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Nevoid basal cell carcinoma syndrome

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INTRODUCTION — Nevoid basal cell carcinoma syndrome (NBCCS) is a rare inherited multisystem disorder that is due to germline mutations in the human homolog of the patched (*PTCH*) gene. The estimated prevalence is between 1 in 57,000 and 1 in 164,000 persons [1-3].

First reported in 1894, the clinical manifestations of NBCCS were more clearly defined in 1960 by Gorlin and Goltz [4]. Affected patients have multiple developmental anomalies and the early onset of multiple nevoid basal cell carcinomas (BCCs) and medulloblastomas, usually by age 35 [5]. Other synonyms for NBCCS include the Gorlin or Gorlin-Goltz syndrome, basal cell nevus syndrome, bifid-rib basal-cell nevus syndrome, basal cell cancer syndrome, and multiple basal cell nevi.

MOLECULAR GENETICS — Nevoid basal cell carcinoma syndrome (NBCCS) is inherited as an autosomal dominant trait with a high degree of penetrance (approximately 97 percent), but variably expressed [6]. The cause is a germline inactivating mutation involving the human homolog of the *Drosophila PTCH1* (patched) gene, which is located on chromosome 9q22.3 [2,7-10]. In most cases, loss of function mutations in *PTCH1* result in premature termination of the PTCH protein [11-14]. Loss of heterozygosity at this site in both hereditary and sporadic basal cell carcinomas (BCCs) suggests that it functions as a tumor suppressor gene (see 'PTCH1 in sporadic basal cell carcinomas' below) [15]. In a manner similar to the retinoblastoma gene, two somatic "hits" in the same cell appear to be required for sporadic cases, while one somatic "hit" plus the inheritance of one defective allele underlies familial cases [16]. (See "Overview of retinoblastoma", section on 'Pathogenesis'.)

Molecular pathogenesis — The only known function of the PTCH protein is as a receptor for the hedgehog (HH) protein, a component of the sonic hedgehog (SHH) signaling pathway (figure 1).

This pathway is important in determining tissue patterning and cell fate in multiple structures within the developing embryo [17,18]. SHH signaling is activated when HH binds to its receptor, a complex that is formed by PTCH and a second protein, Smoothed (SMO), a transmembrane protein (figure 2) [19-23]. PTCH functions as a regulatory molecule for SMO, with PTCH-induced repression of SMO limiting the effect of the SHH signal [20,23].

According to this model, SMO repression is relieved following mutational inactivation of *PTCH1* in patients with NBCCS [24]. This results in constitutive overexpression of the SHH signal, which has been implicated in the development of BCC and other tumors, possibly via activation of the transcription factors Gli1 and/or Gli2 (figure 1) [18,20,25-28]. The evidence to support a link between overexpression of the SHH pathway and tumorigenesis is as follows:

- Transgenic mice overexpressing SMO or SHH in the skin spontaneously produce skin lesions resembling human BCCs [24,29].
- Owing to failure of negative feedback, the mutant *PTCH1* transcript is overexpressed in affected tissues. Such transcripts are found at high levels in the BCCs and odontogenic keratocysts from patients with NBCCS, but not in skin or other types of tumors [30-32].

Influence of race — Race appears to influence the incidence of NBCCS and also modulates its penetrance. Only about 5 percent of all NBCCS case reports involve blacks [33], and a similar low frequency is reported in Asians [34].

The expression of cutaneous BCCs as a component of the NBCCS appears to be blunted in individuals with dark skin as well as Asians [34,35]. Only about 30 to 38 percent of black persons with NBCCS have BCCs (compared to 75 to 80 percent in Caucasians, (see 'Clinical findings' below)), and fewer than 15 percent have more than two BCCs [36]. Because of this, most black patients with NBCCS are diagnosed by asymptomatic odontogenic cysts discovered during routine dental or facial radiography rather than by the appearance of BCCs [37].

PTCH1 in sporadic basal cell carcinomas — Support for the involvement of *PTCH1* in tumorigenesis is supported by the finding of acquired *PTCH1* mutations in approximately one-third of sporadic BCCs [38,39], in xeroderma pigmentosum-associated BCCs [40], as well as some sporadic meningiomas and medulloblastomas. In sporadic BCCs, inactivation of the *PTCH1* gene appears to be a necessary but insufficient step for tumor formation. (See "Epidemiology and clinical features of basal cell carcinoma" and "Histopathology and molecular pathogenesis of medulloblastoma" and "The genodermatoses", section on 'Xeroderma pigmentosum'.)

