JAMA Dermatology Clinicopathological Challenge

Chronic Progressive Pink-Yellow Papules and Nodules in a Middle-Aged Man

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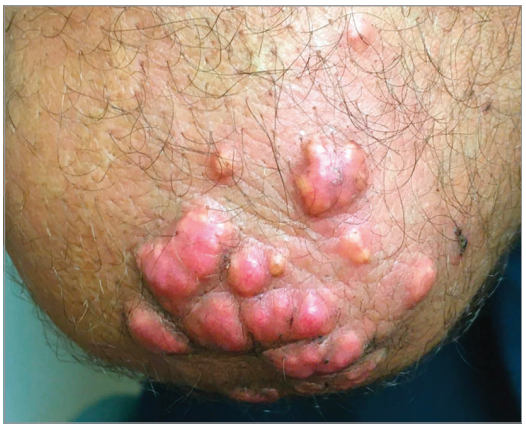
A Clinical image



B Histopathologic image

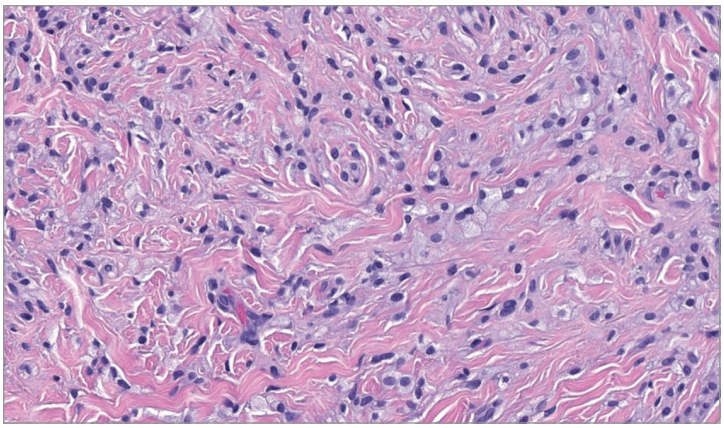


Figure 1. Clinical image of right elbow shows numerous pink-yellow firm papules and nodules (A), and hematoxylin-eosin staining (original magnification, ×200) of shave biopsy specimen shows sheets of foamy lipid-filled histiocytes (B).

A 38-year-old man presented for evaluation of lesions on his elbows for 10 years, hands for 1 year, and knees for a few months. The lesions were progressively increasing in number and size and were occasionally mildly tender with firm pressure. He was unaware of similar lesions or known lipid abnormalities in family members. Physical examination revealed numerous pink-yellow firm papules and nodules on the bilateral elbows (**Figure 1**A) and knees, and linear thin yellow papules on the palmar finger creases. A shave biopsy specimen was taken from a papule on the elbow and sent for histopathologic analysis (Figure 1B). A fasting serum lipid panel was also obtained. Based on the clinical, histologic, and laboratory findings, the patient was diagnosed with an underlying genetic disorder.

WHAT IS YOUR DIAGNOSIS?

- **A.** Familial dysbetalipoproteinemia (type III hyperlipoproteinemia)
- **B.** Familial hypercholesterolemia (type IIa hyperlipoproteinemia)
- **C.** Familial hyperchylomicronemia syndrome (type Ia hyperlipoproteinemia)
- **D.** Sitosterolemia (phytosterolemia or xenosterolemia)

CME Quiz at jamacmelookup.com

Diagnosis

A. Familial dysbetalipoproteinemia (type III hyperlipoproteinemia)

Microscopic Findings and Clinical Course

Histopathologic findings showed aggregates of lipid-filled histiocytes, consistent with xanthoma. The patient's distribution of lesions was consistent with xanthoma striatum palmare, tuberous xanthomas, and tuberoeruptive xanthomas, suggestive of an underlying diagnosis of familial dysbetalipoproteinemia (FD). Lipid profiling revealed elevated cholesterol (519 mg/dL; normal range, <200 mg/dL; for mmol/L, multiply by 0.0259), elevated triglycerides (935 mg/dL; normal range, <150 mg/dL; for mmol/L, multiply by 0.0113), and reduced high-density lipoprotein cholesterol (22 mg/dL; normal range, 40-60 mg/dL). Low-density lipoprotein cholesterol could not be calculated due to the high triglyceride levels. Altogether, the patient's clinical, histologic, and laboratory findings confirmed the diagnosis of FD. He declined genetic testing. Statin therapy was initiated, and after 1 year of treatment, most of the lesions had completely disappeared.

