

# Fabry disease: a case report

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### ABSTRACT

*Fabry disease is a rare X-linked recessive inborn error of metabolism due to deficient activity of the lysosomal enzyme,  $\alpha$ -galactosidase A ( $\alpha$ -Gal A). This results in the tissue accumulation of uncleaved glycosphingolipids within vascular endothelial lysosomes of various organs including skin, heart, kidneys and brain. We report a case of Fabry disease, in an 18-year-old boy, who presented with unilateral leg swelling and angiokeratoma corporis diffusum.*

**Key words:** Fabry disease, angiokeratoma corporis diffusum,  $\alpha$ -galactosidase A activity.

(*BIRDEM Med J* 2021; 11(2): 145-147)

### INTRODUCTION

Fabry disease is a rare X-linked genetic disorder characterized by decreased levels of the  $\alpha$ -galactosidase A enzyme.<sup>1</sup> Deficiency of the enzyme may be partial or complete. As a result of this enzyme deficiency, neutral sphingolipids with terminal  $\alpha$ -galactosyl residues [predominantly globotriaosylceramide (Gb3)]

accumulate in the lysosomes of different tissues and fluids - epithelial cells of glomeruli and tubules of the kidneys, cardiac myocytes, ganglion cells of the autonomic system, cornea, endothelial, perithelial and smooth muscle cells of blood vessels and histiocytic and reticular cells of connective tissue.<sup>2</sup> Males are primarily affected, while females are carriers who may show clinical manifestation.<sup>3</sup>

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**Received:** January 1, 2021

**Revision received:** February 15, 2021

**Accepted:** February 28, 2021

Clinical manifestations are angiokeratoma corporis diffusum, dyshidrosis, lower limb edema, lymphedema, Raynaud's phenomenon, pseudoacromegalis facies, corneal and lenticular opacities, sensorineural hearing loss, acroparesthesia, hypertension, proteinuria, left ventricular hypertrophy, defects in heart valves, arrhythmia, stroke, anaemia, hypothyroidism, osteopenia etc.<sup>2</sup> Diagnosis can be established by skin histology or slit lamp examination of the cornea. In males,  $\alpha$  galactosidase A deficiency in plasma, leukocytes or cultured skin fibroblasts is confirmatory. In women, molecular analysis should be done as enzyme activity is often normal. Both symptomatic and specific treatments are needed.<sup>2</sup>

We report a case of Fabry disease presenting with some unusual findings like lymphadenopathy and splenomegaly along with classical features.

### CASE REPORT

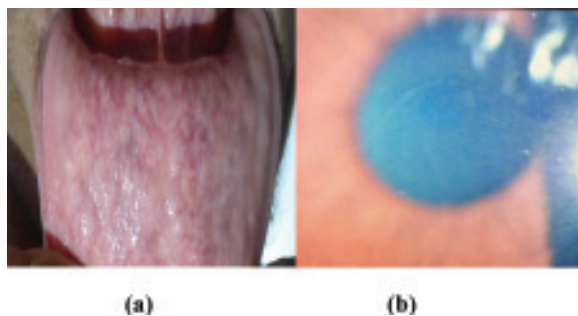
An 18-year-old cotton mill worker, admitted for evaluation of swelling of left leg for 14 days. Swelling extended from mid-calf to downward, aggravated on

walking or standing, partially relieved by taking rest in lying posture. He gave history of recurrent bilateral leg swelling following prolong standing or journey for last 3 years, reduced sweating since childhood and intermittent episodes of pain in the extremities following exertion (acroparesthesia). He also had numerous papules over different parts of the body for 3-4 years. He was the first child of non-consanguineous parents. No member in his family had such type of illness.

He had “pseudoacromegalic face” evidenced by periorbital fullness, bushy eyebrows, bulbous nasal tip, broad alar base, prominent supraorbital ridges and full lips. He was mildly anaemic. Left sided pedal oedema was present. Anterior tibial and arteria dorsalis pedis arterial pulses were feeble bilaterally. He had bilateral inguinal lymphadenopathy which were discrete, firm, mobile and non-tender. There were dark-red to blue-black papules (pin point to <4 mm in size) over mucosal surface of lower lip, back, lower abdomen, inner thighs, scrotum and penis which were painless, occasionally pruritic, did not blanch on pressure and with variable



**Figure 1** Angiokeratomas over (a) lower back and (b) scrotum

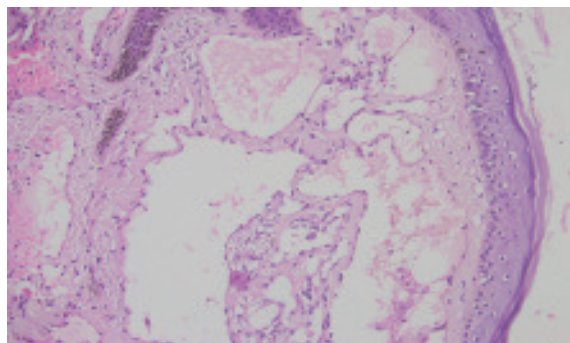


**Figure 2** (a) Angiokeratomas over mucosal surface of lower lip (b) Whorlkeratopathy of left eye

overlying hyperkeratosis. Ophthalmological evaluation revealed “Vortex/whorl keratopathy”.

