CASE 1

Patient: A 24-year-old Thai male from Bangkok

Chief Complaint: Multiple discrete dark-red tiny papules on scrotum and upper thighs for 4 years

Present Illness: The patient presented with burning sensation on both palms and soles since he was 13 years old. This symptom always coexists with the redness and aggravated by fever, hot temperature and exercise. Seven years later he had noticed some dark-red papules on the scrotum with minimal itch Subsequently, the similar lesions had developed on the back, both thighs, knees, and hands. He also had dypsnea when he walked upstairs without other systemic symptoms.

Family History: No other family members developed similar lesions

Personal History: Smoking 1 pack/day for 9 years and social alcoholic drinking

Physical Examination

GA : A Thai man, not pale no jaundice
V/S : BT 37.4 C, BP 110/70 mmHg, PR 80 bpm, RR 16 bpm
Eye examination : Pending
CVS : PMI at 5th ICS MCL, normal S1 S2, no murmur
RS: Clear
Abd : Soft, no hepatosplenomegaly
Ext : No pitting edema
N/S : Normal pinprick sensation test
Other neurological sign was intact
LN: No lymphadenopathy

Dermatological Examination (Figure 1.1-1.3)**:** Multiple discrete non-blanchable dark-red to purplish tiny papules on scrotum, back, both thighs, knees, and hands varying in size 1-3 mm.

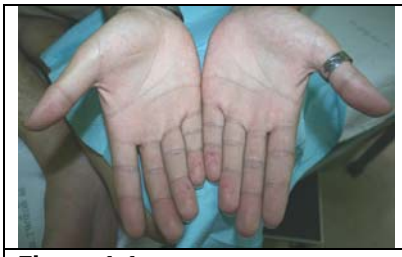

Figure 1.1

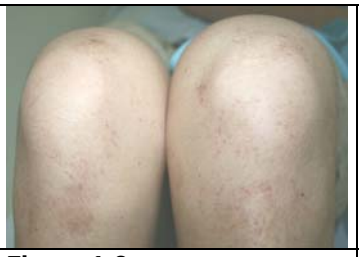

Figure 1.2

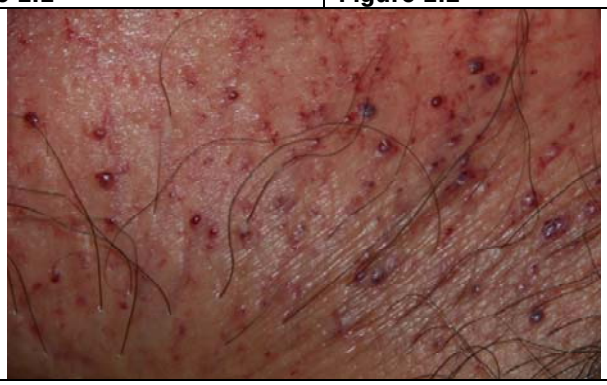

Figure 1.3

Investigations

CBC: WBC 5,660cell/mm3 Hb 14g/dL Hct 42.6%
Plt 306,000cell/mm3
(N 54% L 33% Mo 7% Eo 5% Ba 1%)
BUN 15mg/dL Cr 0.8mg/dL
LFT: AST 14U/L ALT 41U/L ALP 75U/L GGT 41U/L,
TP 72.8 g/L Alb 44.3g/L
UA: Negative protein and glucose, no cellular cast
CXR: Normal
EKG: LVH

2D Echocardiogram: MVP, EF 70%
US kidney: Bilateral hyperechogenicity,
α-galactosidase A activity : Pending
Genomic DNA: Missense, L166R mutation of GLA gene

Histopathology (S10-8825) (Figure 1.4): Ectatic blood filled capillaries in the papillary dermis with overlying epidermal atrophy

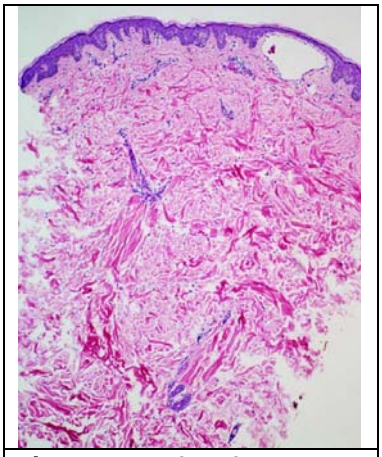

Figure 1.4, H&E 40x

Diagnosis: Fabry disease

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Discussion:

Fabry disease is a rare X-linked recessive metabolic disorder caused by the partial or complete deficiency of a lysosomal enzyme, α-galactosidase A. As a result, neutral sphingolipids predominantly globotriaosylceramide (Gb3) are accumulated in the lysosomes of various tissues including 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.[1]

Fabry is the severe multisystemic disease. The earliest manifestations often start in childhood with episodes of extremity pain often brought about by change of environmental or body temperature, strenuous exercise or stress, fever of unknown origin and hypohidrosis. More specific disease manifestations that are usually present in late adolescence are typical vascular skin lesions termed angiokeratoma and asymptomatic cornea verticillata.

