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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.
Milia: A review and classification

David R. Berk, MD, and Susan J. Bayliss, MD
Saint Louis, Missouri

Milia are frequently encountered as a primary or secondary patient concern in pediatric and adult clinics, and in general or surgical dermatology practice. Nevertheless, there are few studies on the origin of milia and, to our knowledge, there is no previous comprehensive review of the subject. We review the various forms of milia, highlighting rare variants including genodermatosis-associated milia, and present an updated classification. (J Am Acad Dermatol 2008;59:1050-63.)

Milia (singular: milium) are small (generally ≤ 3 mm) white, benign, superficial keratinous cysts. Histologically, they resemble miniature infundibular cysts, containing walls of stratified squamous epithelium several layers thick with a granular cell layer (Fig 1). Although benign primary milia are commonly encountered in clinical practice, milia also occur in a variety of other conditions, many of which are rare. They may arise either spontaneously (primary milia) or secondary to various processes (secondary milia), as few or many lesions, and isolated or associated with other clinical findings. Hubler et al1 proposed dividing milia into primary, secondary, and “other” types, a classification that Wolfe and Gurevitch2 modified. Here, we present an updated classification (Table 1) and review.

ORIGIN
Few studies have investigated the origin of milia.3-6 In general, primary milia are thought to originate from the sebaceous collar of vellus hairs (lower infundibulum), whereas secondary milia are believed to derive from eccrine ducts more commonly than from overlying epidermis, hair follicles, or sebaceous ducts.

Epstein and Kligman3 performed serial sectioning of 4 types of milia: primary milia and secondary milia caused by epidermolysis bullosa (EB), dermabrasion, and experimental autotransplantations of epidermis. They challenged the previously held notion that milia represent plugged hair follicles that then become retention cysts. With primary milia, they observed strandlike connections from milial cysts to the external root sheath of vellus hair follicles, near where the sebaceous ducts attach. With EB, milia were seen in connection with eccrine ducts. Postdermabrasion milia were thought to arise from amputated sebaceous lobules that seemed to initially dedifferentiate, then either redifferentiate into sebaceous glands, which could reconnect to hair follicles, or differentiate into milia. With experimental autotransplantations, milia connected to the external root sheath (near the arrector pili muscle insertion) or to the overlying epidermis.

Tsujii et al4 performed serial sectioning of 69 biopsy specimens of secondary milia from 8 patients with blistering disorders (EB, dermatitis herpetiformis, bullous pemphigoid, herpes zoster, and second-degree burns). In 75% of specimens, milia connected to eccrine ducts, usually at the base of the milium with a 1:1 eccrine duct:milium ratio. In only 1/69 specimens, the milia connected with hair follicles. In the remaining

Abbreviations used:

- APL: atrichia with papular lesions
- BCNS: Basal cell nevus syndrome
- BDCS: Bazex-Dupre-Christol syndrome
- BFH: basaloid follicular hamartoma
- CK: cytokeratin
- EB: epidermolysis bullosa
- EBS: epidermolysis bullosa simplex
- EVHC: eruptive vellus hair cyst
- GBFH: generalized basaloid follicular hamartoma syndrome
- MEM: multiple eruptive milia
- MEP: milia en plaque
- MUS: Marie-Unna hypotrichosis
- OFDS: orofaciodigital syndrome
- OMIM: Online Mendelian Inheritance in Man
- PC: pachyonychia congenita
- SCM: steatocystoma multiplex

From the Departments of Internal Medicine and Pediatrics, Division of Dermatology, Washington University School of Medicine and Saint Louis Children’s Hospital.

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Reprint requests: David R. Berk, MD, Division of Dermatology, Washington University School of Medicine, 660 S Euclid, Campus Box 8123, St Louis, MO 63110. E-mail: DBerk@im.wustl.edu.

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(23%) specimens, serial sections did not demonstrate a connection to either eccrine ducts or hair follicles. Tsuji et al. described incomplete (open) and complete (closed) forms of secondary milia.

Honda et al. examined the structure of secondary milia from 9 biopsy specimens using serial sectioning, 3-dimensional reconstruction, and immunohistochemical staining for cancer antigen-50, carcinoembryonic antigen, and cytokeratin (CK)-19. Staining patterns suggested that complete secondary milia were entirely of eccrine origin (based on the diffuse staining of cyst walls with eccrine markers), whereas incomplete secondary milia were derived from a combination of eccrine tissue and overlying or surrounding epidermis (based on their finding that the apical portions of these incomplete milia did not stain for eccrine markers). They observed that mature eccrine ducts entered at the base of the milia and took an elongated circular course within the milial wall. They hypothesized that this circular path of the eccrine ducts “parallels the growth of milia” and suggests an acrosyringeal origin for secondary milia.

