Case 6
A 69 year-old Thai male from Bangkok
Chief complaint: Asymptomatic multiple yellowish flat-topped papules on neck, axillae and abdomen since childhood.

Present illness: The patient had noticed stable asymptomatic multiple yellowish flat-topped papules distributed on the neck, axillae and abdomen since childhood. He could not remember the initial location of the lesions.

Past history: His left eye had progressive loss of vision for 1 year. He had intermittent claudication for 5 years. He denied history of chest pain, hematuria, hematochezia and melena.

Underlying disease: Hypertension, dyslipidemia, old multiple lacunar infarctions with full recovery, benign prostatic hyperplasia, Parkinson's disease and congenital right eye blindness.

Family history: There is no similar cutaneous lesion or premature atherosclerotic cardiovascular disease in family member.

Skin examination: Multiple yellowish, flat-topped, discrete, and confluent papules in the skin creases of the sides and nape of the neck, both axillae, periumbilical area and inner aspect of the lower lip

Physical examination:
GA: alert, good consciousness, no pitting edema
HEENT: not pale conjunctivae, anicteric sclerae, right eye: blindness (since birth), left eye: VA $20/30^{-2}$ ($20/25^{-1}$ with pinhole)

Fundoscopic examination: angioid streak, choroidal neovascularization with subretinal hemorrhage at left optic disc

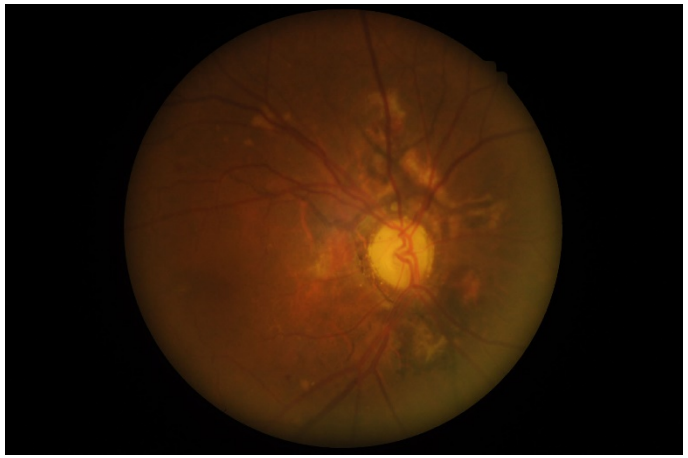

Fig 6.1. Angioid streak

CVS: peripheral pulse full 2+ all, normal s1, s2, no murmur
Abdomen: soft, not tender, normoactive bowel sound, liver and spleen can't be palpated
Neurology: grossly intact, motor power V/V all extremities

