Two Patients With Hailey-Hailey Disease, Multiple Primary Melanomas, and Other Cancers

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Background: Hailey-Hailey Disease (HHD) is an autosomal dominant skin disorder that is characterized by erythematous and sometimes vesicular, weeping plaques of intertriginous regions. Squamous cell carcinoma and basal cell carcinoma arising in lesions of HHD have been described in the literature. To our knowledge, there are no reports of melanoma or noncutaneous malignant neoplasms associated with HHD.

Observations: We discuss the mechanisms of oncogenicity, including genetic, environmental, and iatrogenic factors, in 2 patients with HHD, multiple primary melanomas, and other cancers. Patient 1 had a mucoepidermoid carcinoma of the parotid gland. Patient 2 had a history of acute monoblastic leukemia and malignant peripheral nerve sheath tumor as well as radiologic evidence of an acoustic neurilemmoma.

Conclusions: The cause of the cancers in these 2 patients is likely multifactorial. We describe the patients to draw attention to the possible association between HHD and cancer. Additional research should be performed to determine whether patients with HHD have an increased incidence of cancer.

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H AILEY-HAILEY DISEASE (HHD), also termed familial benign chronic pemphigus, is a rare autosomal dominant skin disease that was first described in 1939 by the Hailey brothers. The disease typically occurs between the second and fourth decades of life and presents with blisters, erythema, and malodorous plaques in intertriginous locations. Longitudinal white bands of the fingernails may be a helpful diagnostic clue. Exacerbating factors include friction, heat, sweating, UV radiation, and superinfection. Family history is often of help in diagnosis; however, up to one-third of cases represent sporadic mutations with no family history. Histologically, HHD is characterized by extensive epidermal suprabasilar acantholysis, which may have the appearance of a “dilapidated brick wall.” In 2000, Hu et al and Sudbrak et al identified the ATP2C1 gene, which is located on chromosome 3q21-q24. More than 80 mutations in this gene have been reported in HHD. The ATP2C1 gene encodes for the human secretory pathway Ca\(^{2+}\)/Mn\(^{2+}\) ATPase (hSPCA1) protein associated with the Golgi apparatus and is expressed abundantly in keratinocytes.

Malignant melanoma of the skin is increasingly common, and patients with 1 melanoma have an increased risk of a second primary melanoma, but a diagnosis of 3 or more distinct primary melanomas is uncommon. We describe 2 patients with HHD, multiple primary melanomas, and other cancers. To our knowledge, the literature contains no prior reports of melanoma or noncutaneous malignant neoplasms associated with HHD. We discuss possible mechanisms of oncogenicity in these patients with HHD.

REPORT OF CASES

CASE 1

A 67-year-old man with Fitzpatrick type III skin presented to the surgical oncology clinic for treatment of multiple primary melanomas. His first melanoma, which occurred when he was 46 years old, was treated with wide excision. More recently, over a 1-year period, he was diagnosed as having 5 additional primary melanomas on his trunk and upper extremities.
Three of the 5 melanomas were Clark level IV, with Breslow depths of 3.45, 4.03, and 5.12 mm; 1 was Clark level III, with a Breslow depth of 0.91 mm; and 1 was Clark level II, with a Breslow depth of 0.28 mm. The latter specimen also contained a separate dermal nodule of melanoma, which was believed to be a metastasis. Most of this patient's specimens have shown concurrent histologic features of HHD and melanoma, as shown in Figure 1. Fine-needle aspiration of a left axillary mass revealed metastatic melanoma, which was surgically resected. The results of other staging were negative at that time, and the patient has been enrolled in an experimental melanoma vaccine trial.

The patient reported significant sun exposure during his life, rare sunscreen use during his youth, and approximately 12 blistering sunburns before the age of 20 years. He had no family history of melanoma. His maternal grandmother, mother, sister, and nephew had HHD.

His medical history was remarkable for HHD, asthma, osteoarthritis, benign colon polyps, benign prostatic hypertrophy, vertigo, nephrolithiasis, hypertension, and gastroesophageal reflux. Also, at the age of 64 years, he was diagnosed as having a high-grade mucoepidermoid carcinoma of the left parotid gland, with metastasis to the left cervical lymph nodes, which was treated with a combination of left total parotidectomy, left superior cervical lymph node dissection, carboplatin, paclitaxel, and local irradiation with a dose of 6600 rad (to convert to grays, multiply by 0.01). His postoperative course was complicated by episodes of gustatory hyperhidrosis.