The mechanism responsible for *PTCH* mutations in sporadic BCCs is probably multifactorial. Exposure to ultraviolet (UV) light is an important risk factor for early onset BCCs, and the *PTCH* gene appears to be a target for UV-induced mutations. However, typical UV signature mutations are found in only 30 to 40 percent of *PTCH1*-mutated sporadic BCCs [14], while they are more prominent in the BCCs of patients with xeroderma pigmentosum [40]. Thus, mutational events other than UV irradiation may also cause *PTCH* inactivation and trigger tumorigenesis [40].

Other mutational events affecting the SHH pathway have also been implicated in the development of sporadic BCCs. These include activating mutations in the *SMO* gene, a reciprocal translocation between chromosomes 9q22.3 (the site of the *PTCH1* gene) and 16p, and mutations in a second *PTCH* gene, *PTCH2* [24,41-43].

CLINICAL FINDINGS — More than 100 clinical abnormalities have been reported in nevoid basal cell carcinoma syndrome (NBCCS). The major manifestations are [44-46]:

- Early development of multiple basal cell carcinomas (BCCs)
- Odontogenic (bone) keratocysts, especially in the mandible
- Palmar and plantar pitting (picture 1)
- Ectopic intracranial calcification, most often of the falx cerebri [47]
- Family history of NBCCS

Minor criteria include [46]:

- Craniofacial anomalies (macrocephaly, frontal bossing, hypertelorism)
- Bifid ribs
- Early onset medulloblastomas (3 to 5 percent)
- Cardiac or ovarian fibromas, often bilateral
- Lymphomesenteric cysts
- Congenital malformations (cleft lip/palate, polydactyly, eye abnormalities, colobomas, cataracts, glaucoma)

The frequency of the major clinical findings (BCCs, jaw cysts, macrocephaly, palmoplantar pits) is between 75 and 80 percent [3,45]. Although medulloblastomas (which are characteristically of the desmoplastic subtype) tend to develop at a young age, many of the classic features of NBCCS (ie, BCCs, palmar pits, calcified falx cerebri) may not be detected until the late teens or young adulthood [3]. (See "Histopathology and molecular pathogenesis of medulloblastoma".)

Basal cell carcinomas — BCCs are found in about three-fourths of all affected Caucasian patients with NBCCS, but are less frequent in affected blacks and Asians (see 'Influence of race' above). Age at first diagnosis ranges from 3 to 53 years old with an average age of 20 to 21 [36].

The number of BCCs can vary from only a few to thousands, and they range in size from 1 to 10 mm [48]. While BCCs frequently occur on sun-exposed areas such as the head, neck, back, chest, and upper limbs, they can occur in any location [3,49]. BCCs arising in NBCCS are histologically indistinguishable from sporadic BCCs. The term "nevoid" does not refer to an association of the BCC with nevi, but instead was coined because early lesions may have the appearance of nevi with a prominent vascular component.

BCCs tend to be more aggressive in patients with NBCCS. Despite this, only a small fraction become locally invasive, and they do so only after puberty [48]. Rarely, patients with NBCCS die as a result of local invasion into brain or lung, or distant metastatic spread [50].

Risk factors

- Sun exposure — Sun exposure is the most important environmental cause of BCC in the general population. However, the relationship between sun exposure and the development of BCCs in patients with NBCCS is unclear. The anatomic site distribution of BCCs suggests that frequent sun exposure may not be essential for the development of BCCs in affected patients. However, the observation that there are more tumors on sun-exposed areas suggests that exposure promotes the development of BCCs in patients with NBCCS [51]. (See "Epidemiology and clinical features of basal cell carcinoma", section on 'Risk factors'.)
- Radiation therapy — Superficial therapeutic radiation, as for psoriasis, increases the risk of nonmelanoma skin cancers, including BCC (see "Epidemiology and clinical

features of basal cell carcinoma", section on 'Risk factors'). Patients with NBCCS are particularly sensitive to the effects of ionizing radiation, and the development of multiple BCCs within irradiated fields in affected patients is well described [49,52-55]. DNA synthesis is abnormally induced in irradiated NBCCS cells, and this abnormality may supply the subsequent mutation necessary for tumor development in NBCCS patients who have been exposed to ionizing radiation [56,57]. Because of this, radiation therapy is generally avoided in patients with NBCCS. (See "Treatment of basal cell carcinomas at high risk for recurrence", section on 'Radiation therapy'.)

