Pediatric Nevoid Basal Cell Carcinoma Syndrome

Stacey Pilkington, DO; Lana H. McKinley, DO; Richard A. Miller, DO

PRACTICE **POINTS**

- Nevoid basal cell carcinoma syndrome (NBCCS) is a multisystem disorder that requires close monitoring under multidisciplinary care.
- The clinical manifestations of NBCCS include multiple basal cell carcinomas, odontogenic keratocysts, palmar or plantar pits, and calcification of the falx cerebri.

Nevoid basal cell carcinoma syndrome (NBCCS) is a rare, autosomal-dominant, cancer-predisposing, multisystem disorder. The clinical manifestations of NBCCS include multiple basal cell carcinomas (BCCs), odontogenic keratocysts, palmar or plantar pits, and calcification of the falx cerebri. We present a case of an 11-year-old boy with Fitzpatrick skin type V who presented with multiple facial lesions and a history of maxillary keratocysts. Skin biopsy was consistent with pigmented BCC of the right nasolabial fold. Further clinical workup revealed multiple pigmented BCCs, palmoplantar pits, and calcification of the tentorium. Genetic testing revealed a heterozygous mutation in the patched 1 gene, *PTCH1*, consistent with NBCCS. This case highlights the treatment considerations in pediatric cases of NBCCS in Fitzpatrick skin type V patients.

Cutis. 2017;100:423-426.

In 1960, Gorlin and Goltz[1] first described nevoid basal cell carcinoma syndrome (NBCCS) as a distinct clinical entity with multiple basal cell carcinomas (BCCs), jaw cysts, and bifid ribs. This rare autosomal-dominant genodermatosis has a minimal prevalence of 1 case per 57,000 individuals[2] and no sexual predilection.[3] Nevoid basal cell carcinoma syndrome is caused by a mutation in the human homolog of a *Drosophila* gene, patched 1 *(PTCH1)*, which is located on chromosome 9q22.3.[4,5] The major clinical diagnostic criteria includes multiple BCCs, odontogenic keratocysts, palmar or plantar pits, ectopic calcification of the falx cerebri, and a family history of NBCCS.[6] Basal cell carcinoma formation is affected by both skin pigmentation and sun exposure; 80% of white patients with NBCCS will develop at least 1 BCC compared to only 40% of black patients with NBCCS.[7] Goldstein et al[8] postulated that this disparity is associated with increased skin pigmentation providing UV radiation protection, thus decreasing the tumor burden. We report a case of an 11-year-old black boy with NBCCS to highlight the treatment considerations in pediatric cases of NBCCS.

Case Report

An 11-year-old boy with Fitzpatrick skin type V presented with a history of multiple facial lesions after undergoing excision of large keratocysts from the right maxilla, left maxilla, and right mandible. Physical examination revealed multiple light to dark brown facial papules (Figure 1), palmar and plantar pitting (Figure 2), and frontal bossing.

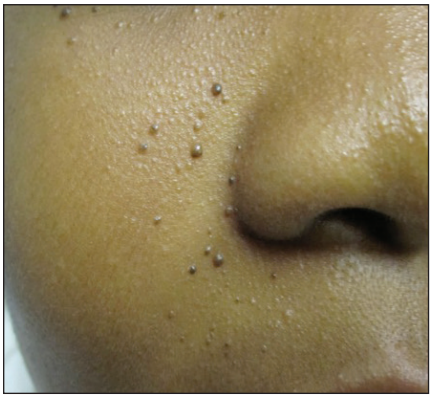

FIGURE 1. Multiple light to dark brown papules located at the nasolabial sulcus.

Dr. Pilkington currently is from Azeal Dermatology Institute, Boulder, Colorado. Dr. Pilkington was from and Drs. McKinley and Miller are from the Nova Southeastern College of Osteopathic Medicine, Largo Medical Center, Florida.

The authors report no conflict of interest.

The eTable is available in the Appendix online at www.cutis.com.

Correspondence: Stacey Pilkington, DO, Azeal Dermatology Institute, 5365 Spine Rd, Ste C, Boulder, CO 80301 (staceyseastrom@gmail.com).

