Pediatric Cutaneous Oncology

Genodermatoses and Cancer Syndromes

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KEYWORDS

• Basal cell nevus syndrome • Photosensitivity disorders • Lynch syndrome
• BAP1-related tumor syndrome • Gorlin syndrome • Skin cancer • Genodermatoses

KEY POINTS

- Early onset skin cancers raise the possibility of an inherited cancer predisposition.
- Dermatologists play a primary role in the management of conditions with predisposition to skin cancer. With adequate management, many affected patients have a normal lifespan.
- This article reviews relevant genodermatoses with an increased risk of skin cancer in young patients and discusses approaches to management.
- Basal Cell Nevus syndrome, Rothmund–Thomson syndrome, Xeroderma Pigmentosum, Lynch syndrome, BAP1 tumor predisposition syndrome, and others are specifically addressed.

Since the complete sequencing of the human genome in 2003, the list of heritable conditions associated with skin cancer continues to expand. Recognition of syndromes by their clinical features gives dermatologists the ability to make a unifying diagnosis. In patients with skin cancer, certain features such as young age of onset, multi-focal primary lesions, and specific pathology signal that further workup for a genetic cause is warranted. Here, we review clinical features of genetic syndromes most likely encountered in a skin cancer-focused practice.

RECOGNIZING INHERITED CANCER SYNDROMES

Most mutations that cause cancer syndromes are present at conception or in the "germ-line." In dermatology patients, certain recognizable characteristics make the presence of a heritable syndrome more likely. For example, multifocal tumors are one such characteristic. Epidermoid cysts when associated with familial adenomatous polyposis (Gardner variant), caused by a germline mutation in the *FAP* gene, usually appear in multiple and possibly atypical locations.[1] In another example, *BAP1*-inactived melanocytic tumors (BIMTs) are atypical appearing dome-shaped, skin-colored to pink to reddish brown papules. The presence of multiple BIMTs in the same individual is considered a marker for the possible presence of a germ-line *BAP1* mutation.[2]

Similarly, cancers related to a genetic syndrome are likely to present with multiple primary tumors of the same or entirely different type. For example, pancreatic cancer and melanoma in the same individual are suspicious of melanoma-pancreatic cancer syndrome caused by a mutation in the *CDKN2A* gene. Another distinction of a genetic syndrome is an earlier age of cancer onset. For

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example, breast cancer in a patient younger than age 50 is more likely to be associated with a germ-line BRCA mutation.[3] In BAP1 germ-line mutation carriers, the average age of uveal melanoma diagnosis is younger at age 53 years compared with 62 years in the general population.[2]

For dermatologists who prefer visual learning and patterns, a pedigree is an especially useful tool for the assessment of family cancer history. When assessing a cancer-affected family, younger ages at cancer diagnosis or a second primary cancer in the same family member each increase the likelihood of a heritable mutation. Certain rare cancer types can also herald genetic predisposition. For example, mesothelioma increases the chance of a *BAP1* germline mutation being present.[4] When following patients with multiple nevi or melanoma, an annual update of their family history is recommended.[5]

Finally, environmental exposures directly influence cancer risk independently of genetics. Ionizing radiation and cigarette smoke are carcinogens that increase somatic mutations leading to cancer. For patients with skin cancer, taking a history that includes ultraviolet light exposure is essential. A patient with an outdoor occupation and history of tanning bed use may present with multiple primary skin cancers independent of a single gene inherited disorder and is not necessarily a good candidate for testing.

In patients with multiple skin cancers and an extensive history of UV light exposure and in whom a single gene cancer predisposition is unlikely, the inheritance pattern is considered "multifactorial." That is, a combination of shared familial factors both genetic or nongenetic increases the patient and family's risk for cancer. Skin cancer prevention recommendations for patients with an extensive skin cancer history due to either environmental exposure or a predisposing genetic mutation are mostly similar.

