Aligned nodules on the forearms

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A 71-year-old Caucasian man presented with yellowish, soft nodules on both forearms, involving only the extensor surfaces (Fig 1, A). The nodules measured between 3 and 13 mm and coalesced to form a long, thin plaque, aligned longitudinally. There was marked photodamage of the face and limbs. The lesions developed over many years, and the patient denied having pain or pruritus. The medical history included nonmelanoma skin cancer, type IIa hyperlipidemia treated with atorvastatin, essential hypertension treated with atenolol, and obesity. An incisional biopsy was performed (Fig 1, B) and histology special stains (Fig 2) were used.
**Question 1:** Considering the clinical and histopathologic (hematoxylin and eosin, ×400) images, what is the most likely diagnosis?

A. Tuberous xanthomas  
B. Nodular amyloidosis  
C. Solar elastosis  
D. Gouty tophus  
E. Nodular colloid degeneration

**Answers:**

A. Tuberous xanthomas—Incorrect. Tuberous xanthomas manifest as firm, painless, yellowish nodules that especially affect pressure areas of the skin, such as the knees, elbows, heels, and buttocks. They can coalesce to form multilobulated masses. They are associated with hypercholesterolemia with increased low-density lipoprotein levels, as seen in this patient, but his pressure sites were uninvolved.

B. Nodular amyloidosis—Incorrect. Nodular amyloidosis is the rarest form of primary localized cutaneous amyloidosis. It manifests as single or multiple firm nodules and/or plaques, which are in some cases bright yellow, on the skin of the trunk, limbs, face, or genitals. Most patients seek care because of the cosmetic appearance only, as the nodules are painless and do not ulcerate. The key to the diagnosis rests on the histopathology.

C. Solar elastosis—Correct. Nodular solar keratosis is rarely seen, but papules containing elastic material are frequently observed, if looked for, on skin areas with extensive actinic damage.

D. Gouty tophus—Incorrect. Tophi are soft-tissue nodules that contain collections of urate crystals. They are usually found on the helix of the ear, fingers, toes, knees, and elbows. They usually appear after many years of untreated gouty arthritis, which this patient never had.

E. Nodular colloid degeneration—Incorrect. Nodular colloid degeneration is a rare condition that affects the face and, in one reported case, the penis. It manifests as soft, yellowish, or red papules, nodules, or plaques. The diagnosis is confirmed histologically.

**Question 2:** Which histologic description corresponds to this diagnosis?

A. Accumulation in the dermis of an amorphous material with irregular clefts and a few pyknotic nuclei. The material is stained bright magenta with periodic acid-Schiff.

B. Masses of elastotic material filling the reticular dermis, separated from the atrophic epidermis by a thin grenz zone.

C. Deposition of pink amorphous material within the papillary dermis, which stains orange with Congo red and acquires a bright apple-green birefringence under polarized light.

D. Deposition of mucin (hyaluronic acid) in the dermis and hypodermis, which stains blue with Alcian blue at pH 2.5. Stellate fibroblasts are seen, and collagen fibers appear attenuated and widely separated.

E. An accumulation of macrophages filled with lipid droplets is seen in the dermis. Frozen sections stained with Oil Red O show, in red, the high number of these cells.

**Answers:**

A. Accumulation in the dermis of an amorphous material with irregular clefts and a few pyknotic nuclei. The material is stained bright magenta with periodic acid-Schiff.—Incorrect. The description corresponds to nodular colloid degeneration. The material in this case is fibrillary and wavy.

B. Masses of elastotic material filling the reticular dermis, separated from the atrophic epidermis by a thin grenz zone.—Correct. The appearance is that of degenerated elastic fibers, which, it was demonstrated later, stained black with the Weigert-van Gieson technique (Fig 2, ×40).

C. Deposition of pink amorphous material within the papillary dermis, which stains orange with Congo red and acquires a bright apple-green birefringence under polarized light—Incorrect. This is the description of amyloid. Congo red staining was performed and was negative.