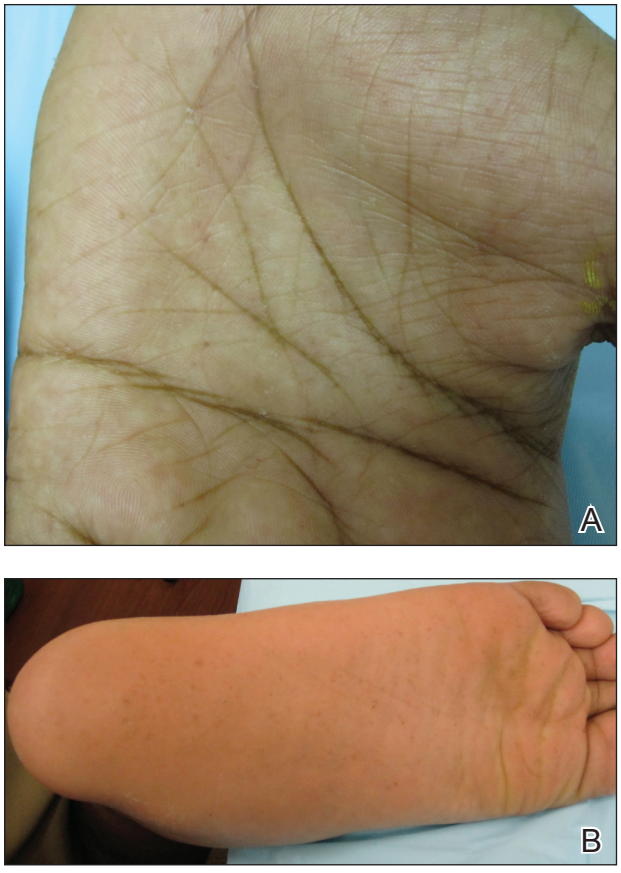

FIGURE 2. Palmar (A) and plantar (B) pitting.

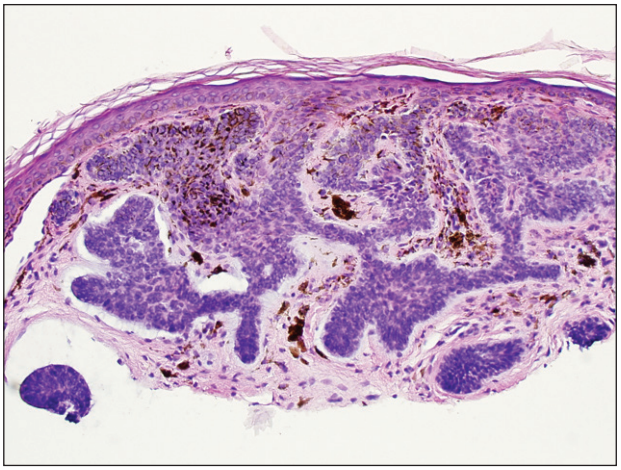

FIGURE 3. Histopathologic evaluation demonstrated aggregates of pigmented basaloid cells, peripheral palisading, and retraction consistent with a pigmented basal cell carcinoma (H&E, original magnification ×10).

He was previously diagnosed with autism and his surgical history was notable only for excision of the keratocysts. The patient was not taking any medications and did not have any drug allergies. There was no maternal family history of skin cancer or related syndromes; his paternal family history was unknown. A shave biopsy was performed on a facial papule from the right nasolabial fold. Histopathologic evaluation revealed findings consistent with a pigmented nodular BCC (Figure 3). The patient was subsequently sent for magnetic resonance imaging of the brain, which demonstrated calcifications along the tentorium. Genetic consultation confirmed a heterozygous mutation of the *PTCH1* gene.

Over the next 12 months, the patient had multiple biopsy-proven pigmented BCCs. Initial management of these carcinomas located on cosmetically sensitive areas, including the upper eyelid and penis, were excised by a pediatric plastic surgeon. A truncal carcinoma was treated with electrodesiccation and curettage, which resulted in keloid formation. Early suspicious lesions were treated with imiquimod cream 5% 5 times weekly in combination with the prophylactic use of tretinoin cream 0.1%. Despite this treatment regimen, the patient continued to demonstrate multiple small clinical pigmented BCCs along the malar surfaces of the cheeks and dorsum of the nose. The patient's mother deferred chemoprevention with an oral retinoid due to the extensive side-effect profile and long-term necessity of administration.

Management also encompassed BCC surveillance every 4 months; annual digital panorex of the jaw; routine dental screening; routine developmental screening; annual follow-up with a geneticist to ensure multidisciplinary care; and annual vision, hearing, and speech-screening examinations. Strict sun-protective measures were encouraged, including wearing a hat during physical education class.