Broekaert et al. sought to elucidate the differentiation state of various epithelial cysts and tumors, including primary milia (10 cases), using immunohistochemical staining for CKs. Milia and larger epidermoid cysts stained nearly identically, with basal layer CK14 reactivity; suprabasal CK1, CK10, and CK16 reactivity; CK5 reactivity in all layers of the wall; and variable CK4 reactivity of the cyst contents. This staining pattern closely resembled that of normal overlying epidermis with the exception of CK16 reactivity, a hyperproliferative marker.

An ideal classification of milia might be based on the origin (sebaceous collar vs eccrine) and staining patterns of milia. Unfortunately, these characteristics are rarely investigated or reported.

### PRIMARY MILIA

#### Congenital milia

Congenital milia occur in 40% to 50% of newborns, favoring the face (especially the nose), scalp, upper aspect of trunk, and upper extremities, without significant racial or sex difference (Fig 2). Congenital milia present with a few or numerous lesions and tend to resolve spontaneously within weeks to several
months. Milia may be less common and of delayed onset in premature newborns. The main differential diagnosis is sebaceous hyperplasia, which appears as follicular grouped pinpoint whitish yellow papules around the nose and upper lip. Like congenital milia, sebaceous hyperplasia is less common in premature newborns. Although rarely required, incision and evacuation of the typical round keratinous contents of milia can confirm the diagnosis.

**Congenital oral inclusion cysts**

There are several types of congenital oral inclusion cysts, which are the oral counterparts of congenital milia. Various terms for these cysts, used somewhat inconsistently, include “Epstein pearls,” “Bohn nodules,” and “gingival (dental lamina) cysts.” Oral inclusion cysts in the newborn present as less than or equal to 3-mm asymptomatic firm, white or translucent papules. Epstein pearls are very common (50%-85% of neonates) keratinous cysts located near the midpalatine raphe and believed to represent epithelium entrapped during palatal fusion. Bohn nodules are keratinous cysts on the alveolar ridges and palate, especially at the hard-soft palate junction, and may represent salivary gland epithelial remnants. Gingival cysts are alveolar keratinous cysts probably derived from the dental lamina, the tooth bud ectoderm. Like congenital milia, oral inclusion cysts resolve within weeks to months and may be more common in full-term neonates. Oral inclusion cysts may also be associated with increased birth weight. Neonates with congenital milia may be slightly more likely to have oral inclusion cysts.

**Benign primary milia of children and adults**

Benign primary milia of children and adults are frequently encountered in clinical practice. Treatment of these lesions is a relatively common reason for dermatology visits, either as a primary or secondary patient concern (Figs 3 to 5). Like congenital milia, benign primary milia of children and adults occur spontaneously. Unlike congenital primary milia, they favor the cheeks and eyelids, along with the forehead and genitalia. Benign primary milia of children and adults tend to be more persistent than congenital lesions.

Although benign primary milia of children and adults usually occur on the cheeks and eyelids, there are several reports of benign primary milia in unusual locations, including the nasal crease, vulva, and areola. Of particular interest are nasal crease milia. A prominent nasal crease believed to be caused by nose rubbing is well recognized in patients who are atopic. Nonatopic
pedigrees demonstrating a prominent nasal groove have also been described. Some patients are born with a row of milia within the nasal crease, suggesting this may be a form of primary milia. The nasal grooves of patients who are not atopic may also develop milia. Some authors have proposed that rubbing causes epidermal invagination, suggesting that nasal crease milia sometimes represent secondary milia.

A subset of preadolescent patients develop “pseudoacne of the nasal crease,” characterized by persistent, acneiform papules within nasal crease milia, in the absence of acne elsewhere. In two patients with pseudoacne of the nasal crease, histopathologic findings included keratin-containing granulomas with mononuclear and foreign body giant cells, suggesting these lesions represent “an evolution from milia into an inflamed epidermal inclusion cyst,” possibly through cyst rupture.