Discussion

Despite being benign, xanthomas often herald underlying lipid metabolism disorders. Xanthomas are classified based on clinical morphologic findings, anatomic distribution, and mode of development, and include tendon, planar, tuberous, tuberoeruptive, and eruptive xanthomas.[1] Histologically, all xanthoma types are characterized by a dense collection of foam cells (histiocytes filled with lipid) within the dermis. Eruptive xanthomas often contain extracellular lipid and a mixed inflammatory infiltrate, whereas tuberous and tendon xanthomas frequently contain cholesterol clefts and fibrosis.[2] Certain xanthomas have been associated with specific underlying lipoprotein disorders, giving them diagnostic utility.[1]

FD is a rare disorder characterized by elevated plasma triglyceride and cholesterol levels.[1,3] Most cases are associated with *APOE-ε2* homozygosity, transmitted in an autosomal recessive mode with variable penetrance.[4] Adult-onset tuberous and tuberoeruptive xanthomas are characteristic of FD.[3] Planar xanthomas in the palmar creases, known as xanthoma striatum palmare (**Figure 2**), are seen in 20% of FD cases and are pathognomonic.[3,5] In the present case, the coexistence of these xanthoma types allowed the diagnosis of FD to be essentially ensured before obtaining confirmatory lipid profiling. By appreciating xanthomas as diagnostic clues, dermatologists can help recognize underlying FD. This is critical given that FD is associated with a substantial increased risk of atherosclerotic cardiovascular disease if untreated.[3] Treatment includes lipid- and cholesterol-lowering agents that mitigate cardiovascular risk and often induces full xanthoma regression.[3]

Familial hypercholesterolemia (FH), an autosomal dominant disorder associated with defects in genes affecting the low-density lipoprotein–receptor pathway, is also characterized by elevated plasma cholesterol and xanthoma formation.[3,4] However, FH has normal triglyceride levels and distinct characteristic xanthomas. Tendon xanthomas, often involving the Achilles tendon and extensor tendons of the digits, and corneal arcus before age 45 years, are highly specific findings for FH, whereas tuberous and tuberoeruptive xanthomas are much less common.[1,3,6] Intertriginous planar xanthomas, typically in the interdigital webspaces, are pathognomonic for homozygous FH.[1,3,7] If xanthomas develop, they usually appear after the third decade of life in heterozygotes and as early as the first decade in homozygotes.[6,7]

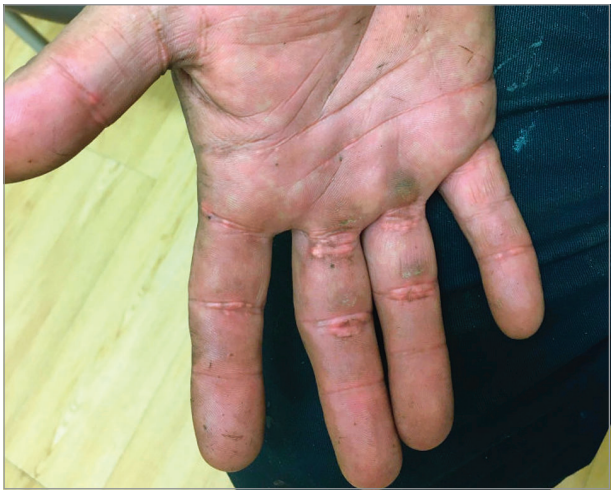


Figure 2. Clinical image of the right palm and palmar fingers shows linear thin yellow papules in skin creases.

Another genetic disorder to consider is familial hyperchylomicronemia syndrome, an autosomal recessive disorder associated with variations in lipoprotein lipase; however, unlike FD, it is associated with transient eruptive xanthomas and very elevated plasma triglycerides.[8] Lastly, sitosterolemia (ie, phytosterolemia or xenosterolemia) is an autosomal recessive disorder (caused by homozygous or compound heterozygous variants in *ABCG5/ABCG8* genes) in which the body accumulates excess plant sterols.[9] This disorder shares several clinical features with other inherited lipid disorders, including xanthoma formation and premature atherosclerotic cardiovascular disease,[3,9] and could be considered but it would be dismissed through laboratory and clinical assessments. Similar to FH and in contrast to FD, patients often present early in life with tendon xanthomas.[9] What distinguishes sitosterolemia from FH, FD, and other lipoprotein disorders is the presence of markedly elevated plasma levels of plant sterols[3,9]; these patients may have elevated total cholesterol levels, but a standard lipid panel does not provide specific diagnostic information.[9]

ARTICLE INFORMATION

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