Comment

Classification and Clinical Presentation—Nevoid basal cell carcinoma syndrome is a multisystem disorder that requires close monitoring under multidisciplinary care. Evans et al[6] defined the diagnostic criteria of NBCCS to require the presence of 2 major criteria or 1 major and 2 minor criteria. The major criteria include multiple BCCs, an odontogenic keratocyst or polyostotic bone cyst, palmar or plantar pits, ectopic calcification of the falx cerebri, and family history of NBCCS. The minor criteria are defined as congenital skeletal anomalies; macrocephaly with frontal bossing; cardiac or ovarian fibromas; medulloblastoma; lymphomesenteric cysts; and congenital malformations such as cleft lip or palate, polydactyly, or eye anomalies.[6] The mean age of initial BCC diagnosis is 21 years, with proliferation of cancers between puberty and 35 years of age.[7,9] Our case is unique due to the patient's young age at the time of diagnosis as well as his presentation with multiple BCCs with a darker skin type. Kimonis et al[7] reported that approximately 20% of black patients develop their first BCC by the age of 21 years and 40% by 35 years. The presence of multiple BCCs is complicated by the limited treatment options in a pediatric patient. The patient's inability to withstand multiple

procedures contributed to our clinical decision to have multiple lesions removed under general anesthesia by a pediatric plastic surgeon.

Due to the patient's young age of onset, we placed a great emphasis on close surveillance and management. A management protocol for pediatric patients with NBCCS was described by Bree and Shah; BCNS Colloquium Group[10] (eTable). We closely followed this protocol for surveillance; however, we scheduled dermatologic examinations every 4 months due to his extensive history of BCCs.

Management—Our case presents a challenging therapeutic and management dilemma. The management of NBCCS utilizes a multitude of treatment modalities, but many of them posed cosmetic challenges in our patient such as postinflammatory hypopigmentation and the propensity for keloid formation. Although surgical excision or Mohs micrographic surgery is the standard of treatment of nodular BCCs, we were limited due to the patient's inability to tolerate multiple surgical procedures without the use of general anesthesia.

Case reports have discussed the use of CO_2 laser resurfacing for management of multiple facial BCCs in patients with NBCCS. Doctoroff et al[11] treated a patient with 45 facial BCCs with full-face CO_2 laser resurfacing, and in a 10-month follow-up period the patient developed 6 new BCCs on the face. Nouri et al[12] described 3 cases of multiple BCCs on the face, trunk, and extremities treated with ultrapulse CO_2 laser with postoperative Mohs sections verifying complete histologic clearance of tumors. All 3 patients had Fitzpatrick skin type IV; their ages were 2, 16, and 35 years. Local anesthesia was used in the 2-year-old patient and intravenous sedation in the 16-year-old patient.[12] Although CO_2 laser therapy may be a practical treatment option, it posed too many cosmetic concerns in our patient.

Photodynamic therapy (PDT) is an emerging treatment option for NBCCS patients. Itkin and Gilchrest[13] treated 2 NBCCS patients with δ-aminolevulinic acid for 1 to 5 hours prior to treatment with blue light therapy. Complete clearance was documented in 89% (8/9) of superficial BCCs and 31% (5/16) of nodular BCCs on the face, indicating that blue light treatment may reduce the cutaneous tumor burden.[13] Oseroff et al[14] reported similar success in treating 3 children with NBCCS with 20% δ-aminolevulinic acid for 24 hours under occlusion followed by red light treatment. After 1 to 3 treatments, the children had 85% to 98% total clearance, demonstrating it as a viable treatment option in young patients that yields excellent cosmetic results and is well tolerated.[14] Photodynamic therapy is reported to have a low risk of carcinogenicity[15]; however, there has been 1 reported case of melanoma developing at the site of multiple PDT treatments.[16] Thus, the risk of carcinogenicity is increasingly bothersome in NBCCS patients due to their sensitivity to exposure. The limited number of studies using topical PDT on pediatric patients, the lack of treatment protocols for pediatric patients, and the need to use general anesthesia for pediatric patients all posed limitations to the use of PDT in our case.