**Milia en plaque**

Milia en plaque (MEP) is a rare disorder (<30 reported cases) characterized by erythematous plaques containing numerous milia. Lesions are usually several centimeters in diameter and located on the head and neck, especially periauricularly, they may also be periorbital, on the nasal bridge, or truncal. Although MEP has been reported in different age groups, it seems to be more common in middle-aged adults with a female predominance. MEP is asymptomatic. Lesions may be indurated, and can be unilateral or bilateral. MEP is associated with pseudoxanthoma elasticum, discoid lupus erythematosus, lichen planus, trauma, and renal transplantation but also arises in healthy persons. Dogra et al suggested that cyclosporine may predispose patients to MEP based on two cases, and its known association with comedones, acne, and cysts. Histologically, MEP demonstrates a lymphocytic infiltrate and keratinous cysts. Simple extraction, retinoids, minocycline, cryotherapy, electrodesiccation, dermabrasion, carbon-dioxide laser, photodynamic therapy, and excision may be beneficial therapeutic options. MEP occasionally regresses spontaneously. The differential diagnosis depends on lesion location and may include nevus comedonicus, xanthelasma, Favre-Racouchot syndrome, follicular mucinosis, trichoadenoma, or lichen planus tumidus folliculans.

**Nodular grouped milia**

Zuehlke and Ceilley described a healthy 18-month-old girl who presented with a 3-month history of an enlarging nodule on the right ankle. She had a “9 × 7 mm nodule studded with small white spherules” that histologically demonstrated numerous keratinous cysts lined by squamous epithelium consistent with a nodule of grouped milia. There was no recurrence 4 months after shave excision. The authors likened this lesion to a milial version of proliferating epidermoid cyst, but smaller and without calcification, necrosis, or dyskeratosis.

**Multiple eruptive milia**

The diagnosis of multiple eruptive milia (MEM) has been applied to lesions that occur spontaneously in too large a number to be classified as simple benign primary milia of children and adults. A few cases have been reported in patients aged 15 to 71 years, favoring the head, upper aspect of the trunk, and/or proximal upper extremities and “erupting” over weeks to months. Response to topical tretinoin has been documented. Langley et al classified MEM into 3 forms: spontaneous (isolated idiopathic), familial (autosomal dominant), and genodermatosis associated. We prefer to define MEM as cases without associated anomalies and, therefore, consider genodermatosis-associated MEM separately. Ratnavel et al described an unusual variant of MEM restricted to the eyelids in a family over 3 generations.

**Generalized milia with nevus depigmentosus**

Taniguchi et al reported a healthy 3-month-old boy who presented with a 2-month history of widespread depigmented macules and patches with numerous tiny white papules restricted to the depigmented areas. Histologically, they identified a small epidermal cyst in the papillary dermis and basal layer hypopigmentation with decreased melanin but a normal number of melanocytes by Fontana-Masson staining, consistent with a diagnosis of nevus depigmentosus and milia formation.
Table II. Genodermatoses associated with milia

<table>
<thead>
<tr>
<th>Genodermatosis</th>
<th>OMIM No.</th>
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<tr>
<td>Bazex-Dupre-Christol syndrome (OMIM 301845)</td>
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<td>Rombo syndrome (OMIM 180730)</td>
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<td>Brooke-Spiegler syndrome (OMIM 605041)</td>
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<td>Orofaciodigital syndrome type 1 (OMIM 311200)</td>
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<td>Atrichia with papular lesions</td>
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<td>Hereditary vitamin D−dependent rickets type IIA</td>
<td>277440</td>
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<td>Pachyonychia congenita type II (OMIM 167210)</td>
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<td>Basal cell nevus syndrome (OMIM 109400)</td>
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<tr>
<td>Generalized basaloïd follicular hamartoma syndrome (OMIM 605827)</td>
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<td>Familial milia and absent dermatoglyphics (OMIM 136000)</td>
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<td>Nicolau-Balus syndrome (OMIM 148210)</td>
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<tr>
<td>Hypotrichosis with light-colored hair and facial milia (OMIM 148210)</td>
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<td>KID syndrome (OMIM 301845)</td>
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<tr>
<td>Epidermolysis bullosa* (OMIM 148210)</td>
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<td>Hereditary porphyrias*</td>
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KID, Keratosis-Ichthyosis-Deafness; OMIM, Online Mendelian Inheritance in Man.
*Best classified as secondary milia.

GENODERMATOSES WITH MILIA

Milia may be a major or minor feature of many genodermatoses (Table II).

Bazex-Dupre-Christol syndrome (OMIM 301845)

