Cutaneous Malignancy in Albinism

Patricia K. Perry, MD, New York, New York
Nanette B. Silverberg, MD, New York, New York

Albinism is a disorder of hypopigmentation affecting the skin, appendages, and eyes. Ultraviolet light-induced cutaneous tumors are common in patients with albinism due to reduced or absent protection from melanin. Squamous cell carcinoma (SCC) is the number one skin tumor seen in patients who are albinos. Although nonmelanomatous skin cancers are more common in patients with albinism, dysplastic nevus and melanoma present a greater diagnostic challenge in this group because of their hypopigmented appearance. We report 2 cases of cutaneous malignancies in patients who had oculocutaneous albinism (OCA). The first case involves a 45-year-old man with OCA type 2 (OCA2) who developed a large SCC of the neck. The second case involves a 24-year-old man with Hermansky-Pudlak syndrome (HPS) who developed amelanotic melanoma. In both cases, hypopigmentation of the lesions contributed to a delay in diagnosis. We review the clinical, diagnostic, and therapeutic concerns for patients with albinism who have cutaneous malignancies.

Case Reports

Patient 1—A 45-year-old African man from Guinea presented with an 8-month history of a large tender draining mass on the right aspect of his neck. The patient reported no fever, chills, recurrent infections, gastrointestinal distress, easy bruisability, or excessive bleeding. He had a medical and family history significant for albinism. He also had myopia and a nonmelanomatous skin cancer of the face a few years prior. The patient recalls having had many blistering sunburns as a child because of his schoolteachers exposing him to the midday sun.

Physical examination revealed a fair-skinned man with yellow hair, nystagmus, and a 7-cm erythematous draining tumor on the right lateral neck (Figure 1). Multiple regular, symmetric brown macules measuring 2 to 4 mm were scattered across his face, neck, chest, and upper extremities. Based on the hypopigmentation of the skin and hair, as well as the melanotic macules, a diagnosis of oculocutaneous albinism type 2 (OCA2) was made.

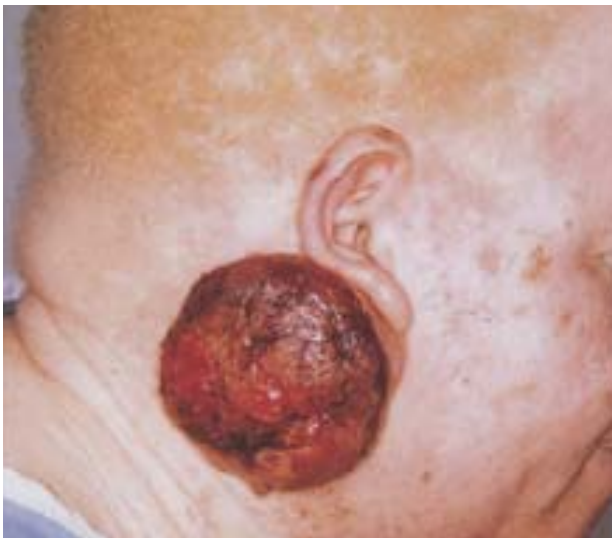

Figure 1. A 7-cm squamous cell carcinoma on the neck of patient 1, a 45-year-old man with oculocutaneous albinism type 2.

Laboratory studies revealed normal blood count, chemistries, liver function tests, and bleeding times. A wedge biopsy of the tumor revealed squamous cell carcinoma (SCC). A computed tomography scan of the neck (with contrast) revealed a homogeneously enhancing mass measuring 4.5×3.5×5.5 cm and involving the dermis and subcutaneous soft tissues lateral to the right sternocleidomastoid muscle with enlarged adenoids and shoddy lymphadenopathy. The tumor was excised under general anesthesia with an extensive lymph node dissection. This was followed by radiation therapy.

Patient 2—A 24-year-old Hispanic male of Puerto Rican descent presented with a one-month history of an enlarging mass on his forearm that bled occasionally. His medical history was significant for a known bleeding diathesis, which had been diagnosed as platelet dysfunction. He also had reduced visual acuity with nystagmus and photophobia and was legally blind. He was fair skinned with blonde hair and pink eyes. His family history was significant. His sisters,

Drs. Perry and Silverberg are from the Department of Dermatology, St. Luke's-Roosevelt Hospital Center, New York, New York.
Reprints: Nanette B. Silverberg, MD, Department of Dermatology, St. Luke's-Roosevelt Hospital Center, 1090 Amsterdam Ave, Suite 11D, New York, NY 10025.

