A case of subungual tumors of incontinentia pigmenti: A rare manifestation and association with bipolar disease

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Key words: bipolar disorder; Bloch-Sulzberger syndrome; genodermatosis; *IKBKG*; incontinentia pigmenti; lines of Blaschko; *NEMO*; NF-kappa-B; psychiatric disease; subungual tumors of incontinentia pigmenti.

INTRODUCTION

Incontinentia pigmenti (IP), or Bloch-Sulzberger syndrome, is an X-linked dominant disorder with male lethality caused by mutations in the *IKBKG* gene (also known as *IKK-γ* or *NEMO*), which is essential for nuclear factor-κB (NF-κB) activation and protects cells against tumor necrosis factor-α–induced apoptosis.[1] In addition to the 4 cutaneous stages of IP (vesiculo-bullous, verrucous, hyperpigmented, and atrophic/hypopigmented), IP is also associated with ectodermal abnormalities, such as pegged teeth, alopecia, and anodontia as well as neurologic and ocular abnormalities. We present a family in which the mother has severe bipolar disorder and subungual tumors of incontinentia pigmenti (STIPs), and the daughter has classic clinical findings of IP.

Abbreviations used:

IP:	incontinentia pigmenti
NF-κB:	nuclear factor-κB
STIPs:	subungual tumors of incontinentia pigmenti

REPORT OF A CASE

A 25-year-old pregnant woman presented with tender subungual hyperkeratotic papules involving all her fingernails and 3 of 10 toenails (Fig 1, *A*). The lesions were present for more than 10 years, and her medical history was remarkable for longstanding symptoms of severe bipolar disorder, which was diagnosed 1 year earlier and treated with aripiprazole and trazodone. Three months after her initial visit, she delivered a healthy girl, who on day 13 of life, had dozens of 0.2-cm vesicles on the right arm in a Blaschkolinear distribution. At 5 weeks, the lesions evolved into 0.5- to 1-cm verrucous papules. Family history was remarkable for depression and similar, but milder, subungual hyperkeratotic papules in the presenting patient's mother. The patient's sister had a history of polysubstance abuse and schizophrenia but did not have any skin abnormalities.

The development of vesicular then verrucous lesions along Blaschko lines fulfilled 3 major criteria for diagnosis of IP in the daughter.[1] Additional history and physical examination of the mother found a history of male stillbirth, multiple peg-shaped teeth, and a 12-cm Blaschkolinear, hypopigmented, atrophic plaque with follicular dropout on the left calf, which were also clinically diagnostic of IP.[1] She had no history of alopecia or ocular abnormalities.

Biopsy of the mother's subungual lesions showed invaginating, hyperplastic epithelium composed of large, eosinophilic keratinocytes with scattered dyskeratotic cells (Fig 1, *B*). Human papilloma virus immunostain and periodic acid–Schiff stain were both negative. Plain radiographs of the mother's hands showed lucencies in the distal phalanges of the first through fourth fingers bilaterally, with adjacent soft tissue swelling. The clinical findings fulfilled the diagnostic criteria for IP and the initial presenting complaint represented STIPs. Confirmatory

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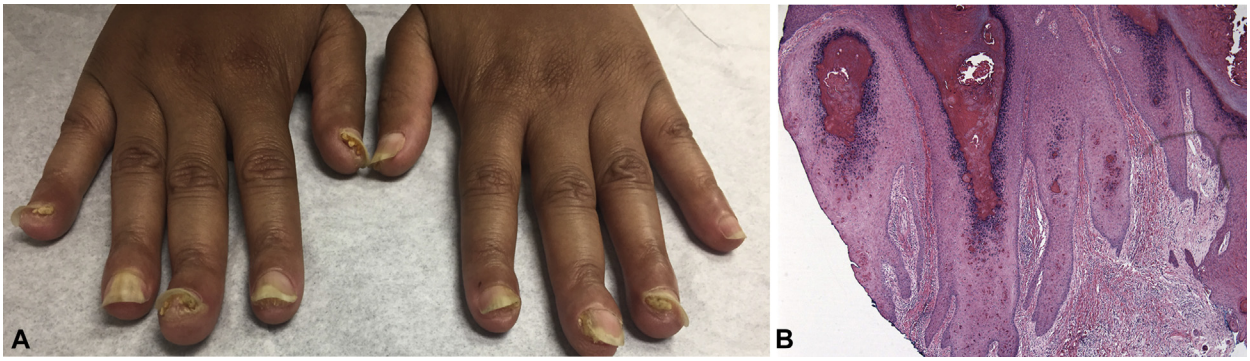