Odontogenic (jaw) keratocysts — Odontogenic keratocysts are cystic lesions of the bone that are lined with keratinized epithelium and thought to originate from the dental lamina. Despite their bland histology, these lesions are locally destructive with heparanase expression, perhaps correlated with the neoplastic properties of NBCCS-associated odontogenic keratocysts [58]. They are neoplastic rather than developmental in origin [59] and are characterized by aggressive clinical behavior, including involvement of the teeth and a recurrence rate that is as high as 60 percent [60].

Recurrence can result from incomplete removal, remnants of dental lamina within the jaw, or the presence of satellite cysts. NBCCS keratocysts have a different immunophenotype from sporadic keratocysts [61]. A 10-year retrospective analysis of 83 patients with odontogenic keratocysts identified six patients (8 percent) with a total of 15 lesions who had NBCCS [62].

The cysts usually develop after the age of seven and peak during the second or third decades [44,48], but they have been reported in children as young as four [36]. The number of jaw cysts averages six (reported range, 1 to 28) [3,36], unlike with sporadic cases where they are typically solitary. Unlike BCCs, there is no racial predilection [33].

Three-fourths of odontogenic keratocysts present in the mandible [36,63]. The most common locations in decreasing frequency are the mandibular third molar region, maxillary third molar region, and mandibular first and second molar region [64]. Approximately one-third are asymptomatic and are detected on routine dental examination, while 50 percent present with jaw swelling, 25 percent with mild pain, and 15 percent with altered taste [65].

Treatment is discussed below. (See 'Odontogenic keratocysts' below.).

Palmar-plantar pits — Palmar and/or plantar pits are highly characteristic of NBCCS, occurring in approximately 80 percent of affected individuals [36,66]. They are asymptomatic nonpalpable shallow depressions (1 to 3 mm) in the skin of the palm and/or soles that are due to partial or complete absence of stratum corneum (figure 1). They may also be found on the sides, web spaces, and dorsum of the fingers and toes [67]. The differential diagnosis should consider punctate keratoderma, pitted keratolysis, and palmar pits of Darier's disease, but the clinical distinction is usually easy.

Pitting generally develops during the patient's 20s and later, but has been reported in much younger patients [49]. In contrast to BCC, there is no racial difference in the frequency of pitting in affected patients with NBCCS [33]. The number of pits is variable but can reach more than 500 in number, particularly in older individuals [67]. They are permanent, and do not wax and wane over time. Soaking the hands in water for 10 to 15 minutes can make their appearance more pronounced [3].

Brain tumors — Medulloblastomas characteristically arise in the midline in the area of the cerebellar vermis. Meningiomas are the next most common brain tumors developing in patients with NBCCS, although they are much less common than medulloblastoma [48,68]. Other tumors and cysts involving the brain have also been reported [48]. (See "Meningioma: Clinical presentation and diagnosis".)

The incidence of medulloblastoma in patients with NBCCS is 5 percent or less, and there is a male predominance of 3:1 [69,70]. In contrast to sporadic medulloblastomas, which most commonly present between the ages of 6 and 10, medulloblastomas characteristically present by age two in individuals with NBCCS. This syndrome should be considered in any atypically young child with medulloblastoma [48]. (See "Histopathology and molecular pathogenesis of medulloblastoma".)

Myogenic tumors — Tumors with myogenic differentiation, including fetal rhabdomyoma and rhabdomyosarcoma (RMS), have been reported in a small number of patients with NBCCS [71]. Fetal rhabdomyomas typically arise in children and younger adults, predominantly in the head and neck region, do not metastasize, and are cured by surgical resection alone [72]. RMS is the most common soft tissue sarcoma of childhood and adolescence. It can occur anywhere in the body, but the most common primary sites are the head and neck region and the genitourinary tract [73]. The tumor is locally invasive with high propensity for distant metastasis to lung, bone marrow, and bone. (See "Rhabdomyosarcoma in childhood and adolescence: Clinical presentation, diagnostic evaluation, and staging" and "Rhabdomyosarcoma and undifferentiated sarcoma in childhood and adolescence: Treatment".)

Intracranial ectopic calcification — Approximately 65 percent of affected persons have calcification of the falx cerebri, but this increases to 80 to 90 percent of those over the age of 40 [36,47]. Other areas of ectopic calcification include the diaphragma sellae in 60 to 80 percent (with complete or partial bridging of the sella turcica), the tentorium cerebelli in 40 percent, and the petroclinoid ligament in 20 percent [74].