Bazex-Dupre-Christol syndrome (BDCS) is an X-linked—dominant disorder consisting of congenital hypotrichosis (85%), follicular atrophoderma (85%), basal cell carcinoma, and milia (75%). In BDCS, milia typically arise during infancy or early childhood, often within the first weeks or months of life, and may be the presenting sign of the disease. Milia are especially prominent on the face, limbs, trunk, axillae, and groin and may improve significantly at puberty. Hypotrichosis in BDCS is congenital and usually diffuse. Patients demonstrate sparse, curly, coarse scalp and body hair, with pili torti and trichorrhexis nodosa. Follicular atrophoderma in BDCS involves the dorsal acral surfaces, face, and extensor knees and elbows. Follicular atrophoderma tends to present after the milia and may result from their resolution. Other features reported in BDCS include hypohidrosis in nearly 50% of patients, trichoepitheliomas, hidradenitis suppurativa, facial hyperpigmentation, “pinched” nose with hypoplastic alae and prominent columella, scarring scalp folliculitis, keratosis pilaris, and hypertelorism. The teeth and nails are typically normal. Because of variable phenotypic expression, affected individuals may present with only hypotrichosis and milia. Inoue et al described a BDCS-like genodermatosis in a Japanese family spanning 4 generations characterized by milia, larger epidermoid cysts, follicular atrophoderma, and variable hypohidrosis usually starting around 20 years of age. This kindred demonstrated perioral atrophoderma and pigmentation and lacked basal cell carcinomas and hypotrichosis.

Rombo syndrome (OMIM 180730)

Rombo syndrome resembles BDCS, with follicular atrophy, milia, and basal cell carcinomas. In contrast to BDCS, cutaneous findings tend to arise around 7 to 10 years of age. Initial features include photodistributed atrophoderma vermiculatum and cyanotic erythema. Milia and telangiectasia appear later. Basal cell carcinomas typically arise during the fourth decade. Trichoepitheliomas are variably described. Although fewer than 10 cases of Rombo syndrome have been reported, inheritance appears to be autosomal dominant. True milia cysts were reported histologically in the original description of the syndrome. However, biopsy specimens in a subsequent report showed vellus hair cysts rather than true milia, suggesting heterogeneity in lesions and/or cases described as Rombo syndrome.

Brooke-Spiegler syndrome (OMIM 605041)

Brooke-Spiegler syndrome is an autosomal dominant disorder caused by CYLD mutations, and characterized by trichoepitheliomas, cylindromas, spiradenomas, or a combination of these. Organoind nevi and malignant transformation of benign adnexal tumors have been reported. Patients may develop salivary gland adenomas and adenocarcinomas. A small subset (Rasmussen syndrome) develop milia.

Orofaciodigital syndrome type 1 (Papillon-League-Psaume, OMIM 311200)

Of the 13 current subtypes of orofaciodigital syndrome (OFDS), only types 1 and 2 manifest skin findings and only OFDS1 includes milia. OFDS1 is an X-linked—dominant, male-lethal disorder characterized by facial dysmorphosis (asymmetry, nasal alar and malar hypoplasia, frontal bossing, hypertelorism, dystopia canthorum, broad nasal ridge, micrognathia, high arched palate, low-set ears), oral findings (multilobed tongue with hamartomas, midline cleft upper lip, soft and hard palate clefts, hypertrophic oral frenulae, missing incisors, supernumerary malpositioned teeth, caries), and digital anomalies (pathognomonic irregular mineralization of the phalanges, clinodactyly-syndactyly of the hands, polydactyly of the feet). The incidence of
OFDS1 is 1:50,000 to 250,000 live births. Expression is highly variable based on random X-inactivation.\textsuperscript{81,82} Extensive milia on the face, scalp, and back of hands are typical during infancy.\textsuperscript{81-84} Milia usually resolve by several years of age, leaving pitted scars. Other features of OFDS1 include patchy alopecia with brittle scalp hair in two thirds of patients (OFDS2 demonstrates isolated coarse hair), abnormal dermatoglyphics, and xerosis. Sweating and nails are normal. Central nervous system anomalies, especially hydrocephalus, porencephaly, and agenesis of the corpus callosum, adversely impact the prognosis. Adults with OFDS1 may present with polycystic kidney disease but otherwise subtle anomalies.\textsuperscript{85,86} Polycystic disease of the pancreas, liver, and ovaries may also occur. The OFDS1 protein may be particularly important in primary cilia formation and function.

