skin over the neck*



**Figure 2**

*Redundant skin with prominent skin folds over the anterior abdominal wall*



The visual acuity was 6/6 bilaterally with comma shaped capillaries on bulbar conjunctiva and sludge phenomenon. On fundoscopy the Cup-disc ratio 0.3 both eyes. There was dull macula reflex with granular appearance (peau d'orange) in both eyes. There was no angioid streaks, nor neovascularisation.

The liver span was 14cm, extending 4cm below the costal margin. It was smooth and Murphy's sign was negative. The spleen was not palpable. The apex beat was not displaced and the rest of the cardiac examination was normal. There were no carotid bruits. The ankle-brachial index was 0.96 bilaterally. The rest of the examination was normal except for the secondary sexual characteristics which were grossly abnormal:-

- axillary hair - None
- pubic hair - Tanner I (None)
- breasts - Tanner IV

The working diagnoses were sepsis, painful crisis and bleeding disorder in a sickler with clinical features of *pseudoxanthoma elasticum*. She was investigated along these lines.

*Investigations:* Hb ranged between 6.8 to 8.9 gm/l, normochromic normocytic. The WBC was 15,000/cumm with 87% neutrophils. The platelet count was normal. A septic screen and blood slides for malaria parasites were negative. An activated prothrombin time, and prothrombin time index [108%, INR0.93] were normal. Total bilirubin 45.5, umol/l (direct 19.0) AST 80.8, ALT 31.6, ALP 610.2 u.l, total protein 83.3g/l albumin 51.2g/l. BUN, creatinine, electrolytes were normal. Uric acid was 770umol/l. urinalysis was normal. Elisa for Human Immunodeficiency Virus, hepatitis B and hepatitis C viruses were all negative. Screening serology for syphilis was also negative. Haemoglobin electrophoresis revealed HbSS.

Abdominal ultrasound scan showed a large liver; no dilated ducts seen, no spleen, innumerable minute mobile gall bladder calculi. Murphy's sign negative; enlarged hyper-reflective kidneys. Carotid doppler revealed normal doppler waveforms and diameters. The liver biopsy revealed features of hepatitis - periportal and lobular; no dilated bile ducts. The skin biopsy showed swollen, clumped and fragmented elastic fibres and calcium deposits in the deep and mid reticular dermis which were consist with *pseudoxanthoma elasticum*.

*Treatment:* She was put on intravenous ceftriaxone 1 gm o.d, paracetamol 1 gm t.d.s folic acid 5 mg o.d.

and was transfused two units of blood. She did not require phytomenadione. Her fever and bleeding resolved and she was discharged home after a week.

Her visits to haematology clinic were few and far between and she did not meet the criteria to warrant hydroxyurea which is standard practice at Kenyatta National Hospital, where all patients who meet the criteria are given hydroxyurea. It is also standard practice to give them pneumococcal and hepatitis B vaccinations but because of her poor compliance she had missed these. However this shortcoming has since been corrected.

## DISCUSSION

The first manifestation of a potential elastic tissue defect in haemoglobinopathies described was angioid streaks. These were first described in the 1950s by Paton, Geeraets and Guerry in sickle cell disease (8,19). Since then there has been many papers published on this association. The first report of extensive diffuse connective tissue disorder, of the pseudoxanthoma type was by Lippman *et al* in 1985. They described seven sicklers with extensive connective tissue disorder including mitral valve prolapse (9). It has also been described in thalassemia major (7,20).

This is the first report of PXE-like syndrome in Kenya with classical skin manifestations with a positive skin biopsy. Although it is possible that the two may occur coincidentally this is unlikely because of the late presentation and the time correlation between the progression of her sickle cell disease and gradual changes seen in the skin as documented in the file. The skin changes were initially non-specific but later became classical, hence the late diagnosis. She had also the bleeding disorder associated with this syndrome. The bleeding was not due to liver disease because the relevant coagulation test was normal and her serum albumin was also normal.

This was a complication of long standing sickle cell disease as she manifested many other late complications such as the delayed development of secondary sexual characteristics. Hepatitis is also a known complication of pseudoxanthoma (2). *Pseudoxanthoma elasticum* unconnected with a haemoglobinopathy had not been described in Kenya. In  $\beta$ -thalassemia and SCD, it is believed that the elastic tissue abnormalities are acquired, despite their clinical, structural and cytochemical resemblance to inherited PXE.

It is not known how this syndrome develops in haemoglobinopathies. Several theories have been put forward to explain the development of this

complication. Elastic tissue injury in these patients may be the result of an oxidative process; induced by the combined and interactive effect of different factors. Plasma membrane micro-particles, derived from the oxidative damage of red cell membrane by the effect of denatured haemoglobin products and free iron are considered to elicit inflammatory and oxidative reactions (10-13). The unbound fractions of haemoglobin and haem, which exceed the binding capacity of haptoglobin and haemopexin in context of chronic haemolysis, also have powerful oxidative properties (14). In sickling syndromes, an excessive free radical production follows the post-occlusive tissue reperfusion (14). Iron overload has a central role in multiple organ injury in these haemoglobinopathies. Unbound iron catalyses the formation of the most toxic hydroxyl radical through the Fenton and Haber-Weiss reactions, causing peroxidation of membrane lipids and proteins (15). The accumulated and prolonged effects of the above mechanisms may result in disturbance of elastin metabolism and structural deterioration of elastic fibres (15). Indirect evidence of increased and prolonged tissue injury in thalassaemic and sickle patients includes activation of polymorphonuclear neutrophils and monocytes and the increased levels of neutrophil elastase and circulating cytokines (16-18).

The aim of this publication is to draw clinicians' attention to severe oxidative stress in sickle cell disease which can cause a different set of complications other than the common complications due to sickling.

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