Characteristic facies and body habitus — Many patients with NBCCS have a characteristic "coarse" facial appearance consisting of frontal bossing, macrocephaly (80 percent), hypertelorism (5 percent), high arched eyebrows (40 percent) and palate, widened nasal bridge (60 percent), and mandibular prognathism (35 percent) [3,5,36,48,75]. In 50 to 60 percent of affected individuals, there are milia scattered on the face among the BCCs. Approximately 15 percent of patients are very tall [75].

Cardiac fibromas — Cardiac fibromas are increased in frequency in patients with NBCCS, developing in approximately 3 percent of affected individuals [46]. These are benign growths, and almost all develop within the ventricular myocardium. Although usually asymptomatic, cardiac fibromas can result in impaired left ventricular function and conduction defects, necessitating resection [76,77]. (See "Cardiac tumors".)

Ovarian fibromas — Ovarian fibromas develop in 15 to 25 percent of girls with NBCCS, and are often calcified and bilateral [3,36,46,78]. Other ovarian tumors including fibrosarcomas are rarely reported [79]. (See "Sex cord-stromal tumors of the ovary: Granulosa-stromal cell tumors", section on 'Fibroma'.)

Bone abnormalities — Occult skeletal abnormalities are frequent in patients with NBCCS. Between 38 to 60 percent have rib abnormalities including bifid ribs, marked widening of the anterior rib ends, and fusion and modeling defects of the ribs [36,48,80]. Occult spina bifida may be seen as a component of NBCCS [80], although it has not been documented in all series [36].

Mesenteric cysts — Single or multiple lymphomesenteric cysts may be seen as a component of NBCCS [78]. They tend to calcify and are usually asymptomatic.

Skin tags — The presence of skin tags in a child may be a clue as to the diagnosis of NBCCS [81]. Biopsy should be considered within the clinical context.

Other anomalies — Among the reported ocular anomalies in patients with NBCCS are congenital cataracts, colobomas (involving the choroids and optic nerve), nystagmus, strabismus, hypertelorism, and telecanthus (10 to 25 percent) [36,46,48]. Cleft palate is seen in approximately 5 percent of affected individuals.

Both pectus deformities and Sprengel deformity (narrow sloping shoulders) are more common in individuals with NBCCS [3,36] (see "Diseases of the chest wall"). Approximately 10 percent of patients have anosmia, which may be a sign of hypogonadotropic hypogonadism; other hypogonadal features include cryptorchidism, gynecomastia, and scanty facial or body hair [3,82].

Minor kidney abnormalities, often diagnosed incidentally or at autopsy, are seen in about 5 percent of patients with NBCCS [48]. Scattered case reports indicate the occasional association of other neoplasms with NBCCS including fetal rhabdomyoma [78,83], non-Hodgkin lymphoma, Hodgkin lymphoma, melanoma, chronic lymphoid leukemia, soft tissue leiomyosarcoma, breast and lung carcinoma, and sinonasal undifferentiated carcinoma (SNUC) [84].

DIAGNOSIS — The diagnosis of nevoid basal cell carcinoma syndrome (NBCCS) is a clinical one with the diagnosis being supported by finding either two major, or one major and two minor, criteria [46]. However, molecular findings (eg, high level of expression of PTCH1 transcripts on odontogenic keratocysts by reverse transcriptase polymerase chain reaction [RT-PCR]) can be used to support the diagnosis in questionable cases [30,31].

DIAGNOSTIC WORKUP — At a minimum, the following studies are indicated in patients suspected of having nevoid basal cell carcinoma syndrome (NBCCS):

- Skull radiograph or CT can demonstrate a calcified falx cerebri, complete or partial bridging of the sella turcica, or a broadened nasal root.
- Panoramic films are recommended to identify odontogenic keratocysts; MRI may be superior in demonstrating the internal composition and structure of the cysts [85].
- Chest x-ray to document rib abnormalities (eg, bifid ribs).
- Hand and foot x-rays will show flame-shaped lucencies (lytic bone lesions) in 30 percent of hand films and 17 percent of foot films [36].

Skin biopsy of a basal cell carcinoma will show nodules and/or strands of atypical basaloid cells which show nuclear palisading, cellular apoptosis, and scattered mitotic activity in the dermis (picture 2A-B). Artifactual cleft formation may be seen between the tumor lobules and the surrounding stroma, which may be mucinous. Solar elastosis is usually present in the dermis.

MANAGEMENT — Pertinent issues in the management of affected patients include surveillance for the development of syndrome-related complications, and specific treatment for postnatal tumors and odontogenic keratocysts. Most other abnormalities are either cosmetic, incidental, or managed as in patients without this syndrome.

