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Senior Resident Peer-to-Peer Case Studies

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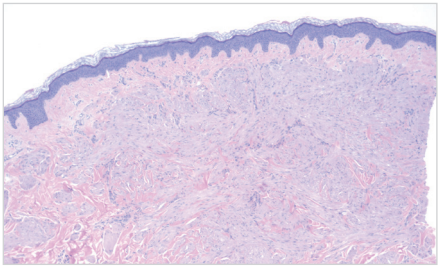
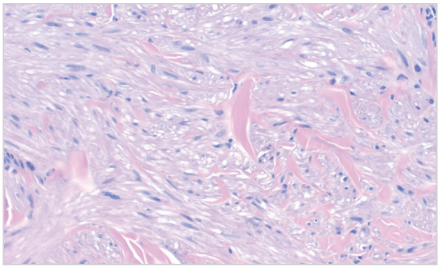
Case Studies authored by our educational partner GW School of Medicine and Health Sciences Dermatology Residency Program.

School of Medicine & Health Sciences
THE GEORGE WASHINGTON UNIVERSITY

1)

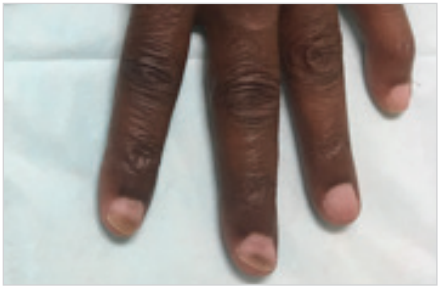




A 35-year-old Caucasian male presented for evaluation of multiple tender pink papules on the trunk, that have been present for many years. The patient notes that his father, who is deceased, also had similar skin lesions. His sister is currently receiving treatment for uterine fibroids. A punch biopsy of a lesion was obtained. Immunohistochemical staining for desmin was positive. Which of the following is true regarding the patient's underlying condition?

A. It is due to a mutation in the CYL-D gene.
B. The skin lesions arise from a proliferation of cells of the Suquet-Hoyer canal.
C. Immunohistochemical staining of the biopsy tissue for S100 would be positive.
D. There is a defect in an enzyme involved in the citric acid cycle.
E. It is due to a mutation leading to impaired DNA mismatch repair.

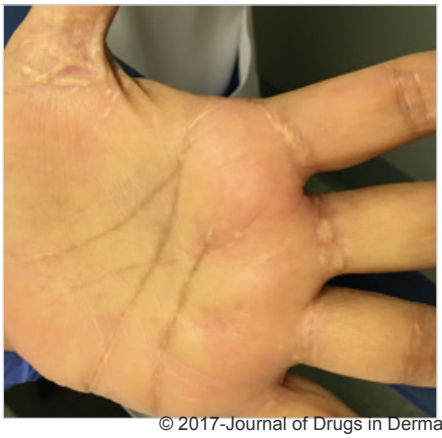
2)



A 65-year-old African American male presents with a one-month history of nail changes of all 10 fingernails. What is the most likely offending drug?

A. Doxorubicin
B. 5-Fluorouracil
C. Zidovudine
D. Hydrochlorothiazide
E. Doxycycline

3)



A 35-year-old Hispanic female presents with a 1-year history of firm, yellow, asymptomatic papules and plaques on the palms. She has a history of hypercholesterolemia and type II diabetes. Her medications include metformin and atorvastatin. Her family history is notable for a father who died of coronary artery disease. Which of the following statements is FALSE:

A. The disease associated with this eruption is inherited in an autosomal dominant fashion.
B. The patient has a Type III hyperlipoproteinemia.
C. The pathogenesis of this patient's underlying disease is due to an LDL receptor defect.
D. This disease may also present with plaques on the elbows and knees.
E. A biopsy of this eruption would likely show foamy macrophages superficial and mid-dermis.

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The content of these case studies, ideal to review during peer study groups, was developed by Julia Schwartz, MD and Thomas Lee, MD under the guidance of dermatologist Adam Friedman, MD, FAAD, Associate Professor of Dermatology, Residency Program Director, Director of Translational Research, Department of Dermatology GW University.

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Answers

1) The correct answer is D: There is a defect in an enzyme involved in the citric acid cycle.

Explanation/Literature Review

The histologic findings are most consistent with cutaneous leiomyoma. Given the family history and multiple lesions on physical exam, hereditary leiomyomatosis with renal cell cancer syndrome (HLRCC) should be at the top of the differential diagnosis.

Patients with HLRCC present with multiple cutaneous leiomyomas. Clinically they may present as skin colored to erythematous papules on the face, neck, trunk and extensor surfaces. Tumors arising from the arrector pili muscles or vascular smooth muscle are often tender, while those derived from genital or mammary smooth muscles are often asymptomatic. Physical contact or rubbing of the lesions may lead to a transient elevation of the papules and nodules, which is also known as the Pseudo-Darier sign. Biopsies of lesions will show interlacing fascicles of spindle-shaped cells with blunt, cigar shaped nuclei with clear, perinuclear vacuoles composed of glycogen. Immunohistochemical staining for smooth muscle markers such as smooth muscle actin and desmin will be positive. Stains for S100 will be negative, differentiating this from other nerve tissue derived neoplasms with a similar spindle-shaped cell morphology. Female patients may also present with uterine leiomyomas, on average, 10 years before the general population. Patients with HLRCC are at high risk of papillary renal cell carcinoma, which can be found in 20-34% of affected families. There is a 70% mortality rate due to metastatic disease within 5 years of diagnosis. Annual screening with MRI is recommended.