Fig 1. Clinical and histopathologic presentation. **A**, Multiple tender, subungual hyperkeratotic verrucous papulonodules on all fingernails. **B**, Invaginating, hyperplastic epithelium composed of large, eosinophilic keratinocytes with scattered dyskeratotic cells (Hematoxylin-eosin stain; original magnification: ×4.)

genetic testing in both mother and child showed deletion in exons 4-10 in *IKBKG*, the mutation present in 80% to 90% of cases of IP.[2]

Treatment of the mother's STIPs included cryotherapy, salicylic acid, and tazarotene 0.1% gel without significant improvement. She was unable to comply with isotretinoin therapy because of her emotional lability requiring inpatient psychiatric admission for 2 months, so ultimately, she underwent excision of her nailbed tumors by plastic surgery, which she tolerated well.

DISCUSSION

First reported in 1966,[3] STIPs are rare painful subungual hyperkeratotic lesions that occur after puberty in patients with IP.[4] There are at least 20 reported cases of STIPs to date, outlined in Table I.[3-18] All patients were female, and in 60% of them, IP was not diagnosed until later in life. Forty-five percent of cases underwent confirmatory genetic testing, and the onset of STIPs typically was 24 years of age. However, diagnosis of STIPs or IP was often delayed by an additional 10 years. More than half of STIP cases were initially misdiagnosed as paronychia, verruca, keratoacanthoma, squamous cell carcinoma, or epidermoid cysts. Pathology findings of STIPs showed dyskeratosis (12 of 15), hyperkeratosis (10 of 15), and hypergranulosis (7 of 15). Similar to the verrucous stage of IP, pseudoepitheliomatous hyperplasia (5 of 15) and parakeratosis (4 of 15) were also reported. STIPs rarely resolve on their own; however, resolution during pregnancy has been reported.[3,4] Treatment includes surgical excision[4,16] and, more recently, oral[12,15] and topical[16] retinoids.

In addition to her STIPs, our patient had a long history of severe bipolar disorder. The association of IP with psychiatric disease has not been previously described to our knowledge. The chromosomal location of *IKBKG* is on Xq28. Association of bipolar disorder with coagulation factor IX and fragile X syndrome previously suggested susceptibility to effective disorders in the same chromosomal region,[19] although a specific causative gene was not identified. There is accumulating evidence for a role of the immune system in psychiatric diseases including schizophrenia and bipolar disorder,[20] and there is correlative evidence for NF-kB activation in bipolar disorder.[21] As observed in keratinocytes in the skin, the inability to activate NF-kB in *IKBKG*-deficient neurons likely increases their susceptibility to apoptosis. However, a direct causal relationship between *IKBKG* deficiency on NF-kB signaling and the neuronal abnormalities in bipolar disorder is yet to be elucidated. In summary, we present a case of IP with associated painful subungual tumors and severe bipolar disease, the pathogenesis of which may relate to loss of the neuroprotective effects of NF-κB.

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Table I. Reported cases of STIPs