**Atrichia with papular lesions (OMIM 209500)**

Atrichia with papular lesions (APL) is an autosomal recessive disorder caused by mutations in \textit{Hairless}.\textsuperscript{87-90} APL is allelic to alopecia universalis congenita.\textsuperscript{88} Although both APL and alopecia universalis congenita demonstrate atrichia, only APL is characterized by widespread milia, especially infraorbitally and on the scalp, elbows, and knees.\textsuperscript{88} These milia tend to appear by 2 to 5 years of age, with a range of 1 to 11 years.\textsuperscript{91,92} Lesion numbers may increase with age\textsuperscript{88} or partially regress with resultant pitting.\textsuperscript{93} Patients with APL may demonstrate hypopigmented whitish streaks on the scalp.\textsuperscript{94} Patients with APL and alopecia universalis congenita may have congenital alopecia, but more typically are born with normal hair that they lose within 4 months to 2 to 3 years of age.\textsuperscript{88,94} Scalp hair is lost with a frontal to posterior progression.\textsuperscript{93} Hair loss is universal except for a minority of patients who retain eyebrows or eyelashes and rare scalp hairs. Nails, sweating, teeth, and growth are normal. Decreased ossification of bone in the hands and wrists has been reported rarely.\textsuperscript{93,95} Histologically, the alopecia of APL and alopecia universalis congenita demonstrates dermal epithelial cysts. Cysts at different depths have distinct CK10, CK17, CK19, and CD34 staining patterns, suggesting infundibular derivation in larger cysts of the papillary dermis, and outer root sheath derivation in smaller cysts of the middle to reticular dermis.\textsuperscript{88}

**Hereditary vitamin D—dependent rickets type 2A (OMIM 277440)**

Hereditary vitamin D—dependent rickets type IIA is an autosomal recessive disorder caused by mutations in the vitamin-D receptor. It may present identically to APL. Of patients, 50% have milia on the face, scalp, upper body, or in a generalized distribution, appearing between 2 years of age and adolescence. In patients whose milia partially regress with time, pitting may develop.\textsuperscript{95} Hair is normal at birth but lost during infancy, usually between 1 to 3 months of age. Eyebrows and eyelashes may persist in some patients. As with APL and alopecia universalis congenita the scalp hair is lost with a frontal to posterior progression.\textsuperscript{93} Scalp histopathology in vitamin D—dependent rickets IIA is identical to APL and alopecia universalis congenita. Other clinical features of vitamin D—dependent rickets IIA include hypocalcemia, hyperparathyroidism, osteomalacia, and rickets.\textsuperscript{88,95}

**Pachyonychia congenita type 2 (OMIM 167210)**

Pachyonychia congenita (PC) is an autosomal dominant disorder (with rare exceptions) associated with mutations in the \textit{KRT6A} or \textit{KRT16} (PC1), or \textit{KRT6B} or \textit{KRT17} (PC2) genes. PC has been classified into multiple types, although classification remains controversial.\textsuperscript{96} PC1 (Jadassohn-Lewandowsky) is characterized by painful focal palmoplantar keratoderma (± bullae), follicular keratoses on the elbows and knees, hyperhidrosis, and oral leukokeratoses. Nail lesions often present during early infancy, although onset of palmoplantar lesions may be delayed for several years. PC2 (Jackson-Lawler) is similar to PC1, with less prominent oral leukokeratoses, more frequent cutaneous cysts, alopecia with pili torti, and (pre)natal or neonatal teeth. Some authors describe PC tarda,\textsuperscript{97} PC3 (prominent ocular lesions, angular cheilosis), and PC4 (laryngeal involvement, prominent hair anomalies, mental retardation) variants.\textsuperscript{98}

The spectrum of cysts in PC is heterogeneous and controversial, but seems to include milia,\textsuperscript{99,100} and larger epidermal inclusion cysts, steatocystoma multiplex (SCM), vellus hair cysts, scrotal and vulvar cysts, and hidradenitis suppurativa (Fig 7). Cysts typically do not develop until puberty, and are commonly on the trunk. Patients with PC1 only have epidermal inclusion cysts, whereas PC2 manifests various cyst types.

**Basal cell nevus syndrome (OMIM 109400)**

Basal cell nevus syndrome (BCNS) (Gorlin syndrome) is an autosomal dominant disorder caused by \textit{PITCHI} mutations, and characterized by numerous anomalies including basal cell carcinomas, odontogenic keratocysts, rib abnormalities, abnormal facies, spina bifida occulta, and calcified falx cerebri. Milia occur in about 30% of patients with BCNS.\textsuperscript{101,102} They may be numerous and are located
periorbitally or on the forehead, in contrast with the larger epidermoid cysts on the trunk and extremities of patients with BCNS. Other cutaneous findings include comedones, palmoplantar pitting, chalazions, and cleft palate/lip.