HLRCC is an autosomal dominant genetic disease due to a mutation in fumarate hydratase, an enzyme in the citric acid cycle, also known as the Kreb's cycle. While the exact mechanism is unclear, it is thought that the impairment of oxidative phosphorylation leads to a hypoxic state with upregulation of vascular endothelial growth factors, cellular proliferation, and prevention of apoptosis, which may give rise to tumors. Genetic testing is required for definitive diagnosis.

Brooke-Spiegler syndrome arises from a mutation in CYLD, characterized by eccrine spiradenomas, cylindromas, and trichoepitheliomas. While spiradenomas may be tender clinically, the histopathology would show well circumscribed dermal tumors with basophilic cells, lymphocyte-like cells, and eosinophilic hyaline droplets within the tumor nodules.

Glomus tumors and glomangiomas are derived from the cells of glomus bodies, also known as Suquet-Hoyer canals, which are modified smooth muscle cells involved in thermoregulation. While they may be tender clinically and also stain positive for smooth muscle markers, histological examination will show blood vessels lined by rows of round basophilic cells with dark nuclei and minimal cytoplasm, which has been described as a "string of black pearls."

Muir-Torre syndrome arises from mutations in MSH2 or MLH1 leading to defects in DNA mismatch repair. It is characterized by sebaceous neoplasms, keratoacanthomas, and internal malignancies, most notably colorectal cancer.

References

1. Patel VM, Handler MZ, Schwartz RA, Lambert WC. Hereditary leiomyomatosis and renal cell cancer syndrome: An update and review. J Am Acad Dermatol. 2017 Jul;77(1):149-158.
2. Menko FH, Maher E, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC). Renal cancer risk, surveillance and treatment. Familial cancer. 2014;13(4):637-644.

2) The correct answer is E: Doxycycline

Explanation/Literature Review

The clinical photo is showing onycholysis of multiple fingernails. Out of the drugs listed, doxycycline is the most likely to cause onycholysis via a phototoxic effect. Doxorubicin, 5-fluorouracil, and zidovudine can result in longitudinal, transverse, or generalized melanonychia. Hydrochlorothiazide can cause a phototoxic and photo-lichenoid skin reaction but does not typically affect the nails.

Onycholysis occurs when the nail plate separates from the nail bed and can result from a number of factors including inflammatory disease, medications, trauma, or infection. Drug-induced photo-onycholysis results from ingestion of an exogenous photosensitizing medication coupled with exposure to ultraviolet radiation. The photo-onycholysis can occur alone or be accompanied by a phototoxic skin reaction. Onychodynia can precede the onycholysis by several weeks. Nail bed splinter hemorrhage can result in dark red discoloration of the nails. The nails will gradually normalize after stopping the offending medications. Doxycycline is a common cause of photo-onycholysis given its widespread use in medicine. Other medications that can cause photo-onycholysis are psoralens, chloramphenicol, oral contraceptives, chlorpromazine, thiazide diuretics, and griseofulvin.

References

1. Chandran NS and Aw DC. Drug-induced photo-onycholysis: an often-neglected phenomenon. Intern Med J 2013;43(12): 1349-1350.

3) The correct answer is C: The pathogenesis of this patient's underlying disease is due to an LDL receptor defect.

Explanation/Literature Review

The clinical picture shows plane xanthomas of the palmar creases. Based on the characteristic rash and clues from the question stem (hypercholesterolemia, family history of heart disease), a diagnosis of familial dysbetalipoproteinemia (Type III hyperlipoproteinemia) should be suspected.

Familial dysbetalipoproteinemia (also known as remnant removal disease or broad beta disease) is an inherited disease of lipid metabolism. Dysbetaliproteinemia is inherited in an autosomal dominant fashion. The pathophysiology of this condition is due to a deficiency of normal apo E in lieu of an isoform, apo E2, which has a much lower affinity for the apo E receptor. Reduced binding to this receptor results in impaired hepatic clearance of chylomicron and VLDL remnants and ultimately leads to increased levels of serum cholesterol and triglycerides. Dysbetaliproteinemia is typically diagnosed in adulthood and is characterized by premature onset coronary artery disease and peripheral vascular disease.

Xanthomas, particularly plane, tuberous, and tendinous, are characteristic and present in 80% of patients with familial dysbetaliproteinemia. Plane xanthomas of the palmar and finger creases, known as xanthoma striatum palmare, are pathognomonic for this disease and present in two-thirds of patients. Biopsy of one of these skin lesions would show foam cells (macrophages with lipidized cytoplasm) in the superficial to mid-dermis.

The main differential diagnosis for plane xanthomas of the palm is familial hypercholesterolemia (type II hyperlipoproteinemia), which is due to a dysfunction in the LDL receptor leading to poor clearance of LDL cholesterol and significantly elevated serum LDL. Patients with homozygous familial hypercholesterolemia present much earlier in life (usually in the first decade) with tuberous, tendinous, and plane xanthomas, as well as widespread and early onset atherosclerosis. Unlike the xanthomas found within the creases of dysbetaliproteinemia, the pathognomonic plane xanthomas of familial hypercholesterolemia are found in the interweb spaces.

References

1. Massengale WT, Hodari KT, Boh EE, and Nesbitt LT. Xanthomas. In: Bolognia, JL, Jorizzo JL, and Schaffer JV, eds. Dermatology. 3rd ed. Philadelphia, PA: Elsevier Saunders; 2012.

2. Parker F. Xanthomas and hyperlipidemias. J Am Acad Dermatol 1985;13(1): 1-30.