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Update on Epidermal Nevi and Associated Syndromes

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Abstract There are several different types of epidermal nevi, including keratinocyte epidermal nevi, nevus sebaceous, nevus comedonicus, and Becker nevus. This article highlights the varied clinical and histologic features of epidermal nevi, discusses recent data on pathogenesis, and provides an update on treatment options. Syndromes associated with epidermal nevi also are described.

Keywords Epidermal · Nevus · Nevi · Keratinocyte · Sebaceous · Comedonicus · Becker · Syndrome

Introduction

A nevus is defined as a hamartoma composed of a circumscribed overgrowth of various cell types. Cell types that reside in the epidermis include keratinocytes, sebaceous glands, hair follicles, apocrine or eccrine glands, and smooth muscle cells. Accordingly, epidermal nevi (EN) can be composed of overgrowths of any of these cells types. EN also have been classified historically as non-organoid or organoid, with non-organoid nevi being purely keratinocytic in composition and organoid EN composed of combinations of the other components listed above [1]. EN generally present at birth or shortly thereafter as linear plaques with varying textural qualities specific to the type of nevus. Although EN affect many as an isolated finding, they may occur in association with certain syndromes or represent mosaic forms of genetic conditions. Therefore, the clinician must be aware of such conditions and evaluate all patients who present with EN for features that may suggest such syndromes [1, 2].

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Keratinocytic Epidermal Nevi

Keratinocytic EN (also known as verrucous or non-organoid EN) typically present at birth or within the first year as a linear tan patch or thin plaque (Figure 1). Lesions follow Blaschko lines, which represent patterns of ectodermal cell migration during embryogenesis. Rarely, extensive EN may present with extensive cutaneous involvement and no systemic abnormalities (referred to as systematized EN or nevus unius lateralis). At puberty, lesions become thicker, more verrucous, and hyperpigmented [3]. There is an inflammatory variant, referred to as inflammatory linear verrucous epidermal nevus (ILVEN), which is typically erythematous and pruritic (Figure 2). Recently, keratinocytic EN presenting as small, scattered, hyperkeratotic papules with histologic features of palisaded "skyline" basal cells has been described. The authors propose that this represents a distinct subset of EN and coined the term PENS (papular epidermal nevus with skyline basal cell layer) [4].

Histopathologic findings include hyperkeratosis and papillomatosis. Microscopic findings are identical to seborrheic keratosis; therefore, clinical history is imperative for the histopathologist to render a clinically relevant diagnosis. It also is important to recognize histologic features of epidermolytic hyperkeratosis (EHK) within an EN. Histologic

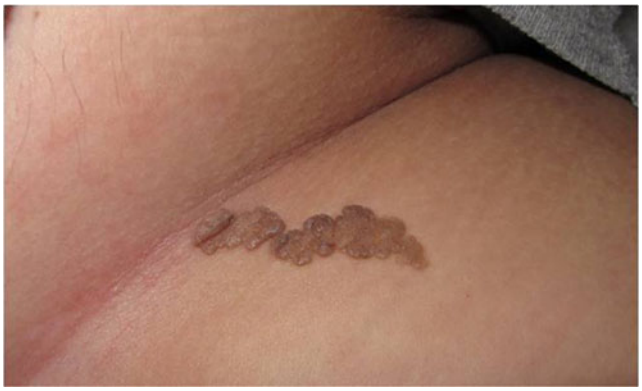

Fig. 1 Keratinocytic epidermal nevus

features of EHK include granular degeneration of the upper layers of the epidermis with large, clumped, keratohyalin granules and compact hyperkeratosis [5]. EHK is associated with mutations in keratins 1 and 10, and EN with EHK are thought to occur because of mosaic mutations in these genes. Patients with EN revealing EHK histology may transmit the mutated gene to their offspring resulting in widespread cutaneous involvement known as epidermolytic hyperkeratosis or bullous congenital ichthyosiform erythroderma and must be counseled about this possibility [6].