Imiquimod cream 5% was shown in randomized, vehicle-controlled studies to be a safe and effective treatment of superficial BCCs when used 5 days weekly for 6 weeks.[17] These studies excluded patients with NBCCS; however, other studies have been completed in patients with NBCCS. Kagy and Amonette[18] successfully treated 3 nonfacial BCCs in a patient with NBCCS with imiquimod cream 5% daily for 18 weeks, with complete histologic resolution of the tumors. Micali et al[19] also treated 4 patients with NBCCS using imiquimod cream 5% 3 to 5 times weekly for 8 to 14 weeks. Thirteen of 17 BCCs resolved, as confirmed with histologic evaluation.[19] One case report revealed a child with NBCCS who was successfully managed with topical fluorouracil and topical tretinoin for more than 10 years.[20] Our patient used imiquimod cream 5% 5 times weekly, which inhibited the growth of existing lesions but did not clear them entirely, as they were nodular in nature.

Chemoprevention with oral retinoids breaches a controversial treatment topic. In 1989, a case study of an NBCCS patient treated with surgical excision and oral etretinate for 12 months documented reduction of large tumors.[21] A multicenter clinical trial reported that low-dose isotretinoin (10 mg daily) is ineffective in preventing the occurrence of new BCC formation in patients with a history of 2 or more sporadic BCCs.[22] Chemoprevention with oral retinoids is well known for being effective for squamous cell carcinomas and actinic keratosis; however, the treatment is less effective for BCCs.[22] Most importantly, the extensive side-effect profile and toxicity associated with long-term administration of oral retinoids prohibits many practitioners from routinely using them in pediatric NBCCS patients.

Nevoid basal cell carcinoma syndrome patients are exquisitely sensitive to ionizing radiation and the effects of UV exposure. Therefore, it is essential to emphasize the importance of sun-protective measures such as sun avoidance, broad-spectrum sunscreen use, and sun-protective clothing.

Conclusion

Nevoid basal cell carcinoma syndrome is a multisystem disorder with a notable predisposition for skin cancer. Our case demonstrates the treatment considerations in a pediatric patient with Fitzpatrick skin type V. Pediatric NBCCS patients develop BCCs at a young age and will continue to develop additional lesions throughout life; therefore, skin preservation is an important consideration when choosing the appropriate treatment regimen. Particularly in our patient, utilizing multiple strategic treatment modalities in combination with chemoprevention moving forward will be a continued management challenge. Strict adherence to a surveillance protocol is encouraged to closely monitor the systemic manifestations of the disorder.