BASAL CELL NEVUS SYNDROME

Basal cell nevus syndrome (BCNS), also called Nevoid basal-cell carcinoma syndrome or Gorlin–Goltz syndrome is a multisystem disorder of autosomal dominant inheritance. The most common genetic cause is a heterozygous, pathogenic variant in either *PTCH1* (known as patched 1) or *SUFU* (suppressor of fused) genes.[6] Mutations in these genes disrupt the sonic hedgehog regulatory pathway. This critical pathway regulates mammalian embryogenesis. Somatic as well as inherited or germ-line disruption of the sonic hedgehog pathway contributes to tumor formation, especially basal cell skin cancers. The estimated prevalence of BCNS is 1 in 40,000 to 1 in 60,000 people, affecting men and women equally.

Individuals with BCNS are predisposed to the early development of basaloid neoplasms and carcinomas (BCC), jaw keratocysts, and ectopic intracranial calcifications in tissues such as the falx cerebri. Characteristic skin findings that affect some, but not all patients include distinctive, asymmetric palmoplantar pits. These individuals are often affected by abnormalities of the ocular, skeletal and genitourinary systems. White patients typically develop more BCCs compared with darker skinned individuals.

BCCs appear at a much earlier age in BCNS compared with the general population, often affecting individuals younger than 20 years of age.[7] For treatment, Mohs micrographic surgery (MMS) has demonstrated efficacy by providing strong cure rates with minimal recurrence rates. However, MMS is problematic in BCNS because follicular-based benign basal cell nevi can obscure the true tumor border, and often a negative margin is virtually impossible to obtain (**Fig 1**). An impactful report appeared in 2014 documenting 40 years of history in a woman with BCNS who underwent simple excision of 730 basal cell carcinomas. Many excisions had positive margins which were not removed with a second procedure.[7] This article advocated that narrow margins are adequate without MMS. The patient was pictured in youth and juxtaposed against herself at a much older age with an excellent cosmetic outcome using this conservative approach.

For small basal cell nevi that are stable and behave in a benign manner, treatment is not needed. For those that become inflamed and grow, destructive treatment is warranted with the consideration of chemotherapeutic treatment

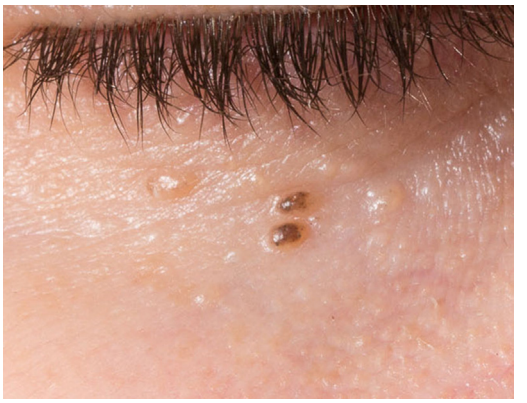

Fig. 1. Multiple, closely approximated follicular-based basal cell nevi in an individual with basal cell nevus syndrome.

such as topical 5-fluorouracil or imiquimod. Cure rates for single lesions are higher than field treatment of multiple lesions. Targeted genetic inhibitors offer another tactic for the treatment of metastatic and especially aggressive tumors. Vismodegib is an FDA-approved systemic treatment of multiple and recurrent BCCs. The use of vismodegib is not without complications and is limited by dose-dependent adverse effects. Side effects such as dysgeusia, alopecia, muscle cramps, weight loss, and others prompted half of patients included in a clinical trial to discontinue the medication. Also, tumors recurred when resistance to vismodegib developed over time.[8] Another systemic inhibitor of the sonic hedgehog pathway, sonidegib, showed a similar problematic side effect profile in patients with advanced BCC.[9]