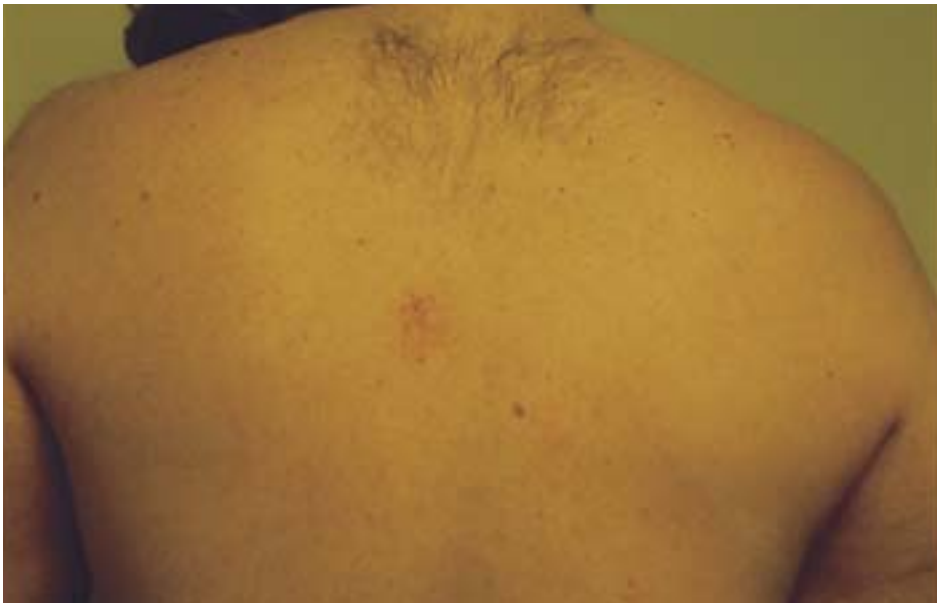

Figure 2. Multiple lentigines and hyperpigmented papules on the back of patient 2 who has Hermansky-Pudlak syndrome.

aged 14 and 22 years, both were known to have fair skin, blonde hair, and a bleeding diathesis. The patient's parents had Fitzpatrick type II skin and dark-brown hair and eyes.

On physical examination, the patient was a pale young man with blonde hair and obvious nystagmus. He had some tan-brown macules on the back measuring 3 to 5 mm (Figure 2), which proved to be lentigines on biopsy, and a 1.2-cm pink plaque on the right forearm. Clinically, the lesion looked like a pyogenic granuloma. The lesion was shaved off under local anesthesia, and the base was electrodesiccated.

Biopsy demonstrated a spindle cell tumor with a lack of maturation and mitoses. An HMB-45 stain confirmed the lesion to be a nodular malignant melanoma (MM) of 4.2-mm depth. A sentinel node biopsy was negative. The area was excised with appropriate margins. The patient has had no recurrence in the past 4 years. Both he and his sisters now observe strict photoavoidance and screening regimens.

Comment

Albinism is a cutaneous condition that results from an alteration in melanin synthesis. Two broad categories—OCA and ocular albinism (OA)—and a variety of subtypes exist. The types are classified based on the gene locus affected. OCA is characterized by reduced or absent melanin synthesis in the melanocytes of the skin, hair, and eyes, resulting in reduced pigmentation. OA is characterized by hypopigmentation of the retinal pigment epithelium. Significant progress in the understanding of albinism was made through the development of the hair-bulb incubation test, which demonstrated that at least 2 genetically distinct types of OCA exist.[1] In this test, incubation with melanin precursors allows for melanin production in the presence of tyrosinase. Some patients were found to have no melanin synthesis (classified as OCA1 or tyrosinase negative) and others had reduced levels of melanin synthesis (classified as OCA2 or tyrosinase positive). More recently, it has been recognized that complete or partial loss of tyrosinase may be seen in OCA1. It has, therefore, been renamed *tyrosinase-related albinism*.

