FEATURE ARTICLE

NCPD 2.0 Contact Hours

Skin Cancer

Basal Cell Nevus Syndrome (Gorlin Syndrome)

Lauren Flowers, Mandeep Sandhu, and Kari Martin

ABSTRACT: Basal cell nevus syndrome is a genetically linked multisystem disorder with a hallmark tendency for development of multiple basal cell carcinomas at a young age. It is associated with a multitude of other anomalies including keratocytes of the jaw, palmar or plantar pits, and ectopic intracranial calcifications. This disease is most commonly caused by loss of function in tumor suppressor gene *PTCH1* resulting in overactivation of the Hedgehog pathway and basal cell carcinoma formation. Diagnosis is largely clinical; patients must meet criteria of both major and minor categories. Genetic testing is warranted in specific situations where clinical diagnosis is unclear or for genetic counseling purposes. Given that basal cell carcinoma is a very common dermatologic disorder, it is important to recognize when it arises in the setting of genetically associated diseases. Early detection allows for proper management and surveillance of not only basal cell carcinomas but also the other multisystem effects of basal cell nevus syndrome. This review gives an in-depth overview of the etiology, pathogenesis, diagnosis, and management of basal cell nevus syndrome.

Key words: Basal Cell Nevus Syndrome, Gorlin Disease, Skin Cancer, Basal Cell Carcinoma, Gorlin-Goltz Syndrome, Nevoid Basal Cell Carcinoma

Basal cell nevus syndrome (BCNS), also known as Gorlin syndrome, Gorlin–Goltz syndrome, or nevoid basal cell carcinoma (BCC) syndrome, is a genetically linked disorder characterized by the development of multiple BCCs at a young age. The syndrome is associated with various developmental anomalies such as skeletal abnormalities, jaw cysts, plantar or palmar pits, and ectopic calcifications (Jones et al., 2011; Krakowski et al., 2022).

There are approximately 4.3 million cases of BCC diagnosed each year in the United States, making it the most common type of cancer (Davis, 2020). Although a vast majority of BCC cases are not linked to a multisystem genetic disorder, it is important to recognize when this disease arises to improve patient care and prevention of future BCCs. Management of BCNS relies on the ability of clinicians to recognize and treat BCCs early in their disease course to improve patient outcomes (Kiwilsza & Sporniak-Tutak, 2012). In addition, given that this is a multisystem disease, multidisciplinary care is pertinent for long-term management and secondary prevention in patients with BCNS (Kiwilsza & Sporniak-Tutak, 2012). Dermatology nurses have the unique opportunity to deliver high-level care in diverse patient populations, and this helps establish maximal dermatologic health (Adamson, 2009). Evidence-based practice guided by continued education on dermatologic diseases, including genetically linked skin cancer syndromes, can help implement optimal dermatology interventions to lower morbidity and improve patient care outcomes (Adamson, 2009).

In this review article, we describe the etiology, pathogenesis, clinical presentation, diagnosis, and management of BCNS.

ETIOLOGY AND CATEGORIZATION

BCNS is inherited in an autosomal dominant pattern with a high degree of penetrance (Jawa et al., 2009). However, BCNS is also characterized by variable expressivity, even within immediate families, which sometimes makes diagnosis challenging (Fisher et al., 2020). Although many cases of BCNS are inherited, sporadic disease development is estimated to occur in up to 50% of cases (Fisher et al., 2020). Prevalence of BCNS is low and is estimated to occur in somewhere between one in 31,000 and one in 256,00 individuals (Fisher et al., 2020). There has been no observed gender or ethnic predilection in BCNS (Bresler et al., 2016; John & Schwartz, 2016).

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BCNS is generally characterized by five major clinically affected body systems: cutaneous, dental or osseous, ophthalmic, neurological, and sexual (Jawa et al., 2009). Most patients exhibit early development of BCCs, keratocystic odontogenic tumors, palmar or plantar pits, and ectopic calcifications (Jawa et al., 2009). The BCCs associated with BCNS appear most commonly between puberty and the age of 35 years, which is much younger than the typical age of onset as seen with sporadic BCCs (Krakowski et al., 2022). In the general population as well as among those with BCNS, risk factors attributed to the development of BCCs include sun exposure, radiation, immunosuppression, and Vitamin D deficiency (John & Schwartz, 2016).