Routine hematological tests were normal except haemoglobin was 11.3 gm/dl. Blood film showed microcytic hypochromic anaemia. There was no proteinuria. There was good bi-ventricular systolic function (left ventricular ejection fraction – 65%) with mild tricuspid regurgitation and mild pulmonary hypertension (pulmonary artery systolic pressure 40 mm Hg) on Echocardiogram. Ultrasonography of whole abdomen revealed splenomegaly (12.1 cm). Colour Doppler study of lower limb vessels showed chronic venous insufficiency and mild reduction of blood flow in anterior tibial and dorsalis paedis of both lower limbs.

Skin biopsy of a papule from lower back showed many dilated thin walled capillaries in the papillary dermis that is the classical feature of angiokeratoma.



**Figure 3** Angiokeratoma showing many dilated thin walled capillaries in the papillary dermis (200×)

The diagnosis was confirmed by very low level of  $\alpha$ -galactosidase A enzyme in serum (2.40 nmol/hr/mg). He was treated in order to manage chronic venous insufficiency.

## DISCUSSION

Fabry disease or Anderson-Fabry disease is the second most common glycosphingolipid storage disorder (after Gaucher disease) with birth frequency of 1 in 1,00,000.<sup>4</sup> German dermatologist, Johannes Fabry and English dermatologist, William Anderson, independently described the first patients with Fabry disease in 1898.<sup>5</sup>

It has X-linked recessive inheritance. The disease manifests primarily in affected hemizygous men but heterozygous women (carriers) also may be severely affected. Accumulation of glycosphingolipids in

different tissues due to deficient  $\alpha$ -galactosidase A activity is the cause of clinical manifestations. The genetic cause is a mutation in the *GLA* gene (encoding  $\alpha$ -galactosidase A), most often point mutations but occasionally small and large deletions or insertions.<sup>6</sup>

Angiokeratoma corporis diffusum and acral pain are the earliest features. Dyshidrosis, anemia, pseudo-acromegalic face, lower limb edema, corneal opacity are also common. Cardiac, renal and neurological involvements are the main causes of mortality.<sup>2</sup>

Along with typical features this patient also had chronic venous insufficiency, splenomegaly and lymphadenopathy. Combination of reduced vascular compliance and pro-thrombotic factors activation can result in vascular complications in Fabry disease like the reported patient.<sup>7</sup> Sinusoidal endothelial involvement resulting in compromise of splenic blood flow may be the cause of congestive splenomegaly.<sup>8</sup> Clinically detectable lymphadenopathy is unusual but may be seen due to glycosphingolipid deposition.<sup>9</sup>

Biopsy of angiokeratoma shows dilated capillary in upper dermis. Elongated brown lamellar bodies in endothelial cells are seen under high power and in polarized light these lipid granules were birefringent. Electron microscopy shows multiple abnormal lysosomes containing lamellated whorled inclusions (Zebra bodies) in endothelial cells.  $\alpha$  galactosidase A level plasma, leukocytes or cultured skin fibroblasts and molecular analysis is confirmatory in men and women respectively. Prenatal diagnosis can be made by demonstrating deficient  $\alpha$ -galactosidase A activity and an XY karyotype, by haplotype linkage analysis, and/or most accurately by demonstration of the specific  $\alpha$ -galactosidase A mutation in chorionic villi or cultured amniotic cells.<sup>5</sup>

Fabry disease is a multisystem disorder and patients need multi-disciplinary approach. Though specific treatment is enzyme replacement therapy (ERT), all symptoms cannot be cleared by it.<sup>2</sup> So, symptomatic treatment is also necessary. Chaperone-based enzyme enhancement therapy can be administered in patients with residual enzyme activity.<sup>10</sup> Genetic counselling is recommended in suspected cases with a family history of Fabry disease and those identified as female carriers of Fabry disease.<sup>11</sup>

**Authors' contribution:** AA, NS, NJP, MY, MAKA managed the case and were involved in preparation of the manuscript. MRR contributed to ophthalmological findings. ATMA contributed to dermatological parts. All authors read and approved the final version for submission.

**Conflict of Interest:** Nothing to declare.

**Consent:** Written informed consent was taken from the patient for publication of his case report along with all the images.

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