**Generalized basaloid follicular hamartoma syndrome (OMIM 605827)**

Generalized basaloid follicular hamartoma (BFH) syndrome (GBFHS) is a rare autosomal dominant disorder described by Wheeler et al.103 in a kindred spanning 6 generations. GBFHS remains a controversial entity and some cases may represent variants of BCNS or multiple hereditary infundibulocystic basal cell carcinoma syndrome.103-105 Detailed discussion of this controversy is beyond the scope of this article. As described by Wheeler et al,103 GBFHS is characterized by numerous often pigmented follicular lesions that resemble milia, comedones, dermatosis papulosa nigra, or acrochordons, and histopathologically correspond to BFHs.104,105 Other major features include milia, scalp hypotrichosis, palmar pits, and hypohidrosis. Those who consider GBFHS a distinct entity emphasize that reported cases have not had the associated neoplasms, bone, or ocular disease typical of BCNS.103-105 Patients with GBFHS usually present at birth or in early childhood. Milia or milia-like papules may be the presenting lesions and tend to affect the face and neck, sometimes in a linear pattern. Microscopically, BFH has been described as closely mimicking infundibulocystic basal cell carcinoma, with folliculocentric vertically oriented cords and columns of squamoid cells and uniform small basaloid cells, horn cysts, no mitoses, and minimal pleomorphism or peripheral palisading. There is loose scant fibrous stroma, with clefting and without mucin.103,106 Comedone- and milia-like lesions demonstrate superficial infundibular cysts associated with rudimentary follicular hamartomas.103

**Familial milia and absent dermatoglyphics (OMIM 136000)**

Several similar families have been reported with absent dermatoglyphics and prominent transient congenital milia. Baird107 first described this autosomal dominant syndrome in a family with absent dermatoglyphics, milia, digital flexion contractures, webbed toes, palmoplantar hypohidrosis, and painful fissured calluses. The milia were congenital and facial, and resolved by 6 months. Cirillo-Hyland et al.108 updated the phenotype of the same family to include acral blistering, onychodystrophy, and a single palmar crease. Reed and Schreiner109 reported nearly identical findings across 5 generations of a separate family. Limova et al.110 described similar findings, with the exception of congenital milia, in another family.

**Miscellaneous/other genodermatoses with milia**

Parrish et al.111 described a family with an autosomal dominant pattern of hypotrichosis, light-colored hair color, and facial milia in 11 individuals across 3 generations. In this family, milia were present at birth, limited to the face, and persisted until “middle adult life.” Although hair density was decreased, individual hairs had a normal microscopic appearance, sulfur content, breaking strength, and growth. Teeth, nails, and dermatoglyphics were normal.

Nicolau-Balus syndrome includes eruptive syringomas, milia, and atrophoderma vermiculata.112,113 To our knowledge, it has not been reported in the literature since 1981. However, numerous case reports associating eruptive syringomas and milia,114-121 without atrophoderma vermiculata, may belong within the same spectrum as the Nicolau-Balus syndrome.

Tzermias et al.122 described a 3-generation family with Naegeli-Franceschetti-Jadassohn syndrome manifesting unusual features including milia and normal sweating. Features more typical of Naegeli-Franceschetti-Jadassohn syndrome were reticular
hyperpigmentation, dental abnormalities, abnormal dermatoglyphics, mild palmoplantar hyperkeratosis, and yellowish nails. The histologically confirmed milia appeared later during early adolescence and were accentuated in flexural areas and on the trunk. Naegeli-Franceschetti-Jadassohn syndrome is an autosomal dominant disorder caused by KRT14 gene mutations (allelic to EB simplex [EBS]).

Multiple studies have noted individuals or families with the co-occurrence and/or hybrid lesions of milia, SCM, and eruptive vellus hair cysts (EVHC). Patrizi et al\textsuperscript{123-126} reported two generations of a family variably affected with numerous milia, SCM, and EVHC. The mother presented with numerous milia on the cheeks (which started at puberty), retroauricular MEP, and widespread steatocystomas and cysts with the histopathologic features of EVHC. Her 1.5- and 6-year-old children demonstrated numerous persistent facial milia. Menni and Piccinno\textsuperscript{124} described a similar family with persistent milia in a 9-month-old girl and SCM in her father. Heard et al\textsuperscript{125} described a father and son with MEM, including lesions with features of EVHC.

Lenane et al\textsuperscript{127} reported the unusual association of milia with KID (keratosis-ichthyosis-deafness) syndrome. The milia were congenital, facial, and clustered on the ears; they resolved spontaneously within 3 months.

Prominent milia have been observed in a case of Loey-Dietz syndrome, an autosomal dominant marfanoid disorder caused by TGFBR1 or TGFBR2 gene mutations and characterized by hypertelorism, cleft palate or bifid uvula, malar hypoplasia, blue sclerae, joint laxity, scoliosis, aortic root aneurysm, and arterial tortuosity (Debra Scarlett, MD, written communication [photographs evaluated]).