Surveillance — For individuals diagnosed with nevoid basal cell carcinoma syndrome (NBCCS), regular visits to a dermatologist every two to three months is recommended, particularly during adolescence. Annual panoramic radiographs of the jaw are

recommended starting at the age of eight, and a cranial MRI to exclude medulloblastoma should be performed annually until the age of eight. Periodically, echocardiography to exclude cardiac fibroma should be performed.

For infants with a family history of NBCCS, early diagnosis may be achieved with the use of screening radiography to look for calcification of the falx, rib anomalies, or calcified ovarian fibromas [3]. Affected patients should be counseled to minimize exposure to ultraviolet light and avoid therapeutic ionizing irradiation (eg, MRI is preferred over CT), if at all possible [52].

Treatment of basal cell carcinomas — Because of the large number of lesions, treatment of basal cell carcinomas (BCCs) in these patients may be extremely difficult. Lesions that are growing or that become invasive should be excised, or curetted and electrodesiccated. More aggressive tumors or those in delicate or high-risk areas benefit from Mohs' micrographic surgery. (See "Treatment and prognosis of basal cell carcinoma" and "Treatment of basal cell carcinomas at high risk for recurrence".)

Multiple surgical procedures are often a source of discomfort, pain, and disfigurement for patients with NBCCS. Carbon dioxide laser therapy can be a useful modality in selected patients for tumors in low-risk areas and has shown efficacy in combination with microscopically controlled excision (Mohs micrographic surgery) [86-90].

Topical tretinoin and 5-FU — Although most of the BCCs are nodular, superficial lesions can be managed by topical application of 5 percent 5-fluorouracil (5-FU) with or without 0.1% tretinoin cream (to enhance penetration of 5-FU) applied twice daily [78]. Tretinoin should be avoided around the eyes.

Topical imiquimod — Case reports are also emerging that suggest a possible role for imiquimod cream as a less-invasive approach to managing and perhaps preventing development of new BCCs in patients with NBCCS. In several reports, imiquimod 5% cream applied three days per week has shown considerable efficacy for superficial BCCs in affected patients [91-95]. In one report, 13 of 17 superficial BCCs were successfully controlled (at least in the short run) after 8 to 14 weeks of three times weekly application [93]. The most common side effect of topical imiquimod is local erythema [96]. (See "Treatment and prognosis of basal cell carcinoma", section on 'Imiquimod'.)

However, the majority of BCCs are nodular in patients with NBCCS. Imiquimod is less successful for nodular BCCs [91], although it may be useful in conjunction with curettage [97].

Other therapies — There is increasing experience with photodynamic therapy (PDT) in patients with NBCCS [98]. As with sporadic BCCs, PDT appears most successful for flat lesions, rather than those that are raised or nodular [90]. (See "Treatment and prognosis of basal cell carcinoma", section on 'Photodynamic therapy'.)

Chemoprevention with oral retinoids — Oral retinoids are not useful therapeutically; few lesions objectively regress [99,100]. They are used more often for chemoprevention rather than treatment of existing BCCs. However, large trials of systemic retinoids as chemopreventive agents have not been conducted in patients with NBCCS. At least one report suggests that low dose isotretinoin (10 mg daily) is ineffective in preventing additional BCCs in patients who have had two or more sporadic BCCs [101]. Because of the need for moderate to high doses and the limited degree of benefit, oral retinoids are seldom to uncommonly used.

Locally advanced and metastatic BCCs — Vismodegib, an agent targeting the sonic hedgehog pathway, offers a new approach for patients with metastatic disease or no longer amenable to local therapy [102]. This approach is discussed separately. (See "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

Odontogenic keratocysts — As noted previously, odontogenic cysts frequently recur following surgery. The treatment of choice is wide surgical excision and curettage with extraction of associated teeth by an experienced oral-maxillofacial surgeon or otolaryngologist [3,48]. Bone and alveolar nerve grafting may be required in some instances. A 10-year retrospective review of 83 cases of odontogenic keratocysts suggests that marsupialization followed by enucleation results in the lowest recurrence rate [62]. Histopathologic examination of tissue is important because several cases of malignant transformation to squamous cell carcinoma have been reported [103-105].

