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Nevoid Basal Cell Carcinoma Syndrome (NBCCS)

Miki Tanioka

Additional information is available at the end of the chapter

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1. Introduction

Nevoid basal cell carcinoma syndrome (NBCCS) is characterized by the presence of multiple basal cell carcinomas associated with palmoplantar pits (Gorlin 1960). The patients are normal at birth and the syndrome manifests as palmoplantar pits in their early childhood. In their teens, odontogenic keratocysts (jaw cysts) develops and they are the first complain to visit hospitals (Evans 1993). Basal cell carcinomas (BCCs) present in their 40's, which is much earlier than sporadic BCCs. The other characteristic signs are bifid rib, calcification of the falx (Kimonis 1997).

NBCCS is associated with a higher risk of medulloblastoma, and ovarian malignancies (figures 1, 2, 3).

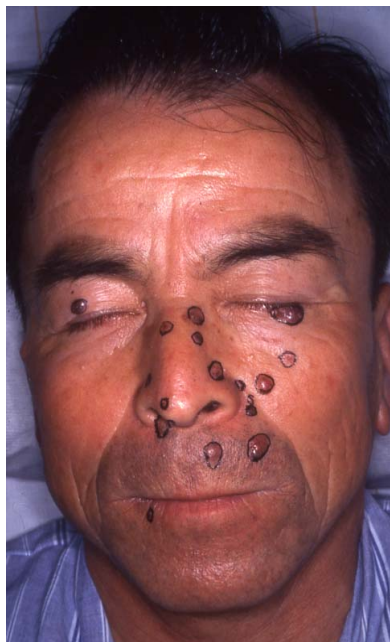


Figure 1. Multile BCCs on the face.

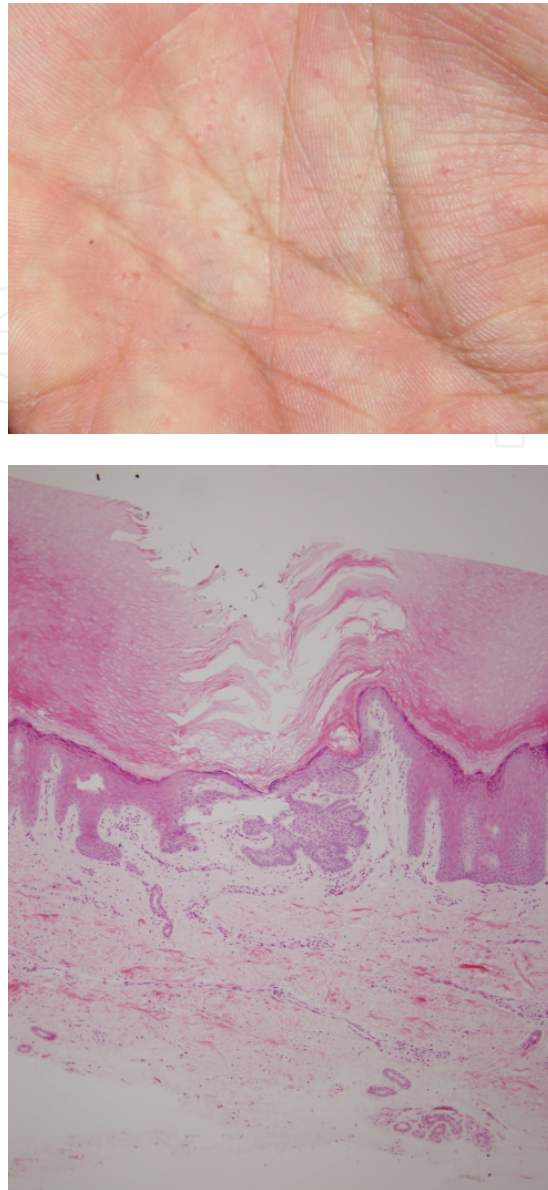


Figure 2. Palmar pits and its pathology.

2. Inheritance

Inheritance was autosomal dominant (Gorlin 1993). About 40% of cases represent a de novo mutation. It occurs in all races, and occurs in both sexes equally. The prevalence is reported to be 1 case per 56,000-164,000 population.