EN are thought to occur because of mosaicism for genetic defects, which affect keratinocyte maturation. Up to 33 % of EN of keratinocyte differentiation have been found to have a mutation in the fibroblast growth factor receptor 3 (FGFR3) gene [7, 8]. Recently, the oncogene PIK3CA has been implicated in the pathogenesis of EN, and in one series PIK3CA was mutated in 27 % of EN. Six percent of EN evaluated in this series demonstrated mutations in both PIK3CA and FGFR3. The specific mutations in these genes that have been identified in EN are distinct from the mutations that are typically found in malignancies associated with FGFR3 and PIK3CA mutations, emphasizing the concept that EN have little to no potential for malignant transformation [9]. Additionally, as noted above, EN with EHK are associated with mutations in keratins 1 and 10.

Treatment of EN is challenging. Topical therapies, such as retinoids, and destructive modalities, such as electrodessication or cryotherapy, may temporarily improve the appearance of lesions, but recurrence is frequent. Definitive treatment involves full-thickness excision, which may not be possible in large or extensive lesions. Carbon dioxide laser is an alternative option; however, scarring and pigmentary alteration are potential complications, especially in patients with darker skin types [10, 11]. Recently, methylaminolevulinate photodynamic therapy has been reported as successful in a single case [12]. More studies are needed to assess whether this will be a viable therapeutic alternative.

Nevus Sebaceous

Nevus sebaceous (NS), also known eponymously as nevus sebaceous of Jadassohn, is a common hamartoma involving epidermis, hair follicles, and sebaceous and apocrine glands. Lesions present at birth as yellow-orange to pink, papillomatous, alopecic plaques, measuring up to several centimeters in length (Figure 3). NS most frequently occur on the scalp or face but may occur in other anatomic locations [13]. As with other EN, NS grow proportionately with the child. During puberty, lesions increase in size and develop a more verrucous and greasy texture. This is thought to be related to increased circulating androgens stimulating nevus components, including sebaceous glands, keratinocytes, apocrine, and eccrine glands, which express upregulated androgen receptors in NS [14]. Secondary eczematization, similar to Meyerson's phenomenon in melanocytic nevi, has been recently reported in association with NS [15]. This change may prompt presentation to the dermatologist, and

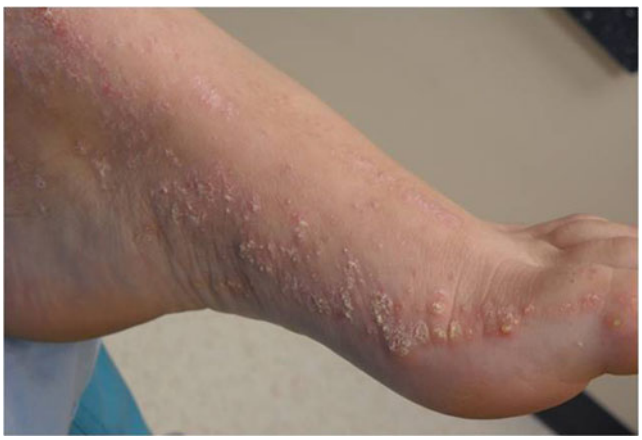

Fig. 2 Inflammatory linear verrucous epidermal nevus (ILVEN)

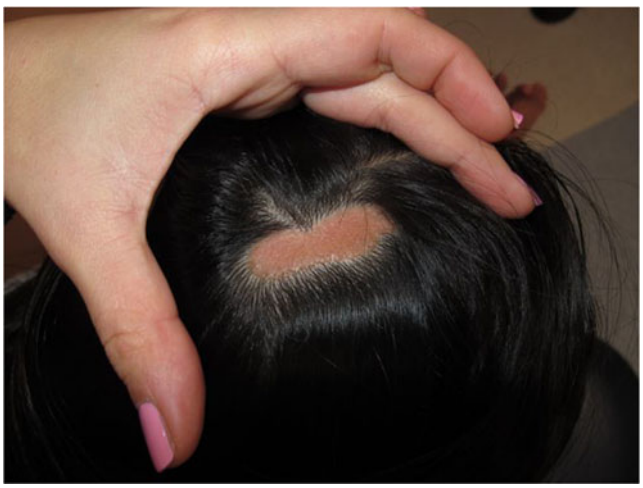

Fig. 3 Nevus sebaceous

if unaware of this phenomenon, may make diagnosis of NS more challenging.