Reduction in size or resolution of odontogenic keratocysts has been reported in some patients treated with vismodegib, an oral inhibitor of the hedgehog pathway that has been used for the treatment of BCC in patients with NBCCS [106]. (See 'Future directions' below and "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

A series of six patients with nine odontogenic keratocysts for whom baseline magnetic resonance imaging (MRI) was available were treated with vismodegib 150 mg per day for 11 to 24 months [107]. Posttreatment MRI showed a 50 percent reduction of the longest diameter of keratocysts in four of six patients. In one patient with complete resolution of one lesion, there was no recurrence nine months after drug cessation. All patients experienced mild to moderate adverse effects of taste loss, muscle cramps, and hair loss; three patients required a brief drug break.

However, additional studies are necessary to determine the role, long-term efficacy, and maintenance regimen of vismodegib for the treatment of odontogenic keratocysts. (See 'Future directions' below and "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

Medulloblastomas — In patients with NBCCS, radiation therapy for medulloblastomas induces hundreds of difficult to manage BCCs; it should be avoided. Often these BCCs are preceded by a "rash" from 6 to 36 months following radiation which represents activated BCCs. A sinonasal tumor developing 17 years after initial irradiation of a medulloblastoma has been reported [108]. Medulloblastomas may also be treated by surgery and chemotherapy. (See "Clinical presentation, diagnosis, and risk stratification of medulloblastoma".)

Vitamin D deficiency — Synthesis of vitamin D in the skin is inhibited by photoprotective measures, and patients with photosensitive disorders such as NBCCS may have an increased risk for vitamin D deficiency. In a retrospective cohort study of 41 patients with NBCCS, the prevalence of vitamin D deficiency (25[OH]D level \leq 20 ng/mL) was significantly greater than the prevalence reported in the general population (56 versus 18 percent) [109]. Thus, clinicians should be aware of the potential for vitamin D deficiency in patients with NBCCS. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment" and "Vitamin D and extraskeletal health".)

Additional studies are necessary to evaluate whether disease-specific factors other than photoprotection contribute to vitamin D deficiency in NBCCS.

Future directions — A placebo-controlled randomized trial found that vismodegib, an oral hedgehog antagonist approved for the treatment of locally advanced or metastatic

BCC, was beneficial for slowing the rate of BCC development and reducing tumor burden in NBCCS [110]. In the trial, patients with NBCCS were treated with either 150 mg per day of vismodegib (n = 26) or placebo (n = 15) for 1 to 15 months (mean, 8 months). At three months, a significantly lower mean per-patient incidence of new, surgically eligible BCCs (diameter >3 mm on nose or periorbital skin, >5 mm on other facial sites, or >9 mm on the trunk or limbs) was detected in the active treatment group than in the placebo group (2 versus 29 BCCs per year). In addition, tumor size decreased to a greater extent in patients who received vismodegib than in those who received placebo, with a few patients achieving complete remission.

Although these findings are promising, adverse effects, such as loss of taste, muscle cramps, hair loss, and weight loss limited the use of vismodegib; 14 of 26 patients (54 percent) discontinued treatment for this reason. In addition, tumors regrew following drug discontinuation. More studies are required to determine whether vismodegib has the potential to truly cure individual BCCs in NBCCS, as well as to clarify the optimal treatment regimen for vismodegib in this setting. (See "Systemic treatment of advanced cutaneous squamous and basal cell carcinomas", section on 'Vismodegib'.)

Some patients with tumors that appear to respond well to vismodegib eventually experience regrowth of tumors despite continued therapy [111,112]. In a series of 28 patients with a total of 230 advanced and nonadvanced BCCs (including five patients with NBCCS), tumor regrowth during treatment was detected in six patients (21 percent) and affected 5 percent of all tumors [111]. The mean time to tumor regrowth was 56 weeks. The reason for this occurrence is unknown.

The topical administration of an inhibitor of the hedgehog pathway may be a future option for the management of patients with NBCCS. In a randomized trial in which 27 BCCs in eight patients with NBCCS were treated with a topical inhibitor of Smoothed or a placebo agent twice daily for four weeks, complete or partial responses were observed in 12 out of 13 lesions treated with the Smoothed inhibitor compared with 1 out of 14 lesions treated with the placebo agent [113]. The effect of this treatment on BCCs in patients without NBCCS is unknown.