D. Deposition of mucin (hyaluronic acid) in the dermis and hypodermis, which stains blue with Alcian blue at pH 2.5. Stellate fibroblasts are seen, and collagen fibers appear attenuated and widely separated.—Incorrect. This description corresponds to pretibial myxedema, which can occasionally be nodular. Alcian blue stain showed no mucin in this case.

E. An accumulation of macrophages filled with lipid droplets is seen in the dermis. Frozen sections stained with Oil Red O show, in red, the high number of these cells.—Incorrect. Foamy, lipid-laden macrophages in the dermis are seen in xanthomas. This is not the image seen in this patient’s biopsy.
Question 3: What is the pathophysiology of this entity?

A. Accumulation of oxidized proteins in skin cells stimulates proteasomal function and the ability of the cell to successfully degrade additional damaged proteins.

B. Ultraviolet radiation produces reactive oxygen species that inactivate cell-surface receptors, including receptors for interleukin 1 and tumor necrosis factor α.

C. Ultraviolet radiation blocks the synthesis of enzymes that degrade the extracellular matrix, such as metalloproteinase 1.

D. There is glycosylation of elastin by chronic ultraviolet radiation.—Correct. Elastin is a durable protein that is prone to glycoxidation by chronic ultraviolet radiation or reactive oxygen species during normal aging. Yoshinaga et al. showed, by applying immunohistochemical studies to ultraviolet-irradiated elastic fibers, that N-(carboxymethyl)lysine, one of the major advanced glycation end products, accumulates in areas of solar elastosis. The authors proposed that N-(carboxymethyl)lysine-modified elastin fibers enlarge and become more tortuous, with decreased elasticity on tensile tests. The fibers also become insoluble and resistant to neutrophil elastase digestion, accumulating as large aggregates. The linear distribution of nodules has been observed in the past, but its cause is not understood.

E. There is increased synthesis of fibrillins by dermal fibroblasts.—Incorrect. Fibrillin-rich microfibrils that reinforce elastic fibers in the dermis are rich in amino acids that absorb energy from ultraviolet radiation and are especially susceptible to damage from ultraviolet radiation.

Answers:

A. Accumulation of oxidized proteins in skin cells stimulates proteasomal function and the ability of the cell to successfully degrade additional damaged proteins.—Incorrect. On the contrary, ultraviolet A radiation is a major contributor to protein oxidation in the skin, which inhibits proteasomal function and reduces degradation of damaged proteins.

B. Ultraviolet radiation produces reactive oxygen species that inactivate cell-surface receptors, including receptors for interleukin 1 and tumor necrosis factor α.—Incorrect. Reactive oxygen species caused by ultraviolet radiation will in fact increase the expression of these surface receptors, resulting in a blocking effect of transforming growth factor β, a cytokine involved in collagen gene transcription.

C. Ultraviolet radiation blocks the synthesis of enzymes that degrade the extracellular matrix, such as metalloproteinase 1.—Incorrect. Ultraviolet irradiation of fibroblasts triggers metalloproteinase 1 (collagenase) and decreases type I procollagen production.

D. There is glycosylation of elastin by chronic ultraviolet radiation.—Correct. Elastin is a durable protein that is prone to glycoxidation by chronic ultraviolet radiation or reactive oxygen species during normal aging. Yoshinaga et al. showed, by applying immunohistochemical studies to ultraviolet-irradiated elastic fibers, that N-(carboxymethyl)lysine, one of the major advanced glycation end products, accumulates in areas of solar elastosis. The authors proposed that N-(carboxymethyl)lysine-modified elastin fibers enlarge and become more tortuous, with decreased elasticity on tensile tests. The fibers also become insoluble and resistant to neutrophil elastase digestion, accumulating as large aggregates. The linear distribution of nodules has been observed in the past, but its cause is not understood.

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Conflicts of interest

None disclosed.

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