PHOTOSENSITIVITY SYNDROMES

Rothmund–Thomson Syndrome

In 1957, the American dermatologist Taylor proposed the eponym Rothmund–Thompson Syndrome (RTS) to characterize a cohort of patients with features of poikiloderma, growth retardation, juvenile cataracts, and skeletal defects.[10] This novel syndrome combined the observations from 2 earlier publications—the first by the German ophthalmologist Rothmund in 1868 and the second by the English dermatologist Thompson in 1936.[11,12]

RTS is an autosomal recessive disorder caused by pathogenic mutations that affect the RecQ family of helicases. Due to their critical importance in DNA maintenance and stability, RecQ helicases are considered guardians of the genome. Specific mutations associated with RTS are *ANAPC1* (Type 1) or *RECQL4* (Type 2).[13,14] The former encodes a subunit of the anaphase-promoting complex while the latter encodes a DNA helicase. These mutations ultimately lead to defects in DNA repair and cell cycle progression.

Classically, dermatologic findings present within the first 3 to 6 months of life with marked photosensitivity of the cheeks, hands, feet, and buttocks. This acute phase creates erythema, edema, and occasionally bullae which then eventuate into a chronic poikiloderma.[15] Many individuals possess dental anomalies, alopecia of the scalp, and sparse eyebrows or eyelashes, especially of the lower lids. The condition affects boys twice as often as girls.[16] RTS Type 1 seems to predispose to the development of juvenile cataracts while RTS type 2 is more strongly associated with skeletal deformities and an increased risk of osteosarcoma.[14] Complicating the diagnosis, significant phenotypic overlaps occur, and not all features are present in all patients.

Overall skin cancer risk is increased in RTS including both nonmelanoma and melanoma skin cancers with an estimated prevalence of about 5%.[17,18] Skin cancer tends to affect these individuals at an earlier age compared with the general population with a mean age of 34.4 years at onset. Careful follow-up skin examinations are required because around 30% of patients develop hyperkeratotic, verrucous papules about the hands, feet, elbows, and knees by adolescence which demonstrates an increased risk of transformation to squamous cell carcinoma in adulthood.[15] Routine cancer screening examinations should occur at least annually with the frequency increased depending on the clinical situation. Skin cancers may be hard to distinguish from surrounding poikilodermatous skin and hyperkeratosis. Confirmed skin cancers may be managed with standard techniques including topical agents (such as 5-flurouracil or imiquimod), electrodessication and curettage, excision, or MMS. With diligent management of these comorbidities, individuals with RTS often have a normal life span.

Xeroderma Pigmentosum

Xeroderma pigmentosum (XP), first described by Hebra and Kaposi in 1874, is a rare, autosomal recessive condition characterized by extreme photosensitivity and increased risk of UV-induced DNA damage and carcinogenesis.[19] James Cleaver elucidated the genetic basis of the condition in 1968 as a defect in DNA repair.[20] The incidence varies across different populations. Early estimates placed the incidence of XP in the United States at 1 in 250,000 births while rates as high as 1 in 20,000 births have been more recently reported in Japan.[21,22] The condition is usually diagnosed within the first 2 years of life secondary to the marked photosensitivity observed in these individuals that includes characteristic lentigines with a freckled appearance.[23] Many genes have been implicated in the pathogenesis of XP; these mutations are traditionally divided into 7 complementation groups (XP-A through G). Each of these encodes a protein associated with a particular step in nucleotide excision repair. With the advent of molecular genetic testing, complementation groups have become outdated. Mutations in *POLH*, which causes XPV, disrupt DNA polymerase eta involved in translesional synthesis.[24] Skin cancers typically have signature mutations of UV light damage. Nucleotide excision repair proteins function to identify and remove UV-induced pyrimidine–

pyramine dimers within damaged DNA; translesional synthesis normally allows specialized DNA polymerases to replicate UV-damaged DNA. As such, these ineffective processes each independently lead to accumulating UV-induced DNA defects in cutaneous cells.[25]