Historically, NS have been reported to have high rates of secondary malignancies, mostly basal cell carcinoma (BCC) [16•]. More recently, authors have argued that many of these BCCs were truly trichoblastomas misdiagnosed as malignancies. These authors found a much lower rate of BCC ranging from 0 % to 0.8 %. Trichoblastoma and syringocystadenoma papilliferum were the most common secondary neoplasms in these series and most frequently occurred in adulthood [13, 17]. A recent review of nearly 5,000 cases of NS showed that 16 % of NS develop secondary benign tumors, whereas 8 % develop secondary malignancies, most commonly BCC, sebaceous carcinoma, SCC, and KA. BCC may be overrepresented in this series, because it included tumors that are thought to have been inaccurately diagnosed. Other less common malignancies that have been reported include melanoma, porocarcinoma, adnexal carcinomas, and leiomyosarcoma. Although infrequent, some of these secondary malignancies were diagnosed in children [16•].

As with other EN, NS is thought to arise from genetic mosaicism. Most cases of NS are sporadic, but rare familial cases have been reported [18–20]. The concept of paradominant inheritance, a nonmendelian inheritance pattern whereby postzygotic loss of heterozygosity results in a mosaic state with focal absence of a wild type allele, has been hypothesized to explain the rare familial cases of nevus sebaceous [19, 21]. The genetic defect leading to NS is unknown, but one study has identified deletions of the Drosophila patched (PTCH) gene in a subset of NS [22]. This is the same gene that is implicated in basal cell nevus syndrome. The importance of this genetic association, in light of recent evidence that BCC are uncommon secondary tumors, is uncertain. Recently, one study found a high prevalence of human papillomavirus (HPV) DNA in NS lesions [23]. However, this study lacked a normal control population, and it remains uncertain whether the HPV is involved in pathogenesis of NS or represents secondary infection of predisposed skin.

Histopathology of NS reveals variable epidermal hyperplasia with hyperkeratosis, acanthosis, or papillomatosis. Sebaceous glands are frequently hyperplastic and numerous but can be hypoplastic or even absent. Hair follicle abnormalities are present in essentially all lesions, and typically have an embryonic or vellus appearance. Ectopic apocrine glands are frequently present [17].

Definitive treatment of a nevus sebaceous is surgical excision. However, the necessity and timing of excision is controversial. Given the recent studies reporting low rates of malignant transformation, some authors believe that early excision is not necessary [13, 17]. Others believe that prophylactic excision should still be pursued because malignant transformation, although rare, can occur. Additionally, even benign growths often require surgical intervention [24]. A prudent approach is to individualize management by weighing patient anxiety about malignant potential and the cosmetic concern, as well as factors, such as size and location of the lesion, the age of the patient, and the feasibility of general versus local anesthesia [16•]. Carbon dioxide laser and photodynamic therapy have reported to improve the cosmetic appearance of NS, but improvement may be transient [25–28]. Also, these modalities do not remove deeper components of NS, leaving a risk of recurrence and development of secondary neoplasms.

Nevus Comedonicus

Nevus comedonicus (NC) is a hamartoma of the pilosebaceous unit that, like other EN, typically presents at birth or during childhood. Clinically, NC lesions consist of linear arrays or clusters of dilated, keratin-plugged follicular orifices resembling comedones. Interfollicular atrophy, which is not present with comedonal acne, may be a clue to diagnosis [1]. Lesions follow Blaschko lines and are typically unilateral, although bilateral lesions have been reported [29, 30]. Lesions may be extensive unilaterally [29]. NC has a predilection for the face, neck, trunk, and proximal extremities [31]. Inflammatory variants can occur, with recurrent pustules, cysts, and secondary bacterial infections. Scarring may occur with this variant [29, 32]. NC lesions have low potential for malignant degeneration, but BCC and SCC arising within NC have been reported [33, 34]. The rarity of such reports suggests that this may be a chance association.

The pathogenesis of NC is unclear. Despite comedone-like appearance of the lesion, appearance of NC is not altered by hormonal variations, such as menarche, menopause, or pregnancy [35]. It has been hypothesized that NC arises from a developmental defect in the mesodermal component of the pilosebaceous unit, wherein the resulting follicular structure is only able to produce soft keratin, which then accumulates [31]. One study found increased filaggrin expression in closed comedones of NC but found no differences in cytokeratin expression between NC and normal skin [36]. Further studies are needed to elucidate the role of keratin and filaggrin in the pathogenesis of NC. As with most other EN, genetic mosaicism has been postulated to contribute to pathogenesis of NC. A somatic mutation in fibroblast growth factor receptor 2 (FGFR2) has been identified in a patient with extensive acneiform nevus [37].

