CASE 2

Patient: A 5-year-old Thai girl from Nakhon Sawan Province

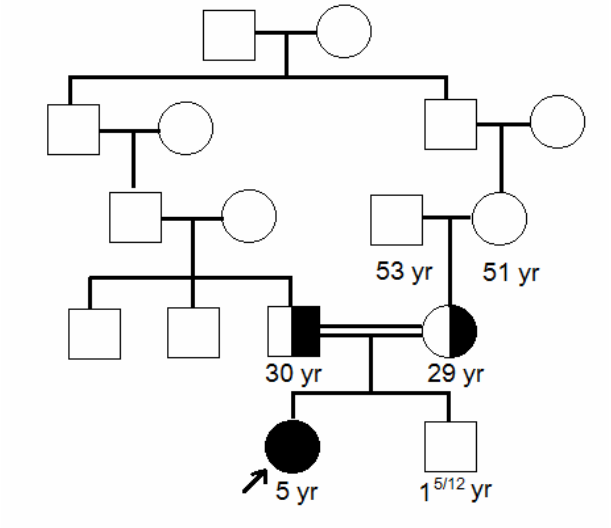
Chief Complaint: Skin lesion at extremities since the age of 2

Present Illness: Since she was 2 years old, her parents started to notice several itchy yellowish papules along both ankles. Skin lesions gradually increased in number and size, involving her elbows, dorsum of hands, thighs and buttocks

Past History: She was born to healthy consanguineous parents from termed and normal pregnancy.

Personal History: Her growth and development are normal, no medication was taken on regular bases.

Family history: Both of her parents had hypercholesterolemia**.** Her grandmother had hypertension at age of 40. None of her family member has similar skin lesion.



Dermatological Examination (Figure 2.1-6)**:** Numerous, discrete and confluent, yellowish to orange, papules and nodules, varying in diameter from 4 mm to 25 mm, located on knuckles, elbows, thighs, knees, ankles and Achilles tendon. There are yellowish, coalescing plaques at buttock and ankles.

Figure 2.1

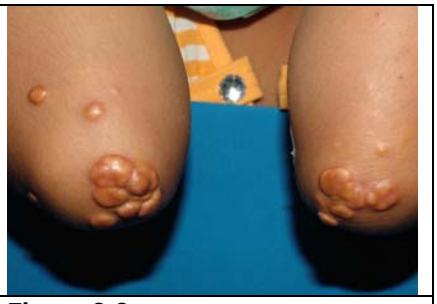


Figure 2.2

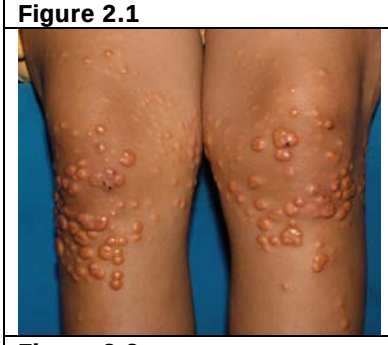


Figure 2.3

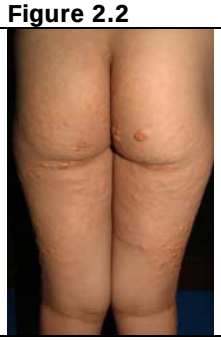


Figure 2.4

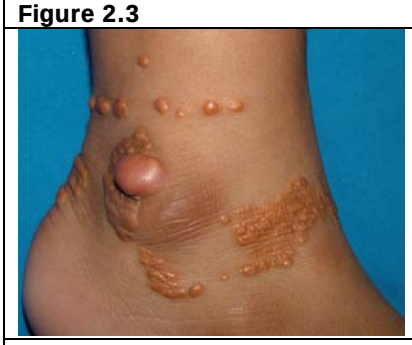


Figure 2.5

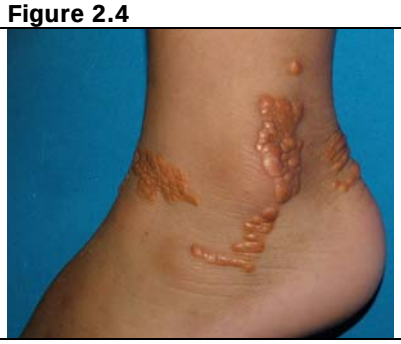


Figure 2.6

Physical Examination: Normal cornea and skin of the eyelids.
Normal cardiovascular system on examination.
No hepatosplenomegaly.