Genodermatoses with secondary milia

Milia are a feature of many types of EB, especially dystrophic EB, EB acquisita, and sometimes Dowling-Meara EBS (EBS herpetiformis) (Fig 8). Other EB types (junctional EB, localized/Weber-Cockayne EBS, generalized/Koebner EBS) demonstrate few or no milia. Depending on the time of presentation, milia may be particularly prominent in the variant of dystrophic EB known as transient bullous dermolysis of the newborn. Jouary et al\textsuperscript{128} described a 4-month-old boy with transient bullous dermolysis of the newborn who presented with a “disturbing milia eruption” on facial and acral extensor skin without other lesions. The history revealed a few small acral blisters during the first days of life. Transient bullous dermolysis of the newborn is a rare, controversial condition characterized by neonatal trauma-induced blisters on the extremities, lasting approximately 2 months, and usually followed by milia.\textsuperscript{126-132} A minority of cases demonstrate a positive family history, oral lesions, onychodystrophy, scarring, or hypopigmentation. Pathologic features include a sublamina densa split, damaged and decreased anchoring fibrils, dilated rough endoplasmic reticulum in basal keratinocytes, and stellate bodies containing procollagen 7 in basal keratinocytes. Several cases\textsuperscript{129-132} have demonstrated COL7A1 gene mutations with autosomal dominant or recessive inheritance.

Kindler syndrome (OMIM 173650) is an autosomal recessive syndrome caused by mutations in Kindlin-1, which encodes an intracellular protein located at the basolateral aspect of basal keratinocytes and is thought to function by attaching the actin cytoskeleton to the extracellular matrix.\textsuperscript{133-135} Kindler syndrome is characterized by acral traumatic bullae during infancy and early childhood, with later sclerotic poikiloderma, photosensitivity, portenodosis, sclerodermod facies, and leukokeratoses.\textsuperscript{133,134} Milia may be prominent when the blisters heal. Esophageal strictures, pseudosyndactylly, and squamous cell carcinomas may develop.

Milia commonly occur in porphyria cutanea tarda (OMIM 176100), the familial form of which is caused by autosomal dominant mutations in the UROD gene. Milia in porphyria cutanea tarda may occur during childhood but tend to develop during the fourth decade affecting blistered photoexposed areas. Milia may also occur in congenital erythropoietic porphyria (Gunther syndrome), variegate porphyria, hereditary

Fig 8. Milia after erosions on digits of infant with Bart syndrome (dystrophic epidermolysis bullosa).
Genodermatoses with milia-like lesions

Milia-like lesions (here, used to describe lesions that resemble milia clinically but not histologically) have been described in several genodermatoses. Marie-Unna hypotrichosis (MUS) (OMIM 146550) is a rare (<20 families) autosomal dominant disorder characterized by the development of wiry, twisted, coarse hair during early infancy, progressive patterned alopecia after puberty (affecting the vertex and hair margins, with high frontal hairline), and loss of eyebrows, eyelashes, and body hair. Scarring, decreased hair density, and hair-shaft defects (longitudinal grooving, torsion, cross-sectional flattening and irregular shapes, increased diameter) are variable. In 1971, Solomon et al\(^{136}\) reported a 5-generation family with MUS with the unusual feature of milia-like lesions on the face at birth, which could be “removed by gently rubbing” and resolved within months, but commonly recurred up to 6 years of age. Biopsy specimen of a single milia-like lesion “revealed that it was in fact the result of a keratinous plug occluding a dilated and deformed hair follicle” without cyst formation. Other rare associations reported with MUS include juvenile macular degeneration\(^{137,138}\) and widely spaced upper incisor teeth.\(^{139}\) Interestingly, multiple studies\(^{140-143}\) have mapped MUS to 8p21, near the Hairless gene mutated in alopecia universalis congenita/APL. However, sequencing has not identified mutations in the Hairless or other candidate genes and alopecia universalis congenita/APL has autosomal recessive rather than dominant inheritance. MUS has also been mapped to chromosome 1, suggesting genetic heterogeneity.\(^{144}\)

Anhidrotic ectodermal dysplasia (Christ-Siemens-Touraine, OMIM 305100) is characterized by anhidrosis, anodontia, and hypotrichosis. Inheritance is usually X-linked recessive (Ectodysplasin-A1 receptor/EDAR mutations) but may be autosomal dominant (Ectodysplasin-A1 receptor/EDAR mutations, OMIM 129490) or recessive (EDAR or EDARADD mutations, OMIM 224900). Other features include typical facies (thick lips, saddle nose, sunken cheeks, frontal bossing), atopy, and decreased salivary, pulmonary, and gastrointestinal secretions. Patients with anhidrotic ectodermal dysplasia may develop numerous prominent milia-like sebaceous facial papules\(^{145,146}\). These lesions tend to gradually increase after puberty and may demonstrate a male predominance. They correspond histologically to immature sebaceous lobules surrounding poorly formed vellus hairs.\(^{145,146}\)