Histopathology of NC reveals epidermal invaginations resembling dilated hair follicles filled with lamellar keratin [31, 35]. EHK has been described in the keratinocytes of the follicular epithelial wall in NC and therefore may represent mutations in keratins 1 and 10 [38, 39]. There has been a single report of a child with generalized EHK, whose father

had two small patches of NC that showed EHK on biopsy [40].

Treatment of NC is generally not medically necessary. However, cosmetically concerning or inflammatory lesions warrant treatment. Surgical excision is the definitive treatment and, as such, extensive lesions can be challenging to treat. Topical therapies, such as ammonium lactate and other keratolytics, retinoids, calcipotriene, or tacalcitol, have been variably effective [30, 31, 41, 42]. Oral antibiotics or intralesional corticosteroids may be effective for the inflammatory variant [32, 35]. Treatment with oral isotretinoin has not been effective for treatment of NC overall but may decrease formation of suppurative cystic lesions [29, 35]. Other reported treatments include manual comedone extraction, dermabrasion, commercially available pore strips, and the erbium:yttrium-aluminum-garnet (YAG) laser [35, 43, 44]. Most recently, complete resolution of NC has been reported with Diode laser treatment in combination with topical retinoid [45].

Becker Nevus

Becker nevus (BN), also referred to as Becker melanosis or pigmented hairy EN, is a common hamartoma that occurs most frequently on the trunk or proximal upper extremities of young men. BN presents as an irregularly bordered, hyperpigmented patch that gradually enlarges and then stabilizes (Figure 4). Unlike other EN, BN does not follow lines of Blashko. Also, unlike most other EN, BN usually appear during adolescence. However, there are reports of BN occurring at birth or during early childhood [46, 47]. Hypertrichosis is common but may be absent, especially in women [1, 48]. Lesions may become more elevated when stroked because of piloerection, called the pseudo-Darier sign. Lesions are typically located on the trunk or proximal upper extremities, but they can occur elsewhere, including the face, which may lead to asymmetric facial hair growth [49, 50•]. Most are solitary, although multiple and bilateral BN have been reported, and has even been reported with extension onto mucous membranes [51–53]. Studies of young, male, military recruits have found a prevalence ranging from 0.25 % to 4.2 % [49, 50•, 54]. Many more cases have been reported in males than in females, but the true male:female ratio is unknown. Some authors postulate that the male:female ratio truly approaches 1:1 due to underreporting of BN in females because of less conspicuous clinical findings [1, 48].

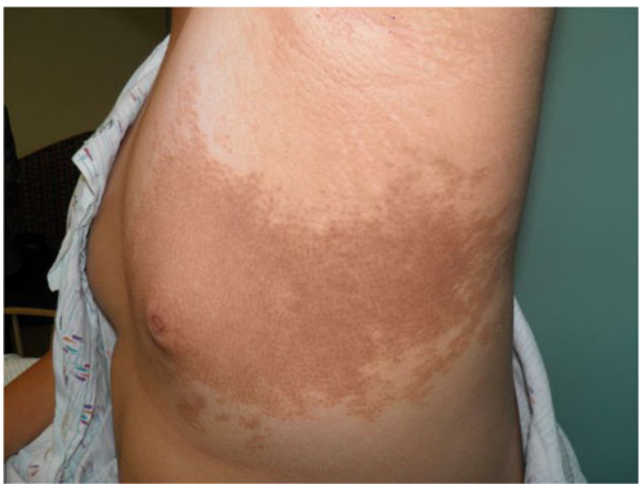

Fig. 4 Becker nevus

Although usually sporadic in occurrence, there are rare reports of familial BN [1, 47]. As in NS, paradominant inheritance is thought to explain the rare familial occurrence and mosaic distribution [21]. BN have been found to be associated with increased androgen receptor density, which may contribute to the pathogenesis of these lesions [1, 55, 56]. Androgen stimulation may explain clinical features, such as pubertal onset, hypertrichosis, acneiform eruptions, acanthosis, dermal thickening, and associated breast hypoplasia in women [55, 56].