PATHOGENESIS

BCNS is caused by an inherited heterozygous loss of function mutation of the tumor suppressor genes *PTCH1* on chromosome 9q22–q31 and less often in *PTCH2* or *suppressor of fused* (Fisher et al., 2020; John & Schwartz, 2016; Krakowski et al., 2022). The development of BCC in BCNS relies on the tumor suppressor gene two-hit hypothesis where patients with BCNS have baseline heterozygosity secondary to germline *PTCH* mutation and lose the additional tumor suppressor sporadically because of traditional BCC risk factors, such as ultraviolet or ionizing radiation (Jones et al., 2011). Double hit of the tumor suppressor gene leads to continuous activation of the Hedgehog pathway, which plays an important role in cellular developmental and regulatory functions (Jones et al., 2011; Krakowski et al., 2022). Aberration of the Hedgehog pathway is a key dysregulation that results in the development of BCC in about 90% of patients with BCNS (Krakowski et al., 2022). There does not appear to be an association of the quantity, severity, or age of onset of BCCs developed in patients with BCNS and the specific *PTCH* mutation type (Jones et al., 2011). Of note, mutations in the *PTCH* gene resulting in the development of BCCs occur sporadically approximately 50% of the time (Jones et al., 2011). Thus, clinical prognosis and prediction of disease burden do not predicate on the determination of specific *PTCH* mutation subtype.

DIAGNOSTIC CRITERIA

Diagnosis of BCNS can be made when (a) one major criterion and molecular confirmation, (b) two major criteria, or (c) one major and two minor criteria are met (Bree et al., 2011); Table 1 lists the major and minor diagnostic criteria. Major criteria include the development of greater than two BCCs (excessive numbers out of proportion to prior sun exposure and skin type) or one BCC before the age of 20 years; histologic evidence of keratocystic odontogenic tumors; three or more palmar or plantar pits; ectopic intracranial calcification typically of the falx cerebri; first-degree relative with a diagnosis of BCNS; or presence of bifid, fused, or markedly splayed ribs (although sometimes considered to be minor criteria; Bresler et al., 2016; Fisher et al., 2020; Jawa et al., 2009; Krakowski et al., 2022).

Over 100 minor criteria have been described (Jawa et al., 2009). Minor criteria include craniofacial abnormalities (macrocephaly, coarse facial features), congenital malformations (cleft palate, cataracts), early-onset childhood medulloblastomas, cardiac or ovarian fibromas (usually bilateral), lympho-mesenteric cysts; other neoplasms (rhabdomyosarcoma, meningioma), or other radiologic skeletal abnormalities (pectus deformity, syndactyly, vertebral anomalies; Fisher et al., 2020; Jawa et al., 2009; Jones et al., 2011; Krakowski et al., 2022).

Diagnosis of BCNS is largely clinical. Approximately 40% of patients with BCNS initially test negative for *PTCH* mutations, and 28% continue to test negative after use of comparative genomic hybridization techniques (Fisher et al., 2020). Thus, genetic testing for *PTCH* mutation is not routinely done. Genetic testing is generally warranted if patients lack sufficient clinical diagnostic criteria, if the patient does not exhibit clinical symptoms but a family member is affected, or for prenatal

TABLE 1. Major and Minor Diagnostic Criteria of Basal Cell Nevus Syndrome

Diagnosis of BCNS can be made when (a) one major criterion and molecular confirmation, (b) two major criteria, or (c) one major and two minor criteria are met

Major criteria

- >5 lifetime BCCs or 1 BCC before the age of 20 years
- Keratocystic odontogenic tumor confirmed by histology, ≥3 palmar or plantar pits
- Ectopic intracranial calcification (typically falx cerebri)
- First-degree relative with a diagnosis of basal cell nevus syndrome
- Presence of bifid, fused, or markedly splayed ribs