SECONDARY MILIA

Secondary milia represent a localized form of milia that may be disease associated, medication associated, or caused by trauma. Secondary milia may resolve spontaneously but tend to persist. Postbullous (particularly subepidermal) milia are the classic disease-associated type.\(^{147}\) EB and porphyria cutanea tarda are typical examples. Other diseases reported with secondary milia include bullous pemphigoid, herpes zoster,\(^{148}\) contact dermatitis,\(^{149}\) bullous lupus erythematosus,\(^{150}\) Sweet syndrome,\(^{151}\) early congenital syphilis,\(^{152}\) lichen sclerosus,\(^{153}\) Stevens-Johnson syndrome,\(^{154}\) staphylococcal scalded skin syndrome, bullous erysipelas,\(^{155}\) dermatitis herpetiformis, lichen planus,\(^{156}\) leprosy,\(^{157}\) leishmaniasis,\(^{158-160}\) phototoxic reactions,\(^{161}\) and bullous amylodiosis.\(^{162}\) Medications associated with secondary milia include benoxaprofen,\(^{163,164}\) topical steroids,\(^{165,167}\) 5-fluorouracil,\(^{168}\) cyclosporine,\(^{169}\) and penicillamine.\(^{169}\) Milia developing after acitretin\(^{170}\) or nitrogen mustard\(^{171}\) treatment in patients with mycosis fungoides may be a result of the underlying disease process rather than the medications. Traumatic superficial abrasions in children are a common cause of secondary milia. Other traumatic causes of secondary milia (Fig 9) include second-degree burns, dermabrasion,\(^ {172}\) radiotherapy,\(^ {173}\) chemical peels,\(^ {174}\) skin grafts,\(^ {175}\) and ablative laser therapy.\(^ {176}\) It is unclear whether trauma creates milia through epidermal implantation or by providing a stimulus for undifferentiated pilosebaceous cells to proliferate. Calcified nodules developing after neonatal heel sticks have been well documented, especially in high-risk neonates after repeated skin

**Fig 9.** Numerous secondary milia at site of intravenous line as newborn.
Some cases may represent calcified milia cysts (Fig 10).

**Milia-like disorders**

Milia-like cysts are seen in certain pigmented lesions, particularly seborrheic keratoses and congenital melanocytic nevi. In the latter, milia-like cysts are more common in newborns and resolve with time. Case reports have highlighted numerous rarer milia-like disorders. An uncommon variant of calcinosis cutis is milia-like idiopathic calcinosis cutis (Fig 11). Patients are often children with Down syndrome and they have solitary or multiple lesions. Scrotal calcinosis may represent calcified milia or syringomas. Noncalcified syringomas may also resemble or occur with milia, independent of the Nicolau-Balus syndrome (which also includes atrophoderma vermiculata). Koransky reported a 3-year-old boy who presented with a centrofacial milia-like eruption as a result of multiple eruptive pilomatrixomas, without evidence of myotonic dystrophy. Rositto et al described a congenital hemangioma with yellowish-white small milia-like structures. Histologically, keratinous epidermal cysts were present. Milia-like lesions are seen in cutaneous follicular T-cell lymphoma. Multiple miliary facial osteomas are rare, tending to affect older adult women with long-standing acne. Carter et al described a case of congenital desmoplastic trichoepithelioma presenting as erythematous plaques with atrophic scarring and milia-like lesions on the head. Connolly and Archer described milia-like lesions on the thigh as the presenting sign of chylous reflux (before other signs of lymphedema) in a 39-year-old woman. Finally, milia-like lesions that histologically resemble colloid milium may be seen in exogenous ochronosis.

**Treatment**

The most effective treatment for an individual milium is simple evacuation, such as by nicking it with a scalpel blade and applying tangential pressure to a comedone extractor or curette. Several articles have described “surgical pearls” for treating milia, including evacuation with a paper clip and enucleation with a bent disposable hypodermic needle. Topical retinoids and mild electrocautery or electrodesiccation are treatment options for multiple milia.

**Conclusions**

In 1956, Epstein and Kligman wrote that “milia are probably the commonest benign tumors of the skin.” They believed that research into the pathogenesis of milia could “[throw] light on the origin of other types of benign growths.” Although their use of the term “tumor” may be challenged in some or all forms of milia, their statement nevertheless highlights how common and perhaps fundamental these lesions are, despite the little attention given to them in the literature and the lack of studies of their origin. We hope the expanded classification presented here demonstrates that milia are not only common but have a rich variety of interesting variants.

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