Histopathological findings may be subtle, with acanthosis, elongated rete ridges, and basal layer hyperpigmentation. There is no associated melanocytic proliferation. The dermis may contain smooth muscle hyperplasia [48, 55]. Clinical identification may be assisted by use of dermoscopy. Dermoscopic features include pigment network, sometimes with a target appearance. Skin furrow and perifollicular hypopigmentation also can be present. Hair follicles and vessels are apparent [57]. BN are not generally considered to have malignant potential. There are few isolated reports of skin cancers developing within Becker nevi, with the small number of reports suggesting a chance association [58, 59]. It has been suggested that patients with Becker nevus may have a higher incidence of other pigmented lesions, including melanoma, at distant sites, but a true association is unclear [60].

Because BN is a benign condition, many patients require only reassurance. Others desire treatment for cosmetic purposes. Excision is not generally an acceptable option given the large size of most lesions. Laser treatment has had variable efficacy for decreasing pigmentation and hypertrichosis. Erbium:YAG laser has been shown to be more effective than Q-switched Nd:YAG laser [61]. Other authors have had success with long-pulse alexandrite laser and fractional resurfacing with 1550-nm wavelength erbium-doped laser [62, 63] Most recently, attempts have been made to treat with fractional ablation using a 10,600-nm laser. This was moderately effective in some patients, but overall patient-reported outcomes of the therapy were negative [64].

Syndromes Associated with Epidermal Nevi

Epidermal Nevus Syndrome

Many syndromes may be associated with cutaneous findings of EN. The term epidermal nevus syndrome (ENS) has been used to describe the association of EN with extracutaneous anomalies. The varying forms of EN can be associated with syndromes that have unique clinical constellations [1]. Even small EN, especially when other cutaneous signs are present, may be associated with syndromes or warrant further consideration for neurocutaneous, genetic, or metabolic disorders, such as hypophosphatemic vitamin D–resistant rickets. Recently, elevated levels of FGF23 have been found in patients with both nevus sebaceous and keratinocytic EN and hypophosphatemic rickets. FGF23 acts as a phosphaturic factor and is therefore likely to be important in the pathogenesis, although the origin of increased FGF23 is yet to be fully elucidated [65, 66•]. Specific syndromes associated with EN are discussed below, with a focus on syndromes that have recent insights elucidated in the literature.

Proteus Syndrome

PS is characterized by mosaic overgrowth, which is irregular, progressive, asymmetric, and can affect many tissues. Extracutaneous abnormalities most frequently involve extremities but can involve any body part [67]. Linear EN are a common feature of Proteus syndrome (PS). In addition to EN, cutaneous manifestations include vascular malformations (most commonly capillary malformations), cerebriform connective tissue nevi, and dysregulated fatty tissue. Cerebriform connective tissue nevi are less common but are fairly specific for PS. These are most commonly located on the soles of the feet. They are generally not present at birth but evolve slowly over time. Growth may stabilize in adulthood [68]. Fatty overgrowth and/or atrophy also are often present. Additionally, several tumors have been reported in patients with Proteus syndrome. The most specific associations are monomorphic adenomas of the parotid glands and bilateral ovarian cystadenomas [67, 69].

Diagnosis of PS is challenging and evolving. Consensus criteria for the diagnosis were initially proposed in 1998 and included general criteria, such as mosaic distribution of lesions, sporadic occurrence, and progressive course. More specific criteria have recently been revised and include: cerebriform connective tissue nevus, linear EN, progressive asymmetric overgrowth, specific tumors before the second decade of life, dysregulated adipose tissue, vascular malformations, lung cysts, and particular facial phenotype [67]. Application of such criteria to cases of PS reported in the literature reveals a high rate of misdiagnosis [70]. Other syndromes, such as neurofibromatosis type 1, Klippel-Trenaunay syndrome, hemihyperplasia, and multiple lipomatosis syndrome, and potentially other undefined overgrowth syndromes share general features with PS and therefore must be distinguished using specific criteria [67].