SUMMARY

- Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant, multisystem disorder, due to mutations in the PTCH1 tumor suppressor gene. (See 'Molecular genetics' above.)
- The primary manifestation of NBCCS is the development of multiple basal cell carcinomas (BCCs), which are histologically identical to sporadic BCCs. While BCCs frequently occur on sun-exposed areas, they can occur in any location and tend to be more aggressive in patients with NBCCS. Important risk factors for the development of BCCs include sun exposure and radiation. (See 'Basal cell carcinomas' above.)
- Individuals diagnosed with NBCCS should undergo frequent surveillance by a dermatologist to facilitate early diagnosis of new nevi. The management of BCCs that are diagnosed can be difficult because of the multiplicity of lesions and the need for multiple procedures. (See 'Surveillance' above and 'Treatment of basal cell carcinomas' above.)
- In addition to BCCs, NBCCS is associated with a variety of other cysts and tumors, including odontogenic keratocysts and medulloblastomas. Therapeutic radiation therapy needs to be avoided in such patients, since this can precipitate the development of numerous, aggressive BCCs. (See 'Clinical findings' above.)

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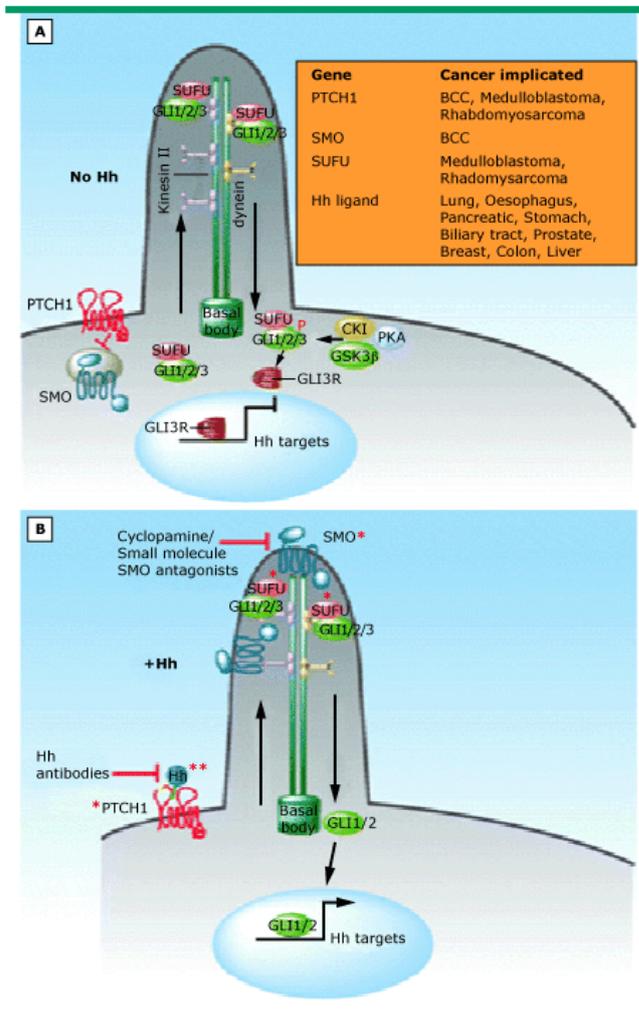
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Figure 1.

Hedgehog signaling pathway in cancer

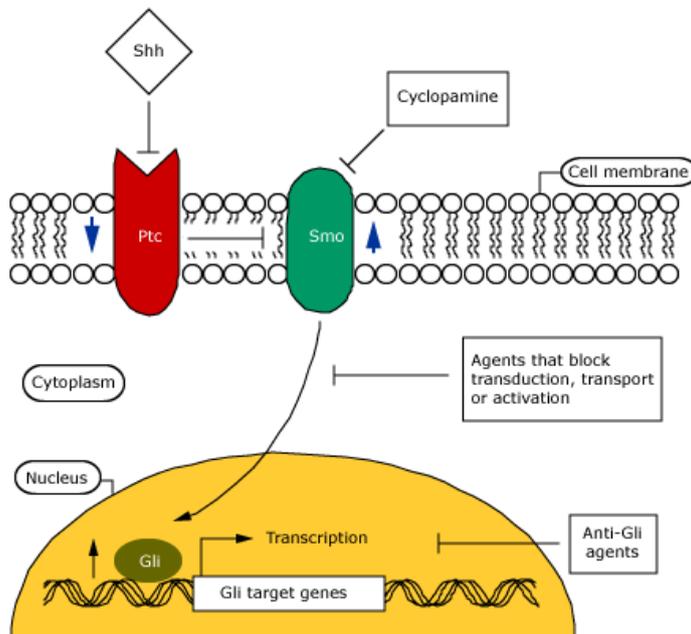


A) In the absence of Hh ligand, Ptc1 inhibits surface localization of Smo and protein kinases phosphorylate Gli proteins, leading to an NH-terminal truncated form, which acts as a repressor of Hh target gene expression. Gli3 is the predominant repressor. SuFu also regulates the pathway by binding to Gli, both in the cytoplasm and in the nucleus, to prevent it from activating Hh target genes. Table, summary of genes implicated in cancer and potential treatment using Hh antagonists or Hh antibodies. B) Hh-mediated (Sonic, Indian, or Desert) inactivation of Ptc1 allows relocation of Smo to the tip of cilia, leading to downstream signaling events and the activation of the Gli proteins. Mutations in the pathway (*) or overexpression of the Hh ligand are highlighted (**) in (A) and (B) along with possible avenues of treatment using antibodies or small molecules (red arrows).