Originally, clinical and biochemical changes were used to define albinism. By 1980, more than 10 separate complex and confusing phenotypes of albinism had been reported. Therefore, current classification is based on the genetic locus involved. Clinical findings vary depending on the degree of impairment in melanin synthesis.[2] In addition to pigmentary alteration of the hair and skin, other findings may include multiple nevi and seborrheic keratoses. Eye findings associated with albinism include nystagmus, photophobia, impaired visual acuity, strabismus, foveal hypoplasia, and a prominent red reflex. Although not a criterion for diagnosis, decreased hearing may occur. Some of the patients may have relative reductions in pigmentation in association with immunodeficiency (eg, Chédiak-Higashi and Griscelli syndromes). Four stages of photodamage have been described in OCA2: erythema, atrophy of the epidermis and hypertrophy of the dermis, solar keratoses, and clinical carcinomas.

Although the general diagnosis of albinism is made on clinical grounds (cutaneous hypopigmentation with or without ocular changes), the most specific diagnosis is made by molecular analysis.

Family history, visual evoked potential test for optic nerve activity, and the hair-bulb incubation test also provide clues as to the specific diagnosis.

The molecular pathogenesis varies according to type. OCA1 occurs as a result of missense, nonsense, frameshift, splice site, and deletion mutations involving the tyrosinase gene (11q14-q21). Different phenotypes are dependent on the effects of the mutation of residual enzyme function, ie, null (OCA1A) versus "leaky" mutations (OCA1B).

OCA2 results from a missense mutation of the P gene (15q11.2-q12), which is a human homologue of the mouse pink-eyed dilution gene. The gene is well-preserved among the species. The function of the P gene is unknown. Affected patients, however, have a reduction in eumelanin synthesis with less effect of pheomelanin.[3] OCA2 is the most common type of albinism seen in patients in sub-Saharan Africa.[4] In this region, patients may be unaware of the genetics of the disease, and a variety of superstitious beliefs have arisen about the origin of pigment loss in albinism. OCA3 is associated with alterations of the gene that encodes tyrosinase-related protein-1 (9p23). This gene regulates eumelanin production and has catalytic activity. It also may act as a dihydroxyindole-2-carboxylic acid oxidase, which acts in its conversion to indolequinone in the eumelanin pathway.

HPS is a variant of tyrosinase-positive albinism, with an autosomal recessive mode of inheritance. HPS is characterized by the triad of OCA, a bleeding diathesis, and a ceroidlike substance deposition in multiple organs (50%), such as the lungs (interstitial fibrosis) and gastrointestinal tract (granulomatous colitis). All the patients have nystagmus, and 78% have strabismus. HPS is believed to be a lysosomal storage defect disorder affecting numerous cytoplasmic organelles, including lysosomes; the melanosomes, which are giant in this disorder; and platelets, which have giant dense bodies. Pigment-laden macrophages are seen histologically. Platelet storage pool and lysosomal membrane defects account for the systemic complaints associated with this syndrome. Affected patients have normal platelet counts but increased bleeding times.[5]

The HPS gene has been localized to the 10q23.1-3 region and is the number one single gene disorder in Puerto Rico.[6] The gene encodes adaptor protein 3 (a transmembrane protein of unknown function). Adaptor protein 3 is expressed in a wide variety of tissues that may account for involvement of the hematological, gastrointestinal, and respiratory systems. In Puerto Rico, the frequency of the gene may be as high as 1 in 21 individuals. As a result, the frequency of the disorder yields a pseudodominant inheritance pattern.[7] Puerto Rican patients with HPS are born with a cutaneous strike against them due to the strong sun exposure they experience in childhood. As a result, cutaneous malignancies in this group are common.