Skin cancer risk in affected individuals is increased by orders of magnitude. XP engenders an estimated 10,000-fold increased risk of nonmelanoma skin cancers and 600 to 8000-fold increased risk of melanoma.[26,27] Skin cancer diagnosis first occurs at a median age of 8 years.[26] Oral cancers, most commonly on the tip of the tongue due to UV exposure, also occur at an increased frequency with an estimated risk 3000 to 10,000 times higher than the general population.[28] Clinically, in about 60% of cases, XP manifests as severe photosensitivity often within the first few weeks of life after sun exposure.[21] Severe blistering sunburn reactions are seen and can wrongly be confused with neglect or infectious etiologies such as cellulitis or impetigo.[27] This extreme photosensitivity is seen in XP subtypes XPA, XPB, XPD, XPF, and XPG; while XPC, XPE, and XPV subtypes have a normal sunburn response but experience abnormal skin pigmentary changes.[29] In early childhood, signs of chronic UV-induced damage present with lentigines (which should be distinguished from more typical ephelides), skin atrophy, actinic keratoses, and stucco keratoses. The cornea is also vulnerable to pain associated with UV exposure. Many patients suffer from photophobia.[27]

The prognosis of this condition rests on the ability to minimize UV exposure and to quickly detect potential malignant skin changes in their earliest stages. The strictest modes of sun protection are used for these patients including physical barrier protection with UV-blocking clothing, UV-protective goggles, and the use of high SPF sunscreens. Individuals may need to be screened for vitamin D deficiency and require significant psychosocial support due to the severe lifestyle restrictions that are required.[30] Actinic keratoses and small, localized BCC may be treated with cryotherapy, topical 5-fluorouracil or imiquimod. A series of 18 patients with XP and 45 primary facial BCC documented adequate response to cryotherapy and only one case of recurrence after a mean follow-up period of 30 months.[31] Surgical excision is preferred for larger lesions and SCC. Given the high tumor burden associated with this condition, narrow margins are preferred with frequent clinical follow-up and re-excision as necessary. MMS offers the ability to obtain irrefutably negative margins, but this procedure may be impractical in a patient who requires frequent surgical excisions.[32] With the burden of actinic damage at a young age, regular skin cancer screening examinations are essential in the early detection of possible malignant change.

Oculocutaneous Albinism

Oculocutaneous albinism (OCA), refers to a group of autosomal recessive disorders characterized by abnormalities in melanin biosynthesis, visual acuity, and a generalized reduction in the pigmentation of the skin, hair, and eyes.[33] Since tyrosine metabolites are required in the embryonic period for proper formation of the optic chiasm and binocular vision, decreased visual acuity is a debilitating feature of this diagnosis. OCA can be subdivided into 8 forms (OCA1-8) each corresponding to distinct gene mutations. OCA1 and OCA2 are the most common forms accounting for 30% and 50% of cases, respectively, although prevalence vary widely according to population.[33–35] OCA1 is caused by mutations in the *TYR* gene that encode tyrosinase. Tyrosinase is the key rate-limiting step in melanin synthesis. OCA2 is caused by *OCA2* mutations. The *OCA2* gene encodes a transmembrane protein responsible for normal melanosome function.[36] These 2 subtypes are most associated with increased risk of skin cancer development. OCA3-4 account for nearly all remaining cases of oculocutaneous albinism worldwide as OCA5-8 has only been reported in single individuals or family cohorts.[37–40] The overall prevalence of OCA is thought to range between 1:17,000 and 1:20,000 in the Western world, and 1 in 70 individuals is thought to be a carrier of an OCA-mutated allele.[41]

