Acne and craniofacial defects

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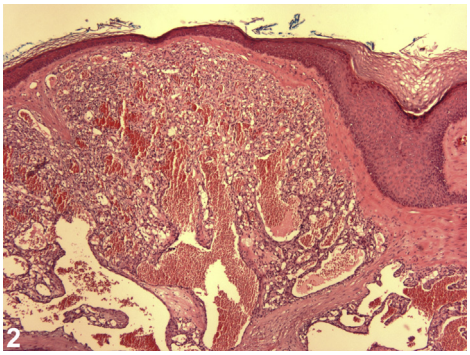

A 37-year-old man with a history of severe acne, craniosynostosis, neurogenic bladder, recurrent urinary tract infections, bilateral hearing loss, and migraines presented with a 3-month history of a pruritic and painful nodule on his chest. Physical examination found a mix of inflammatory and nodulocystic acne involving the face, chest, and back; a flat forehead and midface; syndactyly; hypertelorism with a laterally downsloping slant; and a well-circumscribed 1-cm violaceous exophytic pink to dark red nodule with crusting involving the left upper chest (Fig 1). A shave biopsy of the lesion was obtained (Fig 2).

Question 1: What is the most likely diagnosis?

A. Saethre-Chotzen syndrome

B. Apert syndrome

C. Carpenter syndrome

D. Crouzon syndrome

E. Pfeiffer syndrome

Answers:

A. Saethre-Chotzen syndrome — Incorrect. This *TWIST1*-related craniosynostosis may be associated with hypertelorism and syndactyly; however, it typically presents with characteristic ears (small pinna with large crus), ptosis, and facial asymmetry.[1]

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B. Apert syndrome — Correct. Apert syndrome, a fibroblast growth factor receptor-2 (FGFR2)-related craniosynostosis, involves early symmetric bony fusion of the cranium, spine, fingers, and toes. Patients classically present with a prominent flat forehead and midface, hypertelorism, and laterally downsloping slanting eyes. Additionally, patients may display a small nose, low-set ears, and syndactyly as a result of the bony fusions. Moderate-to-severe acne resistant to many pharmacologic treatments is a dermatologic hallmark of the condition.[1,2]

C. Carpenter syndrome — Incorrect. Although similar craniofacial malformations would be seen in Carpenter syndrome, the vignette does not describe the characteristic finger and toe malformations. This Ras-related protein (RAB23) craniosynostosis characteristically exhibits brachydactyly, syndactyly, aplasia, or hypoplasia of the hands and/or polydactyly of the feet.[1,2]

D. Crouzon syndrome — Incorrect. This FGFR2-related craniosynostosis also presents with eye and cranial malformations; however, these include significant proptosis, a protruding mandible, and external strabismus, without extracranial manifestations involving the hands and feet.[1] Acanthosis nigricans is a dermatologic association with Crouzon syndrome.[1,2]

E. Pfeiffer syndrome — Incorrect. Pfeiffer syndrome can similarly present with mid-facial deformities and hearing loss, but the broad, radially deviated thumbs or big toes characteristic of this syndrome are not described.[1,2] Cutaneous hypopigmentation can also be associated with Pfeiffer syndrome.[2]

Question 2: What is the shave biopsy likely to reveal?

A. Kaposi sarcoma

B. Amelanotic nodular melanoma (ANM)

C. Bacillary angiomatosis

D. Pyogenic granuloma (PG)

E. Nodular basal cell carcinoma (BCC)

Answers:

A. Kaposi sarcoma — Incorrect. Kaposi sarcomas are vascular tumors like PGs, but histopathologically, the absence of atypical spindle cells and bizarre vascular channels helps to differentiate a benign PG from Kaposi sarcoma.[3]

B. ANM — Incorrect. Although they may both present as vascular nodules, ANMs tend to have a dull red hue, bleed less, and be slower growing, whereas most PGs are bright red and friable. On histology, melanin pigment is usually decreased or absent in ANM.

C. Bacillary angiomatosis — Incorrect. PG may clinically be mistaken for bacillary angiomatosis, an infection with *Bartonella* spp primarily seen in HIV-infected individuals, but PG would be distinguished by an absence of granular bacterial material histologically.[3]

D. PG — Correct. PG classically presents as a rapidly growing vascular tumor that can arise from stimuli such as local irritation, acute or chronic trauma, or humoral factors. The acne treatment isotretinoin is also a known cause of PGs.[4] Histologically, the lesion consists of distinctive lobular clusters of capillaries in a dense stroma, accompanied by an inflammatory infiltrate.

E. Nodular BCC — Incorrect. BCCs are malignant tumors associated with chronic sun exposure and have basaloid keratinocytes seen on histology. Lesions may become ulcerated but rarely grow as fast as PGs.

Question 3: What is the best treatment for the acne in a patient with this condition?

A. Topical retinoid

B. Oral antibiotic

C. Isotretinoin

D. Topical antibiotic

E. Benzoyl peroxide

Answers:

A. Topical retinoid — Incorrect. Oral isotretinoin, not topical, is found to be most effective at resolving acneiform lesions associated with Apert syndrome.[5]

B. Oral antibiotic — Incorrect. Although tetracyclines inhibit the FGFR2b downstream expression and activity of metalloproteinases, this inhibition has not been sufficient in treating this gain-of-function FGF2 mutation.[5]

C. Isotretinoin — Correct. The onset of acne in Apert syndrome, and often oily skin, occurs in early puberty. When androgen levels increase, they promote FGF synthesis, activate the gain-of-function FGF2 mutation, and cause the severe acneiform lesions in these patients. FGF2b signaling is known

to play a crucial role in the pathogenesis of acne. Although most drugs target single regions of the FGF2b signaling cascade, oral retinoids disrupt multiple regulatory steps and signals in the FGFR2 pathway and therefore provide the most effective treatment for patients with the gain-of-function FGF2 mutation.[2,5] However, depending on the acne severity, isotretinoin may not be required in all patients. A risk-benefit assessment should be made on an individual case basis because of the numerous known potential side effects of isotretinoin. Of concern, the disruption of FGFR2 signaling during embryonic development yields a teratogenicity risk in postpubertal females.[5]

D. Topical antibiotic — Incorrect. Oral isotretinoin therapy is the best therapy for these patients.[5]

E. Benzoyl peroxide — Incorrect. Although benzoyl peroxide is effective in interrupting acne pathogenesis through the degradation of lysosomal receptors and downregulation of FGFR2b, it is not sufficient in Apert syndrome. The gain-of-function FGF2 mutation in Apert syndrome requires multiple levels of pathway inhibition for successful treatment.[5]

Abbreviations used:

ANM: amelanotic nodular melanoma
BCC: basal cell carcinoma
FGFR2: fibroblast growth factor receptor-2
PG: pyogenic granuloma

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