Malignancies in patients who are albino are thought to develop because of the lack of melanin photoprotection. The most frequently occurring cutaneous malignancy in albinism is SCC, occurring at least twice as much as in individuals with normal pigmentation. A survey of 350 patients in Tanzania who are albino revealed 104 skin cancers. One hundred of these were SCC, 3 were basal cells, and one was MM. Thirty-three of the patients had deep SCC (greater than 4 cm), of which 30 were on the head and neck. The average age of these patients was 31 years.[8]

To our knowledge, there have been 30 reported cases of MM in patients with albinism. About 50% of these lesions have been hypopigmented. Clinically hypopigmented MM resembles pyogenic granulomas.[9-11] Most of the lesions are seen on the extremities and, less commonly, on the chest. Nasal mucosa,[12] gingival, and ocular MM also have been reported.[12,13] Most patients with these disorders were tyrosinase positive. The literature would suggest that the dysplastic nevus syndrome may occur in patients with albinism, and the combination may produce multiple cutaneous MM. A tyrosinase-negative patient with dysplastic nevus syndrome, amelanotic dysplastic nevi, and amelanotic melanomas has been reported.[9] Cutaneous melanocytic malignancies should be screened based on the presence of asymmetry, border irregularity, and diameter changes. Furthermore, rapid growth and ulceration may be the best clues to diagnosis. Histologically, the use of the HMB-45 stain can aid in the identification of melanocytic tumors, even in the absence of noticeable pigmentation.

All patients with albinism should be treated like individuals with Fitzpatrick type I skin. This means they must practice strict sun avoidance and year-round broad-spectrum suncreen use, wear protective clothing, and receive skin cancer screening every 6 months. The incidence of SCC and basal cell carcinoma increases with age; therefore, vigilant observation should be maintained. Eyes should be protected with UV-blocking sunglasses and corrective or tinted lens. An ophthalmic examination is indicated annually for cancer surveillance, as well as for overall visual health. Molecular analysis is not necessary for proper care of patients; however, it should be encouraged because new information about albinism has occurred as a result of these studies.

A mutation database for genes involved in OCA and OA exists.[14] The most current information can be found at www.cbc.umn.edu/tad.

REFERENCES

1. King RA, Witkop CJ. Detection of heterozygotes for tyrosinase-negative oculocutaneous albinism by hairbulb tyrosinase assay. *Am J Hum Genet.* 1977;29:164-168.
2. Setluri V. Sorting and targeting of melanosomal membrane proteins: signals, pathways and mechanisms. *Pigment Cell Res.* 2000;13:128-134.
3. Manga P, Orlow SJ. The pink-eyed dilution gene and the molecular pathogenesis of tyrosinase-positive albinism (OCA2). *J Dermatol.* 1999;26:738-747.
4. Spritz RA, Fukai K, Holmes SA, et al. Frequent intragenic deletion of the P gene in Tanzanian patients with type II oculocutaneous albinism (OCA2). *Am J Hum Genet.* 1995; 56:1320-1323.
5. Biswas S, Lloyd IC. Oculocutaneous albinism. *Arch Dis Child.* 1999;80:565-569.
6. Kinnear PE, Tuddenham EGD. Albinism with hemorrhagic diathesis: Hermansky-Pudlak syndrome. *Br J Ophthalmol.* 1985;69:904-908.
7. Oetting W. King R. Molecular basis of oculocutaneous albinism. *J Invest Dermatol.* 1994;103:131S-136S.
8. Luande J, Henschke CI, Mohammed N. The Tanzanian human albino skin: natural history. *Cancer.* 1985;55: 1823-1828.
9. Pehamberger H, Honigsmann H, Wolff K. Dysplastic nevus syndrome with multiple primary amelanotic melanomas in oculocutaneous albinism. *J Am Acad Dermatol.* 1984;11: 731-735.
10. Streutker CJ, McCready D, Jimbow K, et al. Malignant melanoma in a patient with oculocutaneous albinism. *J Cutan Med Surg.* 2000;4:149-152.
11. Koch SE, Lange JR. Amelanotic melanoma: the great masquerader. *J Am Acad Dermatol.* 2000;42:731-734.
12. Malaguarnera M, Romano M, Pistone G. Metastatic melanoma of the nasal cavity in a patient with oculocutaneous albinism. *Clin Oncol.* 1998;10:404-406
13. Kheterpal S, Shields JA, Shields CL, et al. Choroidal melanoma in an African-American albino. *Am J Ophthalmol.* 1996;22:901-903.
14. International Albinism Center.. Albinism database. Available at: http://www.cbc.umn.edu/tad. Accessed April 9, 2001.