Classically, OCA1 can be split into 2 subtypes based on either absent (OCA1a) or reduced (OCA1b) activity of the tyrosinase enzyme. OCA1a is clinically characterized by the total absence of pigmentation as affected individuals are unable to synthesize melanin due to the presence of 2 null *OCA1* alleles. These patients demonstrate milk-white skin, white hair, and blue irides regardless of familial skin phototype.[42] Ocular symptoms include photophobia, nystagmus, strabismus, and decreased visual acuity resulting in legal blindness for most of these patients.[43] Markers of cutaneous UV-induced photodamage develop in young adulthood and include actinic damage and cutaneous malignancies. OCA1b demonstrates a less severe phenotype with variable pigmentation secondary to variability in tyrosinase activity. Infants with this phenotype may have white terminal hair at birth that then darkens with age due to staining from minerals in water and environmental

exposure.[33] OCA2 most commonly affects Black individuals and has a variable phenotype characterized by different degrees of melanin expression.[44] The skin ranges in color from pink to cream; the hair is yellowish-brown; and the eyes are blue to yellowish-brown.[33] These individuals may develop pigmented nevi over time. SCC is the most common type of skin cancer to develop in these patients; however, BCC and melanoma occur at higher rates than those seen in the general population.[45] With the absence or reduced pigmentation, melanoma poses a particular diagnostic challenge. Heightened vigilance is required to detect changes in pink and red lesions. These amelanotic melanomas may be more advanced at the time of diagnosis (owing to their difficulty in recognition) and are reported to occur most frequently on the back and legs.[46]

Due to the risk of skin cancer, OCA-affected individuals must use life-long photoprotection including avoiding peak hours of UV exposure, use of protective clothing, frequent application of sunscreens containing at least sun protective factor 30, and avoidance of photosensitizing medications when possible.[47] With such strict sun protective measures, vitamin D levels should be screened. Skin cancer surveillance should start in adolescence at routine 6-to-12-month intervals. During these surveillance visits, dermoscopy may help delineate clinically suspicious lesions from benign melanocytic nevi. A recent study in 37 OCA children reported "structureless homogenous" or "globular" as the most common dermatoscopic patterns in benign nevi.[48] Comparatively, dermoscopic analysis of vessels can also help to identify high-risk lesions. Patterns that should prompt further investigation include linear, irregular vessels, and polymorphous-appearing vessels over a central disposition of dotted vessels.[49] With the management of these potential comorbidities, and accommodations for patients with decreased visual acuity OCA typically enjoy a normal life span.

LYNCH SYNDROME

An especially common and relevant cancer syndrome for dermatologists is Lynch syndrome (hereditary nonpolyposis colorectal cancer). Lynch syndrome is the most common form of hereditary colorectal carcinoma with an estimated prevalence of 1:279 from a 2017 study by Win and colleagues.[50] This syndrome accounts for approximately 3% of new cases of colorectal carcinoma and 2% to 3% of endometrial cancer.[51] Most pertinent to dermatologists are the cutaneous manifestations. Historically, Muir–Torre syndrome described a subset of patients with Lynch syndrome with characteristic skin manifestations including sebaceous neoplasms and keratoacanthoma. This subset of patients is now grouped into the larger domain of Lynch syndrome.

In patients with Lynch syndrome, symptoms of colorectal carcinoma such as gastrointestinal bleeding, abdominal pain, or a change in bowel habits are often the first sign of disease.[52] Among these individuals, about 9% have cutaneous characteristics consistent with the Muir–Torre variant of Lynch syndrome.[53] Cutaneous malignancies develop in affected individuals at an average age of 53 (range 23–89).[54] Inactivating mutations in genes which encode proteins implicated in mismatch repair underpin Lynch syndrome. The most well-known genes include *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[55,56] Microsatellite regions of DNA are made up of highly repetitive sequences that commonly "mismatch" during cell division. The result of this defective mismatch repair leads to microsatellite instability and tumor formation. In cases associated with the characteristic skin lesions, most of the patients harbor mutations in *MSH2*.[55] Typical cutaneous lesions include sebaceous tumors such as sebaceous adenoma and sebaceous carcinoma.[57] The most specific cutaneous lesion from this condition is the sebaceous adenoma (**Fig. 2**).[58] In nonsyndromic patients, sebaceous neoplasms have a predilection for the face, and examination reveals yellowish to pink papules often with a central dell. In patients with Lynch syndrome, these characteristic skin lesions are frequently present on the trunk.[59] Molecular testing of these skin tumors is critical for early diagnosis as these sebaceous tumors will precede the development of visceral malignancy in more than 50% of affected patients.[57]