Investigations:

Serum lipid (mg/dL)	Patient	Father	Mother
Chol	910	362	297
LDL	871	297.9	226.2
HDL	18	46.1	60
Trig	106	89.8	54

FBS: 72 mg/dl,
LFT: ALP 287 U/L, GGT15 U/L, AST 28 U/L, ALT 24 U/L,
TP 77 g/L, Alb 37.6 g/L, TB 0.3 mg/dL, DB 0.1 mg/dL
CBC: Hct 32.7% MCV 67.2 fL,
WBC 12,0000 /uL (N 41%,L 48%), plt 395,000 /uL
Echocardiogram: Normal LV systolic and diastolic function, normal coronary arteries, otherwise normal.
Serum for LDL receptor gene analysis: pending result

Histopathology (S09-19736) (Figure 2.7-8): Diffuse infiltrate of uniform xanthoma cells with small central nuclei and pale abundant foamy cytoplasm

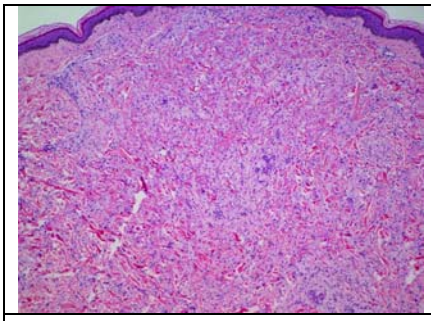


Figure 2.7, H&E 40x

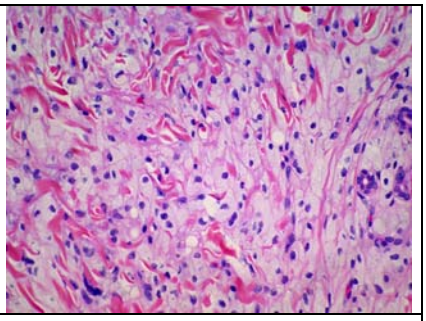


Figure 2.8, H&E 200x

Diagnosis: Familial homozygous hypercholesterolemia with tendinous, tuberous, and intertriginous xanthomas

Treatment: Dietary modificaiton, cholestyramine 4g after 3 meals, genetics, pediatric endocrinology and nutrition consultation

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Discussion:

Xanthomas are a tumor-like proliferation of lipid-laden foam cells occurring most frequently in patients with disorders of lipid storage and lipid metabolism. Xanthomas develop because of lipid leakage from the vasculature into the surrounding tissues, where macrophages subsequently

phagocytize these lipids. They can also develop secondary to systemic diseases such as hypothyroidism, obesity, biliary cirrhosis, cholestasis, diabetes mellitus, nephrotic syndrome, monoclonal gammopathy, and drug therapy with retinoids, estrogen and protease inhibitors.[1-2] Frederickson et al. classified primary hyperlipoproteinemias into five major types (types I–V).[3]

Familial hypercholesterolemia (FH) or Frederickson Type II hyperlipidemia is an autosomal codominant disorder caused by >750 mutations in the LDL receptor gene.[4] Elevation plasma LDL-C due to delayed catabolism of LDL from the blood with normal triglycerides, severe xanthomatosis, corneal arcus and premature atherosclerotic vascular event are markers of this condition.