Systemic complications of PS include orthopedic deformities related to limb overgrowth, with severe functional and cosmetic consequences. Patients are particularly predisposed to deep venous thrombosis and pulmonary embolism, which can result in early death [71]. Patients frequently also have perioperative thrombotic complications, which has lead to recommendations for perioperative anticoagulation [67]. PS patients are predisposed to a wide variety of tumors, but routine screening imaging is not recommended and should be symptom-guided [67]. Management of these patients requires a multidisciplinary approach, with specialty consultations as needed. The psychosocial effects of this disfiguring and progressively debilitating condition are immense and should be addressed [72].

The genetic basis of PS continues to be elucidated. It has long been postulated that the syndrome results from somatic mosaicism, with an underlying gene defect that would be lethal in a nonmosaic state [67]. Recently, Lindhurst et al. discovered a mosaic activating mutation in the oncogene AKT1 in 26 of 29 patients with PS. AKT1 is an enzyme that mediates cell proliferation and apoptosis [73••]. PTEN (phosphatase and tensin homolog) is a tumor-suppressor gene that encodes a protein tyrosine phosphatase that antagonizes the phosphoinositol-3-kinase/AKT pathway. Previously, there have been reports of patients diagnosed with PS who were found to have PTEN germline mutations [74–76]. Some authors assert that those patients were likely misdiagnosed and should rather be classified as Proteus-like syndrome or type 2 segmental Cowden syndrome (because Cowden syndrome is caused by germline PTEN mutation) [73••, 77]. Although there remains debate in the literature, the recent discovery of mosaic AKT1 mutations in PS patients is a significant advancement toward our understanding of the pathogenesis of PS.

Rapamycin is an inhibitor of mTOR (mammalian target of rapamycin), which is an important component of the PTEN/AKT1 pathway. Patients with PTEN mutation-related overgrowth syndromes have been successfully treated with rapamycin. Given the shared pathway in PTEN and AKT1 mutations, rapamycin or other drugs may be developed to target this pathway and hopefully represent future avenues of medically managing this complex syndrome [78].

Segmental Overgrowth, Lipomatosis, Arteriovenous Malformation, and Epidermal Nevus Syndrome

SOLAMEN syndrome (segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus) is a recently described syndrome based on patients with family members

who have documented Cowden syndrome. These patients had features that were unusual for Cowden syndrome and had overlapping features with PS, including progressive overgrowth, lipomatosis, and vascular malformations, but did not meet criteria for PS. The investigators suggested that the probands had segmental exacerbation of Cowden disease, caused by germline PTEN mutations with mosaic inactivation of the wild-type PTEN allele [79]. These patients also could fit a diagnosis of type 2 segmental Cowden disease, which contributes to ongoing debate about diagnosis and categorization of these overgrowth syndromes [77].

CLOVE Syndrome

CLOVE syndrome (congenital lipomatous overgrowth, vascular malformations, and epidermal nevi) is another recently described ENS based on patients with features similar to PS, but did not meet diagnostic criteria. Patients have congenital bilateral overgrowth of the feet and congenital complex truncal vascular malformations. EN also are a common, although not universal, feature. Overgrowth in these patients is described as "ballooning," referring to a gradual increase in soft-tissue mass, in contrast to the progressive and distorting overgrowth in PS [80, 81]. Central nervous system (CNS) malformations and seizures also may be a component of the syndrome [82]. One author has proposed expanding the acronym to CLOVES to emphasize associated scoliosis and skeletal and spinal anomalies [83]. PTEN mutation analysis has been negative in patients with CLOVE syndrome [80]. Recently, Kurek et al. identified somatic PIK3CA mutations in six of six patients with CLOVE syndrome. PIK3CA is involved in the PTEN/AKT1 pathway, which could explain similarities between CLOVE syndrome and PS [84••].

Nevus Sebaceous Syndrome

The majority of children with NS are otherwise healthy, but an association with neurologic, ocular, skeletal, and other extracutaneous manifestations defines nevus sebaceous syndrome. It also is known eponymously as Shimmelpenning syndrome, Shimmelpenning-Feuerstein-Mims syndrome, Solomon syndrome, Jadassohn syndrome, and others. Although there are several subtypes of ENS, it is sometimes referred to plainly as epidermal nevus syndrome [1].