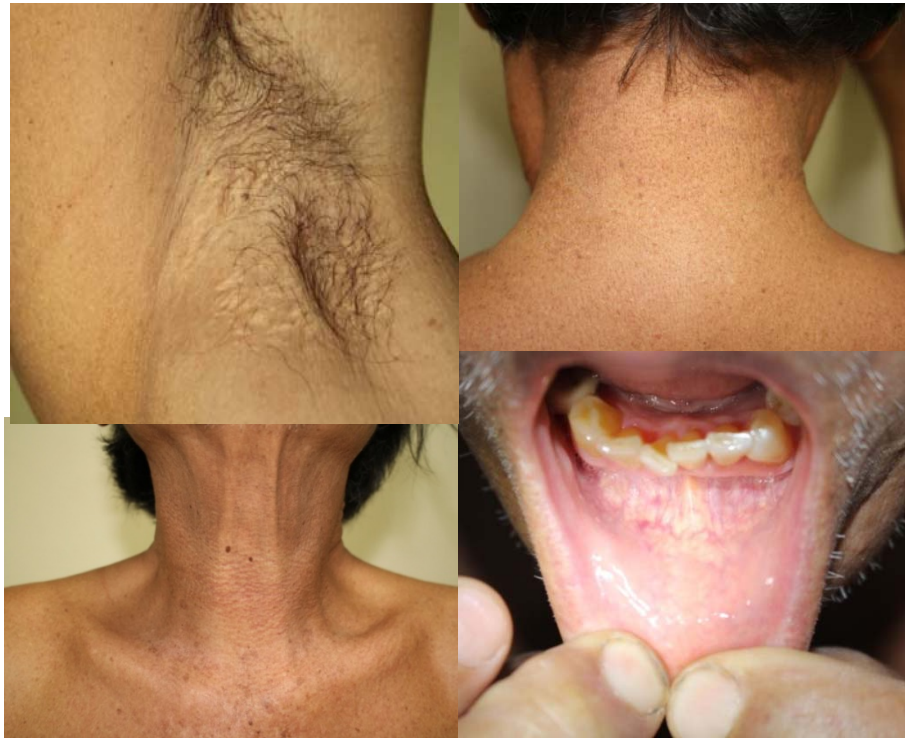

Fig 6.2 Skin lesion

Lab investigation:
CBC: WBC 7530/cumm, N 58 %, L 33%, M 7%, Eo 1%, B 1%, platelet 225,000/cumm, Hb 13 g/dL Hct 40%
UA: WNL
Stool occult blood: negative
BUN 14 mg/dL, Cr 0.81 mg/dL
Ca: 8.9 mmol/L

Histopathology: (S16-21834A, infraumbilical area)

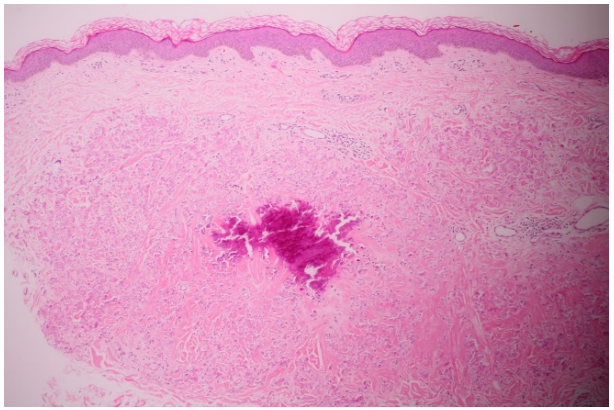

Fig. 6.3 H&E

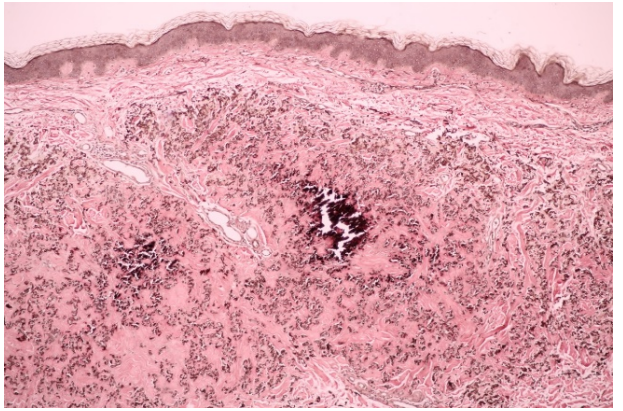

Fig 6.4 Von Kossa

- Multiple deep basophilic to purplish fragmented elastic fibers surrounded by thick homogenized collagen in the dermis.

Diagnosis: Pseudoxanthoma elasticum

Treatment:

- Genetic counseling
- Cardiology consult for evaluation of cardiovascular function and intermittent claudication
- Intravitreal injection of bevacizumab to the left eye
- Lifestyle modifications: Avoidance of high cholesterol foods, smoking cessation and unthreatened aerobic exercise

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Discussion:

Pseudoxanthoma elasticum (PXE) is a type of rare hereditary disease that affects connective tissue, causing mineralization of elastic fibers in the skin, eyes, cardiovascular system, as well as the digestive system.[1] Statistical analysis has indicated that the incidence of the disease is about one in 50,000.[2] The disease affects women more often than men at a ratio of 2:1. The main pathological changes in the skin are the degeneration, swelling, rupturing, and mineralization of elastic fibers.[3] The genetic defect has been mapped to the ABCC6 gene encoding an ATP-dependent transmembrane transporter on chromosome 16p13.1.[4,5,6] Autosomal dominant and autosomal recessive patterns of inheritance have been described, but recent molecular genetic studies show only evidence for a recessive inheritance pattern.[4]