The characteristic skin findings in AK are dark-red to blue-black telangiectatic papules, up to 4 mm. in the superficial layers of the skin, do not blanch with pressure and often show verrucous surface. A cluster of lesions tends to occur on the thighs, scrotum, around umbilicus, the hip, the knees and buttocks in the "bathing trunk area"

However, the importance of Fabry disease lies in the progressive renal and cardiac deterioration as well as a high propensity to develop ischemic stroke. The kidney involvement is the most common cause of death, usually associated with progressive proteinuria following a decline in glomerular filtration rate,and leading to end-stage renal disease around the third to fifth decade.[2]

Fabry disease should be suspected in patients with specific diagnostic signs such as angiokeratoma or vascular ectasia on the buccal or conjunctival mucosa. However, other differential diagnosis should be considered as shown in the Table 1.[1]

A presumed diagnosis of Fabry disease must be confirmed by the finding of low α-galactosidase A activity on peripheral blood white cells or cultured skin fibroblasts. [1]

NAME	ENZYME DEFICIENCY	GENE	CLINICAL FINDINGS	DERMATOLOGIC FINDINGS
Sphingolipidoses				
Fabry	α-Galactosidase A	Xq22	Acroparesthesias, heart and renal failure , stroke, cornea verticillata	Angiokeratoma corporis diffusum, telangiectasias,hypo/anhidrosis, lymphedema
GM1 gangliosidosis	β-Galactosidase	3p21-3pter	Facial dysmorphism, hematologic signs, mental retardation, organomegaly	Angiokeratoma corporis diffusum
Glycoproteinoses				
Aspartylglucosaminuria	Aspartylglycosaminidae	4q32-33	Coarse facies, macroglossia, organomegaly, ocular findings, cardiac valve involvement	Angiokeratoma corporis diffusum, facial angiofibromas, oral fibromatosis and leukokeratosis
Fucosidosis	α-Fucosidase	1p34	Mental retardation, coarse facies, growth retardation, recurrent respiratory infections, dysostosis multiplex, visceromegaly	Angiokeratoma corporis diffusum, widespread telangiectasias, acrocyanosis, purple transverse distal nail bands, increased vasculature in hands and feet, sweating abnormalities

NAME	ENZYME DEFICIENCY	GENE	CLINICAL FINDINGS	DERMATOLOGIC FINDINGS
β-Mannosidosis	β-Mannosidase	4q22-q25	Mental retardation, neuropathy, hearing loss, recurrent infections	Angiokeratoma corporis diffusum in bathing trunk area
Sialidosis II	Neuraminidase	6p21.3	Mental retardation, dysostosis multiplex, vacuolated lymphocytes, subtle coarse facial features	Angiokeratoma corporis diffusum
Multiple enzyme deficiency				
Galactosialidosis	β-Galactosidase and neuraminidase	20q13.1	Dwarfism, gargoyle facies, mental retardation, seizures, corneal clouding, dysostosis multiplex, and hearing loss	Angiokeratoma corporis diffusum scattered along entire body, especially knees, elbows, and bathing trunk area
Kanzaki	α-N-acetylgalacto saminidase (αNacetylgalacto saminidase)	22q11	Mental retardation, coarse facial features, ocular signs, hearing loss, neuropathy	Angiokeratoma corporis diffusum of entire body, more dense on the bathing trunk area, axillae, and breasts Telangiectasias on lips and oral mucosa

Specific therapy for Fabry disease has been developed in the last few years, enzyme replacement therapy (ERT) is the first specific therapy for Fabry disease. Two forms of α-galactosidase A for ERT exist. These are agalsidase alfa and agalsidase beta. Both are approved in Europe and many other countries, but in the US the FDA approved only agalsidase beta.[3] Oral enhancing-enzyme therapy(chaperones) are being developed in trials, but are not available in clinical use.[4]

Fortunately, standard 'non-specific' medical and surgical therapy is effective in slowing deterioration or compensating for organ failure in Fabry patients. Effective anti-platelet agents such as clopidogrel and aspirin/ long acting dipyridamole should be used to prevent strokes in all patients. The kidney dysfunctionresponds well to angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB). Renal transplantation is as effective in end-stage renal disease. The neuropathic pain is often treated with relatively low doses of anti-epileptic medication such as carbamazepine, neurontin andlamotrigine. Non-steroidal anti-inflammatory drugs are less effective and narcotics are effective but usually avoided.[5,6]

In this case, the diagnosis was confirmed by both decreasedα-galactosidase A activity and GAL gene mutation. Carbamazepine was prescribed for acroparesthesia , ASA to prevent stroke. Renal function test and urine analysis were followed to detect early kidney dysfunction. Specific enzyme therapy is recommended. Unfortunately, it is not available in Thailand. Smoking and alcohol cessation with genetic couselling were advised.

References

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6. Schiffmann R. Fabry disease. Pharmacology & Therapeutics 2009;122:65–77.