Study	Gender, age at classic IP	IP suspected at birth	Genetic testing	Age at first STIP (y)	Misdiagnoses	Delay in diagnosis (y)	Radiographic findings	Histopathology	Treatment
Hartman,[3] 1966	F, birth	No	No	20	Verruca, epidermal cyst	10	Yes	Dyskeratosis, hyperkeratosis, hypergranulosis, parakeratosis, PEH	Spontaneous regression with pregnancy
Pinol et al,[5] 1973	F, infancy	No	No	15	n/a	n/a	n/a	Hyperkeratosis, hypergranulosis, parakeratosis, pyknotic nuclei	Electrocautery
Pinol et al,[5] 1973	F, infancy	No	No	16	n/a	n/a	None	Hyperkeratosis, hypergranulosis, parakeratosis, pyknotic nuclei	Surgical excision
Mascaro et al,[6] 1985	F, birth	No	No	23	n/a	5	Yes	Dyskeratosis, hyperkeratosis, hypergranulosis, PEH	Surgical excision
Hermanns and Piérard,[7] 1986	F, birth	n/a	No	16	n/a	n/a	n/a	n/a	n/a
Simmons et al,[8] 1986	F, birth	No	No	22	n/a	3	Yes	Dyskeratosis, hyperkeratosis, parakeratosis, PEH, acanthosis, papillomatosis	Electrodessication and curettage
Moss and Ince,[9] 1987	F, n/a	n/a	No	22	n/a	0.4	n/a	n/a	Spontaneous resolution
Adeniran et al,[10] 1993	F, birth	No	No	25	Chronic paronychia, KA, verruca	4	Yes	Hyperkeratosis, hypergranulosis with irregular acanthosis, parakeratosis, nonspecific infiltrate in dermis	Surgical excision
Abimelec et al,[11] 1995	F, birth	Yes	No	10	Verruca	n/a	None	Focal dyskeratosis with whorled pattern, hyperkeratosis with parakeratosis, papillomatosis, lymphohistiocytic infiltrate in upper dermis	2% fluorouracil + betamethasone diproprionate-3% salicylic acid
Malvehy et al,[12] 1998	F, n/a	Yes	No	n/a	n/a	n/a	Yes	Dyskeratosis, hyperkeratosis, hypergranulosis, PEH	Etretinate, 1 mg/kg x 6 mo with resolution
Nicolaou et al,[13] 2003	F, n/a	No	Yes	11	n/a	46	n/a	n/a	Aresenic; radiotherapy; antifungals, topical steroids

Continued

Table I. Cont'd

Study	Gender, age at classic IP	IP suspected at birth	Genetic testing	Age at first STIP (y)	Misdiagnoses	Delay in diagnosis (y)	Radiographic findings	Histopathology	Treatment
Montes et al,[4] 2004	F, birth	No	Yes	25	Verruca, KA, callus, SCC	29	Yes	Dyskeratosis, acanthosis, papillomatosis	Surgical excision; topical treatments (not specified); spontaneous regression
Montes et al,[4] 2004	F, birth	Yes	Yes	18	Epidermal inclusion cyst,verruca	0	No abnormalities	Dyskeratosis, hyperkeratosis, epidermal hyperplasia	surgical excision; spontaneous regression
Bittar et al,[14] 2005	F, n/a	No	Yes	45	Lichen planus	2	n/a	n/a	n/a
	F, n/a	No	Yes	40	n/a	5	n/a	n/a	n/a
Young et al,[15] 2005	F, birth	Yes/infancy	Yes	25	Verruca, SCC treated with amputation	n/a	Yes	Dyskeratosis, PEH, keratinizing epithelium with cystic structures	Acitretin, 25 mg/d x2 mo
Donati et al,[16] 2009	F, birth	No	Yes	28	Squamous neoplasia	3	n/a	Dyskeratosis, hypergranulosis, PEH, acanthosis	Retinoic acid 0.05% cream BID x6 months
Lamb et al,[17] 2012	F, birth	Yes/infancy	No	27	Paronychia, SCC resulting in thumb tip amputation	n/a	Yes	Dyskeratosis, PEH	Surgical excision with resolution; acitretin, 50 mg/d + topical isotretinoin 0.05% gel without response
Mahmoud et al,[18] 2014	F, birth	Yes	Yes	30	Verruca, SCC resulting in left third fingertip amputation	10	Yes	Dyskeratosis, hyperkeratosis, PEH	n/a
Current case	F, n/a	No	Yes	15	Verruca	10	Yes	Subungual keratin and parakeratin with dyskeratotic cells	Salicylic acid 27.5% daily. Tazarotene 0.1% gel; referral to plastic surgery for excision

Note: Delay in diagnosis refers to the time between appearance of the first STIP and arrival at the correct diagnosis.
IP, Incontinentia pigmenti; *KA*, keratoacanthoma; *n/a*, not available; *NF-κβ*: nuclear factor-*κβ*; *PEH*, pseudoepitheliomatous hyperplasia; *SCC*, squamous cell carcinoma; *STIPs*, subungual tumors of incontinentia pigmenti.

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