The most frequent extracutaneous manifestation of nevus sebaceous syndrome is CNS involvement, including seizures, developmental delay, and occasionally structural brain abnormalities [1, 85]. Ophthalmologic abnormalities, including epibulbar lipodermoid and coloboma, also are common. A range of musculoskeletal, cardiovascular, and urogenital manifestations have been described [85, 86]. There can be associated endocrine abnormalities, including hypophosphatemic rickets and precocious puberty [66•].

Nevus sebaceous syndrome is believed to result from mosaicism of a gene defect that would be lethal if inherited as a germline mutation. The timing of the mutation during embryogenesis may determine the phenotype of patients such that a mutation occurring late in embryogenesis could result in an isolated NS, whereas a mutation early in embryogenesis could have more extensive consequences manifesting as NS syndrome [19]. As discussed earlier, a high incidence of HPV DNA has been found in NS. As such, HPV infection of a pluripotent stem cell early in embryogenesis could theoretically play a role in the pathogenesis of NS syndrome [23].

Workup for patients with suspected NS syndrome should include a thorough cutaneous, neurologic and ophthalmological examination, with consideration of electroencephalography, neuroimaging (CT or MRI), skeletal radiography, and liver and renal function testing as well as serum and urine calcium and phosphate levels [1, 85, 87].

Phacomatosis Pigmentokeratotica

The term phacomatosis pigmentokeratotica (PPK) refers to the association of a NS and a papular nevus spilus. Extracutaneous abnormalities, including neurologic, ophthalmologic, musculoskeletal, and endocrine findings, have been reported but are not universal [1, 88–90]. The distribution of the EN usually follows lines of Blaschko, whereas the nevus spilus is arranged in a checkerboard pattern. Different types of melanocytic neoplasms can develop within the nevus spilus, including malignant melanoma [91]. True BCC may develop in the nevus sebaceous at a higher rate than in typical NS [1]. Neurologic and other systemic abnormalities as seen in NS syndrome also can be seen [1, 88, 90].

The pathogenesis of PPK is unknown. However, it is hypothesized to result from didymosis (twin spotting phenomenon), whereby somatic recombination during embryogenesis causes a heterozygous stem cell to give rise to two different populations of daughter cells, each homozygous for a recessive mutation. In this case, this results in lesions consistent with both NS syndrome and nevus spilus syndrome [1, 88].

Nevus Comedonicus Syndrome

Like other ENS, NC in association with other developmental anomalies is referred to as nevus comedonicus syndrome. Extracutaneous manifestations include skeletal abnormalities (spinal deformities and limb defects), cataracts, and CNS abnormalities. Abnormalities are typically ipsilateral to the location of the NC; therefore, presence of a NC and ipsilateral cataract should be a clue to diagnosis [1]. Recently, oligodontia has been identified in a patient with NC syndrome and may represent another component of the

syndrome [92]. NC also may be a marker of occult spinal dysraphism [93]. The etiology of NC syndrome is unclear, but it may result from mosaicism of FGFR2 mutation or of an unknown lethal autosomal mutation [1, 92].

Becker Nevus Syndrome

Becker nevus syndrome refers to presence of a BN with associated developmental defects. The most frequent finding is ipsilateral breast hypoplasia, mainly occurring in female patients, but also in males. Other commonly associated defects include musculoskeletal anomalies (most commonly limb asymmetry or scoliosis) and soft tissue or cutaneous abnormalities (most commonly supernumerary nipples or ipsilateral patchy extramammary fatty tissue hypoplasia) [1, 94].

As noted above, paradominant inheritance has been proposed as the genetic basis of familial Becker nevus and Becker nevus syndrome, but the exact genetic defect remains unknown. The presence of increased androgen receptors within BN, as outlined above, may contribute to the pathogenesis of at least some of the associated defects in BN syndrome [94]. In keeping with this, improvement of breast hypoplasia in association with BN syndrome has been reported after treatment with spironolactone [95].

Conclusions

The various types of epidermal nevi have different clinical presentations, which should be recognized to counsel patients appropriately about the natural history, potential complications, and treatment options for these lesions. Providers also need to be aware of syndromes that can be associated with epidermal nevi, because the cutaneous findings can be a clue to the diagnosis of related neurologic, ocular, musculoskeletal, metabolic, or other anomalies.

Disclosures The authors reported no potential conflicts of interest relevant to this article.

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