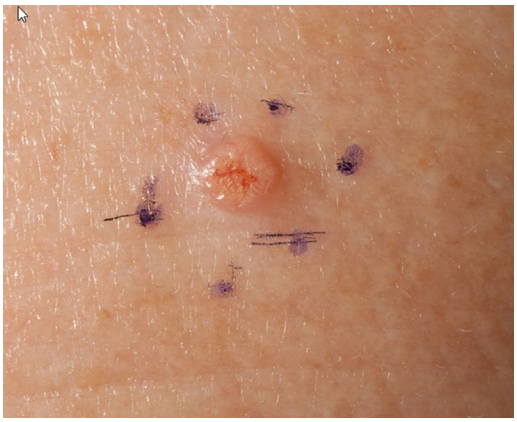

Fig. 2. Sebaceous adenoma in a Lynch syndrome-affected patient with characteristic pink to yellow color and telangiectasias.

Tumor testing is distinct from germ-line mutation testing of blood or saliva. The genetic derangement that characterizes cancer typically occurs well *after* conception. Typically, these somatic tumor mutations are not transmissible to future generations. In skin cancer, somatic genetic changes are often characteristic of ultraviolet (UV) light damage.[60] Somatic mutation testing usually takes place on actual tumor tissue, although, increasingly, next-generation technology can distinguish tumor DNA that makes its way into the blood or other body fluid. Mutations detected in this way are considered postzygotic and not heritable because they represent mutations specific to the tumor. For some specific somatic mutations, however, detection in tumor tissue raises the possibility but does not confirm inheritance from birth. Cutaneous sebaceous carcinomas are a relevant example for dermatologists. On a sebaceous carcinoma tumor specimen, immunohistochemical stains for mismatch repair mutations (eg, *MLH1*, *MSH2*, *MSH6,* or *PMS2*) reveal the presence or absence of somatic mutations associated with Lynch syndrome.[61] Universal immunohistochemical staining is not currently performed on all sebaceous tumors, though at least one study supports its usefulness.[61] A heterozygous pathogenic mismatch repair mutation (eg, *MLH1*, *MSH2*, *MSH6* or *PMS2*), when present in the germline, causes Lynch syndrome. That is, molecular diagnosis of Lynch syndrome requires confirmation in another tissue. Tumor staining establishes the presence or absence of a Lynch syndrome somatic mutation. Follow-up germline testing of blood or saliva is then required to confirm if a Lynch syndrome diagnosis is present. If so, extra-cancer surveillance according to established guidelines is recommended.

Simple excision may be undertaken for the management of benign sebaceous adenoma to prevent recurrence and possible malignant transformation. Management of sebaceous carcinoma is typically pursued via MMS to ensure complete tumor removal; however, if this procedure is not available, WLE with 1 cm margins down to the deep fascial plain is recommended.[62,63] Prolonged and frequent follow-up is recommended for these patients with a history of sebaceous carcinoma every 6 months for 3 years then annually thereafter.[63]