No genotype/phenotype relations have been reported.

3. Cutaneous presentation of NBCCS

Palmoplantar pits are the earliest clinical signs in their childhood. The keratinocytes under the pits are BCC-like, and its keratinization is abnormal, therefore the reduced stratified corneum looks like a pit.

Multiple basal cell carcinomas usually develops over their 40's. Usually sporadic BCC develops on the sun-exposed area in elderly people, especially on the face.

However, in NBCCS, BCC can develop on any areas of the body, which are not generally exposed to sunlight, such as the palms and soles of the feet and in younger people.



Figure 3. Multiple odontogenic keratocysts (jaw cysts) in the jaw.

4. Molecular genetics of NBCCS and its molecular mechanism

The responsible genes for NBCCS are the *PTCH1* gene on chromosome 9q22, the *PTCH2* gene on 1q32 and the *SUFU* gene on 10q24-q25 (Johnson 1996, Hahn 1996, Smyth 1999, Pastorino 2009). These genes mutations result in abnormalities in sonic hedgehog (SHH) signaling pathway components, which lead to the development of basal cell carcinomas. The sequence of *PTCH2* identities with 54 % of that of *PTCH1*. All three mammalian hedgehogs bind both receptors with similar affinity, so *PTCH1* and *PTCH2* cannot discriminate between the ligands.

No founder effects have been reported and almost all mutations are speculated to be *de novo*. No genotype/phenotype relations have been reported. Each person who has this syndrome is affected to a different degree, some having many more characteristics of the condition than others (Tanioka 2005).

Both *PTCH1* and *PTCH2* are coding a twelve transmembrane receptor whose ligand is sonic hedgehog (SHH)(Ingham 2011). SHH is a ~45kDa precursor and undergoes autocatalytic processing to produce an ~20kDa N-terminal signaling domain and a ~25kDa C-terminal domain with no known signaling role. SHH can signal in an autocrine fashion, affecting the cells in which it is produced.

In the absence of SHH, *PTCH1* inhibits Smoothed (SMO), which is a downstream membrane protein in the SHH pathway (Taipale 2002). SMO is regulated by a small molecule, the cellular localization of which is controlled by *PTCH* (Strutt 2001).

The molecular mechanism is not fully understood, however, it should be associated with cholesterol (Davies 2000). *PTCH1* has a sterol sensing domain (SSD), which has been shown

to be essential for suppression of Smo activity. In addition, PTCH1 has homology to Niemann-Pick disease, type C1 (NPC1) that is known to transport lipophilic molecules across a membrane. It is believed that PTCH regulates SMO by removing oxysterols from SMO. PTCH acts like a sterol pump and removes oxysterols that have been created by 7-dehydrocholesterol reductase. Upon binding of a SHH protein or a mutation in the SSD of PTCH the pump is turned off allowing oxysterols to accumulate around SMO.

The binding of SHH relieves SMO inhibition, leading to activation of the GLI transcription factors: the activators Gli1 and Gli2 and the repressor Gli3 (Shimokawa 2006). The sequence of molecular events that connect SMO to GLIs is poorly understood. However, in NBSSC, it is believed that activated Gli leads to the upregulated cell cycle of BCC cells (Epstein 1998). Recently, some drugs that blocks the SHH pathways have been developed and many clinical trials are undergoing.

5. Management of NBCCS

Management is careful examination and monitoring for malignant degenerations. Surgical interventions of jaw cysts can correct or minimize deformities. Surgical removal of basal cell carcinomas and medulloblastomas are recommended. Recently, a drug, vismodegib, which target the SMO are proved to be effective to control unresectable BCC and newly development of BCCs in NBCCS patients (Sekulic 2012, Tang 2012). Vismodegib is a new orally administered hedgehog-pathway inhibitor that produces objective responses in locally advanced and metastatic basal cellcarcinomas. Vismodegib reduces the basal-cell carcinoma tumor burden and blocks growth of new basal-cell carcinomas in patients with the basal-cell nevus syndrome. The adverse events associated with treatment led to discontinuation in over half of treated patients. Those included loss of taste, muscle cramps, hair loss, and weight loss.

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