Skin manifestations are the most prevalent characteristic of PXE and they are generally the first physical signs of the developing disorder.[6] The characteristic cutaneous findings are small, yellowish papules coalescing into plaques, which present classically along the sides of the neck, giving rise to a "gooseflesh" or "plucked chicken skin" appearance. Other sites of predilection are the axillae, periumbilical area, groin, perineum, and thigh.[5,6,7] These skin lesions are usually noted in the second or third decade.[8] In older individuals the involved skin is lax and hangs in large folds.[9] Although not pathognomonic of PXE, the characteristic eye findings are angioid streaks, which result from the rupture of elastic laminae in the Bruch membrane of the retina. They are irregular, reddish-brown, or grey lines that radiate from the optic disc. The typical age of onset is between 15 and 25 years and they appear to be present in at least 85 percent of patients with PXE.[5,7] Although angioid streaks are asymptomatic at first, they become the sites of choroidal neovascularization and subretinal hemorrhages later in life; central vision loss may occur in the case of macular involvement.[8]

Generalized involvement of all large and medium sized arteries occurs. Eventually, manifestations of cardiovascular diseases develop and they result from the slow and progressive calcification of the elastic arterial walls. Reduction of vessel lumen causes ischemia; the excessive fragility of the vessel wall is responsible for hemorrhages.[8] Clinically, intermittent claudication is often the first sign of accelerated atherosclerosis and is the most common cardiovascular symptom, occurring in 30 percent of patients. Coronary artery disease and renovascular hypertension

may occur at a much younger age in PXE patients and can result in angina pectoris, myocardial infarction, congestive cardiac failure, renal failure, or stroke.[5,9]

The diagnosis of PXE is based on physical findings and histological examination of the affected skin. Histologically, fragmented calcified elastic fibers are seen in the mid and deep reticular dermis, by use of elastic stains (e.g., Verhoeff-van Gieson, Orcein, or Weigert) and stains for calcium deposits (e.g., von Kossa).[5] To facilitate and unify the clinical diagnosis of PXE, three major diagnostic criteria (characteristic skin involvement, characteristic histopathological features of lesional skin, and characteristic ocular disease) and two minor criteria (characteristic dermatopathological features in nonlesional skin and family history of PXE in first degree relatives) were defined at the Consensus Conference of 1992.[6]

A routine annual review of the cardiovascular and ophthalmological status of affected persons is imperative in order to treat early hypertension and other risk factors for cardiovascular disease, such as hypercholesterolemia, cigarette smoking, diabetes mellitus, obesity, and physical inactivity. This routine annual review is still imperative to avoid the sequelae of angioid streaks that extend into the macula of the eye.[7]

There is no standard treatment for PXE. If the appearance of the skin lesion becomes a cosmetic problem, plastic surgical excision has been used successfully.[4] Laser photocoagulation can prevent retinal hemorrhages and neovascularization.[7] To reduce the risk of bleeding, platelet inhibitors such as aspirin and non-steroidal anti-inflammatory drugs as well as warfarin should generally be avoided.[5]

Idiopathic hyperphosphatemia has been associated with PXE.[11,12] Excessive dietary intake of calcium should be avoided in childhood and adolescence. The reason for this is that a correlation between the severity of PXE and high calcium intake has been suggested.[13] Regression of an acquired form of the disease (periumbilical perforating PXE) occurred with hemodialysis that corrected metabolic imbalances secondary to end-stage renal disease.[14] Moreover, there is a report on a clinical, histopathological, and electron-microscopic regression of PXE after the imposition of a low-calcium diet.[15] In a small study of six patients treated with aluminum hydroxide, three patients showed a significant clinical improvement of their skin lesions. The three patients also showed a histopathological regression of the disease in their target lesions.[9] There is one case report of PXE treated successfully with tocopherol acetate and ascorbic acid.[10] Finally, in a case of dystrophic calcinosis cutis related to PXE, the use of oral phosphate binders was shown to be encouraging as a possible treatment option.[16]

Our patient was diagnosed with PXE due to characteristic features of skin involvement, histopathological findings (short and fragmented elastic fiber with some calcium deposition in the dermis) and angioid streaks. He underwent a complete eye examination. Choroidal neovascularization with subretinal hemorrhage at Lt. optic disc was found and treated with intravitreal injection of bevacizumab. Cardiology was consulted to evauluate cardiovascular function and intermittent claudication. Lifestyle modifications were advised to reduce cardiovascular risk factors.

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