CANCER AND CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY SYNDROME

A rare cancer syndrome, directly related to Lynch Syndrome, with special relevance to pediatric dermatologists is Cancer and Constitutional Mismatch Repair Deficiency Syndrome (CCMRD). The condition is inherited recessively and caused by biallelic mutations in mismatch repair genes, most commonly *PMS2* and *MHS6*.[64] The first reports, which were published in 1999, described the clinical characteristics of offspring from consanguineous marriages of Lynch Syndrome families.[65,66] A particularly virulent cancer syndrome, hematologic malignancies develop during early childhood in these offspring. These affected individuals were also noted to have cutaneous stigmata of neurofibromatosis. Since that original description, Wimmer and colleagues characterized the first cohort of 146 patients with this condition.[67] The most commonly reported tumors in this group of patients include CNS tumors (glioblastoma multiforme, high-grade glial tumors, medulloblastoma), hematologic malignancies, and/or polyposis. Nearly all affected patients were diagnosed in childhood before 18 years of age. High mortality, at more than 70%, is reported among those affected with this condition.[68] The cutaneous features of this condition include café-au-lait macules (CALM) and hypopigmented macules. The CALM tend to have jagged borders as opposed to the smooth borders typically associated with neurofibromatosis.[69] Diagnostic criteria for this condition have been proposed which include: (1) café-au-lait spots and/or hypopigmented skin lesions (2) history of parental consanguinity, or (3) positive family history of hereditary nonpolyposis colon cancers.[67] This condition highlights the importance of a broad differential and the need to obtain a thorough history when evaluating patients with multiple CALM.

BAP1 TUMOR PREDISPOSITION SYNDROME

BRCA1-associated protein (*BAP1)* tumor mutations are similarly relevant to dermatologists. BAP1-inactivated benign melanocytic nevi or "melanocytomas" have been reported as an identifying feature in some individuals who carry a germ-line null mutation in *BAP1*.[70] Increased cancer surveillance for uveal melanoma, mesothelioma, cutaneous melanoma, and renal cancer is recommended for individuals confirmed to carry germ line, pathogenic *BAP1* mutations. Apart from these well-known examples of tumor testing potentially revealing a germ-line mutation that requires follow-up confirmatory testing, few studies describe whether patients should be offered germ-line testing for other somatic mutations detected by tumor testing.

Clinically, BAP1-inactivated benign melanocytic nevi present as well-marginated, skin-colored to red/brown, pedunculated or dome-shaped

papules typically distributed most commonly on the head and neck, followed by trunk and extremities.[71,72] Multiple lesions are characteristically present in individuals with germline mutations (ranging from 5 to 50 lesions in individual members of affected families).[73] Dermatoscopic findings associated with these lesions have been reported. Interestingly, structureless with eccentric dots/globules pattern and network with raised structureless areas pattern was significantly associated with germline mutations.[72] Ultimately, diagnosis relies on the histopathologic evaluation of biopsy specimen. Excisional biopsy is the preferred method to ensure accurate histopathologic diagnosis. No specific guidelines exist for the management of these lesions once histopathologically confirmed, often re-excision is pursued to guarantee complete removal. Once a diagnosis is established, genetic testing should be considered if a patient has a history of multiple such lesions, a strong family history of such lesions exists, or the lesion is diagnosed in a young patient.[74]

INTERNAL CANCER SYNDROMES (EG, BRCA, DICER 1)

Familial Melanoma

Some authors divide melanoma-related single gene cancer predisposition disorders into "melanoma dominant" and "melanoma subordinate." Melanoma dominant mutations describe those which predominantly increase melanoma risk and may increase the risk of other specific cancers, but not to the same degree as melanoma. *CDKN2A* is considered the most commonly inherited mutation in 30% to 40% of families that present with multiple melanomas in multiple members and meet diagnostic criteria.[75]

Since a mutation in *CDKN2A* primarily increases melanoma risk and increases pancreatic cancer risk, but to a lesser degree, it is considered "melanoma dominant."[4] Another "melanoma dominant" mutation is *BAP1* which increases the risk of mesothelioma but to a lesser degree than melanoma. An example of a melanoma subordinate mutation is *BRCA* which increase melanoma risk but not to the same degree as breast and ovarian cancer[4,76]. Since patients with "melanoma dominant" and "melanoma subordinate" mutations may present in dermatology clinics with the same phenotype of multiple primary or early onset melanomas, this overlap impacts testing strategies for a genetic diagnosis.[4] When features of single gene cancer syndromes overlap, targeted multi-gene panels that interrogate many different well-known cancer genes at once are an efficient testing option.