REFERENCES

1. Gorlin RJ, Goltz R. Multiple nevoid basal cell epitheliomata, jaw cysts, bifid rib-a syndrome. *N Engl J Med.* 1960;262:908-911.
2. Evans DGR, Farndon PA, Burnell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. *Br J Cancer.* 1991;64:959-961.
3. Gorlin RJ. Nevoid basal cell carcinoma (Gorlin) syndrome. *Genet Med.* 2004;6:530-539.
4. Farndon PA, Del Mastro RG, Evans DG, et al. Location of gene for Gorlin Syndrome. *Lancet.* 1992;339:581-582.
5. Bale AE, Yu KP. The hedgehog pathway and basal cell carcinomas. *Hum Mol Genet.* 2001;10:757-761.
6. Evans DGR, Ladusans EJ, Rimmer S, et al. Complications of the naevoid basal cell carcinoma syndrome: results of a population based study. *J Med Genet.* 1993;30:460-464.
7. Kimonis VE, Goldstein AM, Pastakia B, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. *Am J Med Genet*. 1997;69:299-308.
8. Goldstein AM, Pastakia B, DiGiovanna JJ, et al. Clinical findings in two African-American families with nevoid basal cell carcinoma syndrome. *Am J Med Genet.* 1994;50:272-281.
9. Shanley S, Ratcliffe J, Hockey A, et al. Nevoid basal cell carcinoma syndrome: review of 118 affected individuals. *Am J Med Genet.* 1994;50:282-290.
10. Bree AF, Shah MR; BCNS Colloquium Group. Consensus statement from the first international colloquium on basal cell nevus syndrome (BCNS). *Am J Med Genet A.* 2011;155:2091-2097.
11. Doctoroff A, Oberlender SA, Purcell SM. Full-face carbon dioxide laser resurfacing in the management of a patient with the nevoid basal cell carcinoma syndrome. *Dermatol Surg.* 2003;29:1236-1240.
12. Nouri K, Chang A, Trent JT, et al. Ultrapulse CO_2 used for the successful treatment of basal cell carcinomas found in patients with basal cell nevus syndrome. *Dermatol Surg.* 2002;28:287-290.
13. Itkin A, Gilchrest BA. δ-Aminolevulinic acid and blue light photodynamic therapy for treatment of multiple basal cell carcinomas in two patients with nevoid basal cell carcinoma syndrome. *Dermatol Surg.* 2004;30:1054-1061.
14. Oseroff AR, Shieh S, Frawley NP, et al. Treatment of diffuse basal cell carcinomas and basaloid follicular hamartomas in nevoid basal cell carcinoma syndrome by wide-area 5-aminolevulinic acid photodynamic therapy. *Arch Dermatol*. 2005;141:60-67.
15. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. *Br J Dermatol.* 2002;146:552-567.
16. Wolf P, Fink-Puches R, Reimann-Weber A, et al. Development of malignant melanoma after repeated topical photodynamic therapy with 5-aminolevulinic acid at the exposed site. *Dermatology.* 1997;194:53-54.
17. Geisse J, Caro I, Lindholm J, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol.* 2004;50:722-733.
18. Kagy MK, Amonette R. The use of imiquimod 5% cream for the treatment of superficial basal cell carcinomas in a basal cell nevus syndrome patient. *Dermatol Surg.* 2000;26:577-579.
19. Micali G, Lacarrubba F, Nasca MR, et al. The use of imiquimod 5% cream for the treatment of basal cell carcinoma as observed in Gorlin's syndrome. *Clin Exp Dermatol.* 2003;28:19-23.
20. Strange PR, Lang PG. Long-term management of basal cell nevus syndrome with topical tretinoin and 5-fluorouracil. *J Am Acad Dermatol.* 1992;27:842-845.
21. Sanchez-Conejo-Mir J, Camacho F. Nevoid basal cell carcinoma syndrome: combined etretinate and surgical treatment. *J Dermatol Surg Oncol.* 1989;15:868-871.
22. Tangrea JA, Edwards BK, Taylor PR, et al. Long-term therapy with low-dose isotretinoin for prevention of basal cell carcinoma: a multicenter clinical trial. Isotretinoin-Basal Cell Carcinoma Study Group. *J Natl Cancer Inst.* 1992;84:328-332.

APPENDIX

eTABLE. Management Protocol for Surveillance of Pediatric Patients With NBCCS[a]

Baseline MRI of the brain with contrast and epilepsy protocol • Repeat yearly until 8 years of age, then discontinue • Repeat sooner if symptomatic
Baseline cardiac ultrasound • Repeat sooner if symptomatic
Baseline dermatologic examination • Repeat yearly until first BCC • After first BCC, repeat every 6 months or more frequently as needed
Baseline digital panorex of jaw (as soon as tolerated) • Repeat yearly until first jaw cyst • After first jaw cyst, repeat every 6 months until no cysts for 2 years or until 21 years of age • Repeat more regularly if needed for symptoms or occurrence
Baseline spine film at 1 year of age or time of diagnosis (digital if possible) • Repeat if symptomatic • If abnormal, repeat per scoliosis protocol every 6 months
Pelvis ultrasound in girls at menarche or 18 years of age • Sooner if symptomatic or if symptoms develop • Repeat if abnormal
Routine developmental screening (well-child visits) • If fails screening or not meeting milestones, further developmental assessment and testing is warranted • If school age with difficulty learning in school, cognitive evaluation and testing is warranted
Annual vision, hearing, and speech screenings • Continue through school age
Baseline ophthalmology evaluation • Repeat if symptomatic
Initial psychological evaluation • To establish a relationship for support and counseling • Follow-up would be based on individual recommendations from the initial evaluation
Baseline medical/clinical genetics evaluation • Repeat annually to ensure multidisciplinary care recommendations are being followed
Molecular diagnosis • If necessary to confirm diagnosis
Minimize ionizing radiation exposure and maximize protection • Radiographs warranted for evaluation of valid medical problems • Utilize nonionizing/digital imaging modalities if possible

Abbreviations: NBCCS, nevoid basal cell carcinoma syndrome; MRI, magnetic resonance imaging; BCC, basal cell carcinoma.
[a]Repeat any test if patient becomes symptomatic.

Reprinted with permission from Bree and Shah; BCNS Colloquium Group.[10]