QUESTION 75

Which one of the following features is most suggestive of autosomal dominant familial hypercholesterolaemia rather than other causes of hypercholesterolaemia?

A. Tendon xanthomas.
B. Corneal opacities.
C. Lipaemia retinalis.
D. Eruptive xanthomas.
E. Recurrent pancreatitis.

Answer: A

XANTHOMAS

- Xanthelasma palpebrarum
  - Most common
  - Asymptomatic
  - Usually bilateral and symmetrical
  - Soft, velvety, yellow, flat, polygonal papules around the eyelids
  - Common in the upper eyelid near the inner canthus
  - May be associated with hyperlipidemia of any type

- Tuberous xanthomas
  - Are firm, painless, red-yellow nodules
  - The lesions can coalesce to form multilobated tumors
  - Usually develop in pressure areas, such as the extensor surfaces of the knees, the elbows, and the buttocks
  - Particularly associated with hypercholesterolemia and increased levels of LDL
  - Can be associated with familial dysbetalipoproteinemia and familial hypercholesterolemia
  - May be present in some of the secondary hyperlipidemias (e.g., nephrotic syndrome, hypothyroidism).

- Tendinous xanthomas
  - Appear as slowly enlarging subcutaneous nodules related to the tendons or the ligaments
  - Most common locations are the extensor tendons of the hands, the feet, and the Achilles tendons
  - Associated with severe hypercholesterolemia and elevated LDL levels
o Can also be associated with some of the secondary hyperlipidemias, such as cholestasis

- Eruptive xanthomas
  
o most commonly arise over the buttocks, the shoulders, and the extensor surfaces of the extremities
o Rarely, the oral mucosa or the face may be affected
o Lesions typically erupt as crops of small, red-yellow papules on an erythematous base
o May spontaneously resolve over weeks
o Pruritus is common
o May be tender
o Associated with hypertriglyceridemia, particularly that associated with types I, IV, and V (high concentrations of VLDL and chylomicrons)
  o May also appear in secondary hyperlipidemias, particularly in diabetes

- Plane xanthomas
  
o Mostly macular and rarely form elevated lesions
o Can occur in any site
o Involvement of the palmar creases is characteristic of type III dysbetalipoproteinemia
o Can also be associated with secondary hyperlipidemias, especially in cholestasis
o Generalized plane xanthomas can cover large areas of the face, the neck, and the thorax, and the flexures can also be involved
o May be associated with monoclonal gammopathy and hyperlipidemia, particularly hypertriglyceridemia

- Xanthoma disseminatum and verruciform xanthoma are particular forms of xanthomas that occur in normolipemic patients
  - Xanthoma disseminatum develops in adults as red-yellow papules and nodules with a predilection for the flexures. Characteristically, the mucosa of the upper part of the aerodigestive tract is involved. It has a benign clinical course and usually resolves spontaneously.
  - Verruciform xanthoma predominantly occurs in the oral cavity of adults as a single papillomatous yellow lesion. Verruciform xanthoma is considered to be a reactive condition with benign behavior, and it is treated with local excision.

- Lipoprotein patterns can be determined as follows:
  
o I - Elevated triglyceride levels with increased chylomicron levels
  o IIa - Elevated cholesterol level because of increased LDL level
  o IIb - Elevated cholesterol and triglyceride levels because of increased LDL and VLDL levels
A: Tendonous xanthoma are associated with severe hypercholesterolaemia and elevated LDL levels, including FH.

B: Corneal opacities (corneal arcus) are a feature of hypercholesterolaemia and is associated with familial forms but many subjects with normal cholesterol levels also have corneal arcus.

C: Lipaemia retinalis is associated with extremely elevated triglyceride levels – blood becomes a creamy white colour so in this picture arteries and veins can only be distinguished by the vessel size.

D: Eruptive xanthoma – Associated with hypertriglyceridaemia
**FAMILIAL HYPERCHOLESTEROLAEMIA**
- Autosomal dominant
- Severe elevations of total cholesterol and LDL
- Heterozygous form in 1/500

**PATHOPHYSIOLOGY**
- Absent or grossly malfunctioning LDL receptors
- Gene for receptor is located on short arm of chromosome 19
- Receptor is the primary determinant of LDL uptake
- LDL binds to receptor, apolipoprotein B-100 (apoB) is critical in this process
- Receptor also can bind apoE which is found on most lipoproteins other than LDL

5 classes of mutations:
1) Null alleles that result in complete absence of LDL receptor
2) Defective transport alleles, which disrupt normal folding and lead to failure of transport of the receptor to the cell surface or transport of a truncated, mutated receptor
   a. 2a: completely block the transport of the receptor from the endoplasmic reticulum to the Golgi apparatus
   b. 2b: partial blockade of transport of the receptor from the ER to the Golgi apparatus
3) Defective binding alleles that affect the binding of LDL and in some cases VLDL also
4) Defective internalisation alleles that affect the concentration of receptors in the clathrin-coated pits for internalisation by hepatocytes
5) Defective recycling alleles that prevent dissociation of the receptor and the ligand and thus interrupting recycling of the receptors