Homozygous FH is a rare disease occurring in approximately 1 in 1,000,000 persons. This condition characterized by extremely high cholesterol levels, multiple types of xanthoma formation. Tendinous xanthomas are the most common type, follow by xanthelasma, tuberous and subperiosteal xanthomas.[1] Symptomatic coronary artery disease

is noted in early childhood. The diagnosis of homozygous familial hypercholesterolemia is usually based on the presence of: a) Untreated serum LDL cholesterol level > 400 mg%; (b) appearance of xanthomas in the first decade of life; (c) documentation in both parents of hypercholesterolemia or clinical features of the heterozygous state; (d) confirmation by DNA analysis for LDL receptor gene mutations; and (e) intertriginous xanthomas have been described as occurring characteristically in this subtype.[5-6]

Severity and prognosis of homozygous FH can be classified due to amount of LDL receptor activity: those with <2% of normal activity (receptor negative) and those with 2-25% of normal activity (receptor defective). Untreated, receptor-negative patients rarely survive beyond the second decade, while patients with receptor defective have a better prognosis but almost invariably develop clinically apparent atherosclerotic vascular disease by age 30.[4]

Heterozygous FH is caused by the inheritance of one mutant LDL receptor allele and occur in 1 in 500 persons, making it one of the most common single-gene disorders. Patients have two to three fold elevations in LDL-C (200-400 mg/dL) and normal triglyceride. The clinical hallmark is 1)the presence of tendon xanthomas during the third to sixth decades and 2) development of premature and extensive atherosclerosis leading to coronary artery heart disease.[7] The age of atherosclerotic cardiovascular disease is highly variable depending on defect in LDL receptor gene and coexisting risk factor. Untreated men have a 50% chance of having myocardial infarction before age 60.[4]

Apart from LDL-receptor mutations, familial defective apolipoprotein B-100 (FDB), autosomal recessive hypercholesterolemia (ARH), and phytosterolemia can result in

phenotypes similar to that of FH.[8] FDB caused by mutations within the gene encoding apo B100, the LDL receptor cofactor. Mutant apo B100 proteins have a reduced affinity for the LDL receptor. Patients tend to have lower cholesterol levels than those with FH, but they still have a high risk of developing premature atherosclerosis. ARH is caused by mutations in the phosphotyrosine binding domain of a putative adaptor protein, which prevents normal internalization of the LDL receptors in the liver. The clinical phenotype of ARH is similar to that of homozygous FH but is more variable and less severe. The parents of the affected patients have normal lipid levels.[8] Phytosterolemia results from excessive absorption of plant sterols from enterocytes and reduced biliary excretion. These patients develop xanthomas but the LDL cholesterol level remains unaltered.

The diagnosis of homozygous FH has traditionally been achieved by clinical evaluation. Our patient was born from consanguineous parents who are possibly heterogenous FH indicated by their approximately two folds elevation of serum LDL-C with normal triglyceride. She developed severely elevated LDL-C and multiple types of xanthomas, including pathognomonic, intertriginous xanthomas in early childhood. To confirm diagnosis, LDL receptor gene analysis was performed. Moreover,this could predict the prognosis and dictate treatment.

Dietary modification, drug therapy with statin in combination with bile acid sequestrant may results in reduction in plasma LDL-C in heterozygous FH, but are less efficacious in homozygous FH, especially those with profound deficit in functional hepatic LDL receptors.[9] Probucol, drugs that has both lipid-lowering and antioxidant effect, can lower cholesterol level in patient with homozygous FH, presumably through

mechanism independent of LDL receptors.[10] Ezetimibe, a selective inhibitor of dietary and billiary cholesterol absorption, has been shown to reduce LDL-C by 20% in children with homozygous FH.[11] Other treatment options for unresponsive patients are liver transplantation or LDL aphresis.[7]

In addition to treat FH patient, it is crucial to give complete genetic counseling and to establish the diagnosis in other family members. Early diagnosis and prompt treatment may prevent premature atherosclerotic vascular disease. Our patient's younger brother has 50% and 25% risk of having heterozygous and homozygous FH respectively. His serum lipid profiles are pending for results.

References

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