RESOURCES

For patients with a suspected cancer predisposition, consultation with a genetics professional is recommended.[76] A typical visit includes a three-generation targeted family history and drawn pedigree. Pretest counseling requires discussion about potential equivocal or noninformative results, insurance discrimination based on a new diagnosis, and disclosure of nonpaternity and impact on the family. Potential benefits are also discussed, especially the potential for enhanced screening based on results to detect cancers at an early and curable stage. If the patient chooses to proceed, targeted testing is offered for relevant mutations according to the patients' personal and family history. A multi-gene panel is an efficient choice due to overlapping phenotypes of cancer syndromes, especially in an individual who develops more than one melanoma.[76]

SUMMARY

Childhood skin cancer is rare, and its diagnosis should spark the clinical suspicion of an underlying genetic cancer predisposition syndrome. In many of these conditions, the skin is often the first clue to a potential diagnosis. Dermatologists play a crucial role in the detection and treatment of skin cancers; thus, working knowledge of these genodermatoses and their extracutaneous clinical associations is necessary to recommend management and improve care. For example, several conditions discussed impact vision. Affected patients typically worry about skin surgery that could impact one or both eyes making them temporarily blind due to bandage placement. Establishing a correct diagnosis in these patients ultimately may involve referral to genetics professional services for testing, and the threshold for referral should be based on heightened clinical suspicions.

Advances in genomics have provided information underlying genetic pathways implicated in these conditions and afford insight into potential therapeutic targets. Genetic testing offers the ability to confirm clinical suspicion, and, with accurate diagnosis, the risks of future cancer development can be mitigated with appropriate strategies. While these exciting developments have increased understanding of these conditions, the results of genetic testing can be mired in myriad psychosocial concerns including the potential for discrimination. Early referral to geneticists who can guide appropriate investigations is recommended in these cases to review the benefits of testing and discuss potential ramifications. Additionally, those

experienced in clinic genomics can develop comprehensive, personalized management plans for each patient.

CLINICS CARE POINTS

- Diagnosis of a BCC at a young age should prompt concern for BCCN syndrome. The presence of palmoplantar pits may serve as a clinical clue.
- Mohs micrographic surgery may not be the first choice for the treatment of BCC in patients with BCCN due to the inability to obtain negative margins.
- The presence of poikiloderma in childhood should heighten suspicion of a photosensitivity disorder such as RTS
- Skin cancer may arise in hyperkeratotic or poikilodermatous lesions of patients with RTS
- Blistering sunburns in infancy are a hallmark of XP
- Lentigines may be a presenting sign of XP and distinguish from other photosensitivity disorders
- In OCA, pink to red nevi deserve extra-diagnostic scrutiny to exclude amelanotic melanoma
- Skin cancer prevention with strict sun protection and regular screening examinations allow individuals with photosensitivity disorders to have a normal life span
- Sebaceous neoplasms occurring outside of the head and neck, especially sebaceous adenoma, raise the possibility of Lynch Syndrome
- CCMRD syndrome shares phenotypical overlap with neurofibromatosis
- Obtain relevant family history including cancer history in patients with multiple CALMs
- "Melanoma dominant" mutations are associated with an increased primary risk of melanoma, examples include *CDNK2A* and *BAP-1* mutations
- Diagnosis of melanoma in patients with family histories of melanoma and/or pancreatic cancer may suggest *CDKN2A*mutations
- An example of a "melanoma subordinate" cancer mutation is *BRCA* which typically presents with breast and ovarian cancers
- Genetic testing can help guide appropriate screening measures and preventative care for patients with increased tendencies

DISCLOSURE

J.L. Hand is a section editor for Genetic skin disorders at UpToDate, Inc. The authors have no other disclosures.

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