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Figure 2.

The Shh-Gli pathway and potential sites for blocking it with therapeutic agents



Sonic hedgehog (Shh) acts on the membrane receptor complex formed by Patched (Ptc) and Smoothened (Smo) to inhibit the repression of Smo by Ptc. Smo is then thought to send the signal intracellularly through several cytoplasmic transduction steps (not shown), leading to the nuclear action of the Gli proteins, which regulate target genes. Thick blue arrows pointing up or down indicate activating or inactivating mutations, respectively, that might induce the pathway. Inhibitors of the pathway with potential therapeutic value (red lines) include: agents that block the action of Smo in the receptor complex, such as the plant alkaloid cyclopamine; agents that inhibit specific aspects of the transduction of the signal, including the nuclear import or activation of Gli proteins; and agents that specifically inhibit Gli function.

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Picture 1.

Palmar pits associated with nevoid basal cell carcinoma syndrome



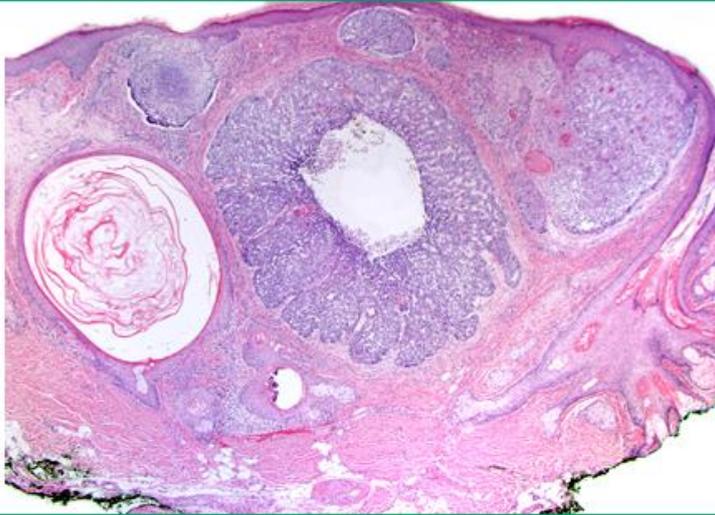
Palmar surface of hand showing 1-to-2 mm, sharply marginated, depressed red lesions, ie, palmar pits.

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Picture 2.

Nodular basal cell carcinoma (10x)

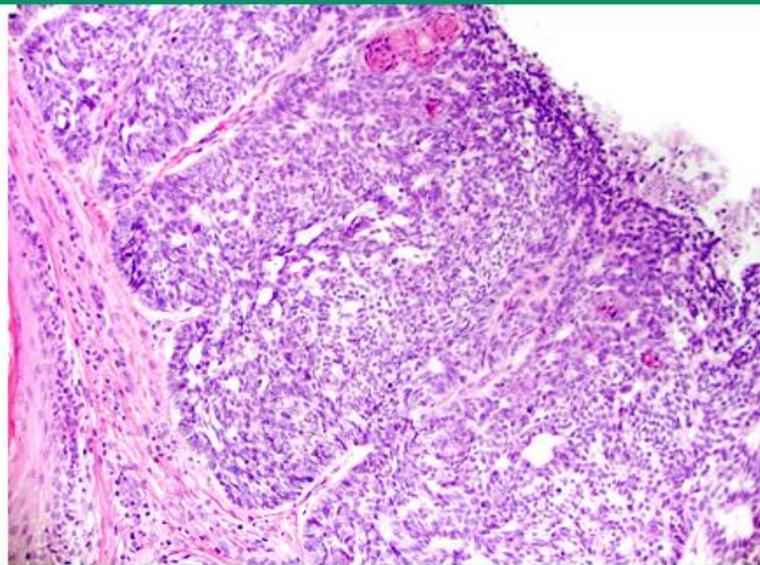


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Picture 3.

Nodular basal cell carcinoma (20x)



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