Minor criteria

- Craniofacial abnormalities
  - Macrocephaly, frontal bossing, hypertelorism, coarse facial features
- Congenital malformations
  - Cleft palate, cataracts, glaucoma, colobomas
- Childhood medulloblastomas
- Cardiac or ovarian fibroma
- Lympho-mesenteric cysts
- Other tumors
  - Rhabdomyosarcoma, meningioma
- Skeletal abnormalities
  - Sprengel deformity, pectus deformity, syndactyly, shortening of the fourth digit, vertebral anomalies (hemivertebrae, wedge-shaped vertebrae, fusion of vertebrae), abnormal bridging of the sella turcica

Note. BCNS = basal cell nevus syndrome; BCC = basal cell carcinoma.

testing if there is a known familial mutation (Spiker et al., 2022).

In addition to clinical examination, radiographic imaging is an important step to aid in diagnosis confirmation and continued disease management and surveillance. Initial radiographic imaging that should be performed includes panoramic x-ray of the jaw; magnetic resonance imaging of the brain; echocardiogram; pelvic ultrasound in female patients; and x-rays of the chest, skull, spine, long bones, and hands (John & Schwartz, 2016).

Differential diagnosis includes but is not limited to other rare dermatologic disorders with predilection of early-onset skin cancer development including xeroderma pigmentosum, Bazex–Dupré–Christol syndrome, and Rombo syndrome (Bresler et al., 2016).

CLINICAL PRESENTATION

Approximately two thirds of patients with BCNS present with recognizable facial features such as macrocephaly, frontal bossing, hypertelorism, and coarse facial features (Jones et al., 2011). Keratocystic odontogenic tumors tend to occur in the second decade of life and present in multiples, most often in the mandible (Jones et al., 2011; Krakowski et al., 2022). The finding of multiple jaw keratocysts developing in younger than adulthood may be relatively specific for the diagnosis of BCNS (Jawa et al., 2009). In addition, ectopic calcifications are present in over 90% of patients with BCNS and usually develop by the age of 20 years (Jones et al., 2011). The calcifications may be noted as an incidental finding on head imaging (Kalogeropoulou et al., 2009).

Furthermore, acral pits are a common finding among patients with BCNS, which are permanent and increase in number with disease progression (John & Schwartz, 2016). As many as 30%–65% of patients with BCNS have palmar or plantar pits by the age of 10 years; and over 80%, by the age of 15 years (John & Schwartz, 2016). Acral pits, which can vary between pale pink to skin-colored small depressions, can be witnessed under dermatoscopy as red globules within sharp boarders (John & Schwartz, 2016). Histological evaluations show hypokeratosis, palisading basal keratinocytes, basal cell hyperplasia, and the presence of vessels in the papillary dermis (John & Schwartz, 2016).

BCC CLASSIFICATION IN BCNS

BCC development in BCNS commonly affects sun-exposed areas of the face and the nape of the neck. An individual's development of BCC can vary from just a few to hundreds over a lifetime, with a median number of eight (Bresler et al., 2016; John & Schwartz, 2016; Jones et al., 2011). The developmental age of first BCCs in BCNS has a median range of 20–25 years, with some reports of as early as 2 years and as late as 65 years (Jones et al., 2011). Significant proliferation of new BCCs tends to occur between puberty and the age of 35 years (Jones et al., 2011). BCCs in BCNS can be more aggressive than sporadic BCCs (Bresler et al., 2016). However, overall, BCCs in BCNS tend to behave similarly to sporadic BCCs; therefore, they rarely metastasize (Jones et al., 2011).

On physical examination, BCCs appear similarly to sporadic BCCs as pearly papules with telangiectasias at the base (Bresler et al., 2016). Ulceration is possible if left untreated, but this rarely occurs before adolescence (John & Schwartz, 2016). Dermatoscopy reveals "arborizing telangiectasia, ulceration, spoke wheel structures, blue–gray ovoid nests or globules, and shiny white areas of crystalline consistency" (John & Schwartz, 2016, p. 70). Comparable with sporadic BCCs, the histopathology of BCNS-associated BCCs reveals cells characterized by strongly stained nuclei and poorly defined cell membranes arranging as nests, islands, or sheets. Similar to sporadic BCCs, on histopathology, BCCs of BCNS present with characteristic deeply staining nuclei and in distinct cell membranes within cells that are arranged in nests and islands or sheets (Jones et al., 2011). A histologic clue that is known to occur in BCCs associated with BCNS, although not specific for, is the presence of incidental small early buds of superficial BCC in the setting of an unremarkable physical examination (Bresler et al., 2016). The main types of sporadic BCCs are nodular, superficial, morpheaform, and fibroepithelial, with additional variations classified as cystic, micronodular, and basosquamous (Davis, 2020). In BCNS, the main subtypes that have been documented are nodular, micronodular, superficial, infiltrative, and fibroepithelioma (John & Schwartz, 2016).

Skin of Color

Patients with a lighter skin pigment tend to experience higher rates of and earlier onset development of BCCs compared with their darker skinned counterparts; however, skin pigmentation is not advantageous at preventing disease inheritance or from developing other anomalies (da Silva Pierro et al., 2015; John & Schwartz, 2016). It has been cited that only approximately 40% of Black patients with BCNS develop BCCs and tend to have a much lower total number compared with white individuals (Jones et al., 2011). Development of multiple BCCs in Black individuals is a rare finding (Kulkarni et al., 2003). Thus, in genetically predisposed individuals, darker skin pigmentation may offer a protective factor against BCC. However, lack of BCC development may, in turn, delay proper diagnosis of BCNS, resulting in delayed treatment and genetic counseling (da Silva Pierro et al., 2015). This highlights the importance of understanding the various components of BCNS to aid in diagnosis despite the presence or absence of BCCs.

MANAGEMENT

Treatment of BCCs in BCNS can be difficult as each lesion must be approached individually. Typical BCC management consists of surgical excision and curettage and destruction;

however, the procedural complications of pain and scarring can be a considerable burden for patients with BCNS with a high tumor burden at a young age (Fisher et al., 2020). Although BCCs rarely metastasize, significant local tissue destruction and potential infiltration into underlying organs can occur, and patients with BCNS are at a higher risk given their tumor burden (Davis, 2020). Multiple nonsurgical treatment options are available: topical imiquimod with or without curettage, 5% 5-fluorouracil with or without 0.1% tretinoin cream, oral retinoids, photodynamic therapy, laser therapy, topical solasodine glycoalkaloids, or topical tazarotene (Fisher et al., 2020).

Vismodegib received FDA approval in 2013 as the first Hedgehog pathway-targeted small molecule that directly inhibits signaling constituents known in the development of BCCs in BCNS (Bresler et al., 2016). This therapy has shown promising results in adults but is associated with irreversible growth plate fusion in children (Fisher et al., 2020). Therapeutic goals for children consist of sufficient cancer control with attempts to minimize any discomfort or scarring (Fisher et al., 2020).

Long-term management of patients with BCNS consists of frequent dermatologic evaluations in combination with BCC preventative measures, such as skin protection from ultraviolet exposure as well as use of Vitamin D, retinoids, and phototherapy (Fisher et al., 2020; John & Schwartz, 2016). Patients with BCNS should also receive annual radiologic screening for medulloblastomas (until the age of 8 years) and keratocystic odontogenic tumors. Any radiotherapy is contraindicated in patients with BCNS (Bresler et al., 2016).

PROGNOSIS

The extensive tumor burden and multisystem effects in patients with BCNS can diminish quality of life (John & Schwartz, 2016). With early detection and routine surveillance, development of BCCs can be caught and treated early before the progression of disease. Prognosis of BCC is generally very good, with most cases curable on early detection (Krakowski et al., 2022). In patients with BCNS, many of the BCCs can be more difficult to treat and more aggressive than sporadic BCC. On average, 32% of patients are found to have greater than 250 BCCs that are difficult to treat with current treatment options (Solis et al., 2017).

CONCLUSION

Given the characteristic physical findings of BCNS and its associated nondermatological findings, increased education and exposure to diagnostic criteria are important throughout the healthcare system. In particular, nurses, who have diverse roles within the healthcare system, are in unique positions to be able to adeptly diagnose BCNS and work toward an earlier diagnosis of BCNS in our patients. ■

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