CASE 2

A 35-year-old man with Fitzpatrick skin type II presented to the surgical oncology clinic for treatment of his first melanoma, on the right side of the upper part of his back. The melanoma, which was at least a modified Clark level III with a Breslow depth of at least 0.83 mm, extended to the base of the biopsy specimen. Sentinel nodes of the right axilla were negative for metastasis. The patient subsequently noted a papule on the plantar aspect of his left foot. Because of the atypical clinical appearance of the lesion, it was initially treated as a callus and a plantar wart (Figure 2). Ultimately, it was diagnosed as an acral lentiginous melanoma, which was at least Clark level IV, with a Breslow depth of at least 8 mm. Wide resection was performed, and a sentinel lymph node biopsy revealed 2 positive nodes in the left groin. Also, a third melanoma, which was Clark level II, with a Breslow depth of 0.33 mm (Figure 3A), was diagnosed on the right arm. A metastatic workup was negative for distant disease.

The patient had HHD, numerous dysplastic nevi, and a history of approximately 12 basal cell carcinomas of the arms and back (Figure 3B). He had a history of significant sun exposure with minimal sunscreen use as a youth. He also reported experiencing approximately 6 blistering sunburns before he was 20 years old. His mother had numerous atypical nevi and a melanoma. His father and paternal aunt had HHD. There was no family history of neural tumors.
The patient's medical history was notable for several malignant neoplasms. At the age of 19 years, he developed leukemia. Initially, his leukemia was of an indeterminate type; therefore, while awaiting final typing, he was treated with 2 doses of vincristine sulfate and 7 days of prednisone. After additional testing, he was diagnosed as having acute monoblastic leukemia, M5 subtype, which was treated with cytarabine and daunorubicin hydrochloride. Subsequently, he received 1200-rad total-body irradiation and high-dose cyclophosphamide and methotrexate therapy in preparation for an allogeneic stem cell transplant, which was donated by his HLA-matched sister. After transplantation, he was placed on a regimen of cyclosporine for approximately 5 months. He has had no recurrence of leukemia or other hematologic disorder.

At the age of 30 years, he developed a malignant peripheral nerve sheath tumor of the cervical spine, which was resected and treated with 4860 rad of localized radiation therapy. More recently, a mass of the right cerebellopontine angle was noted on magnetic resonance imaging; this finding was suggestive of a vestibular schwannoma.

Both patients described herein were diagnosed as having HHD, multiple primary melanomas, and at least 1 other type of cancer. The mechanism underlying carcinogenesis in these patients is likely multifactorial. Contributing factors include skin type and excessive exposure to UV radiation. We discuss the possible genetic and iatrogenic mechanisms of oncogenicity in these 2 patients.

Although there are reports of cutaneous malignant neoplasms arising in HHD, to our knowledge there are no reports of melanoma arising in patients with HHD. There are 4 reports of squamous cell carcinoma and 2 reports of basal cell carcinoma arising in lesions of HHD. Presumably, the impaired epidermal barrier may allow infection with oncogenic strains of human papillomavirus, thus promoting the development of squamous cell carcinoma. Human papillomavirus was detected in 1 case of HHD-associated squamous cell carcinoma.

Based on the findings of molecular studies of HHD, there are additional data to suggest that, in theory, patients with HHD may be predisposed to neoplasia. In 2007, Okunade et al demonstrated that a heterozygous mutation of the ATP2C1 gene in mice leads to an increased incidence of squamous cell tumors in aged adult mice. They suggested that this mutation leads to Golgi stress,
increased apoptosis, and a genetic predisposition to cancer. Also, cancer transformation is commonly associated with rearrangement of calcium channels, leading to cellular proliferation and impaired apoptosis. Therefore, it is possible that the aberrant calcium signaling in HHD may promote an oncogenic environment. Cialfi et al demonstrated that HHD keratinocytes undergo oxidative stress, which may contribute to DNA damage. They also found downregulation of Notch1 and Itch in HHD keratinocytes. It has been reported that Notch1 may act as a transforming oncogene in human melanocytes; therefore, in terms of Notch1 levels, patients with HHD should, in theory, be at decreased risk for advanced melanomas. Decreased Notch1 levels may not be a sufficient protective factor, as suggested by the multiple advanced melanomas in our 2 patients.

Alternatively, the chemotherapy and localized radiation therapy that patient 1 received for his mucoepidermoid carcinoma may have placed him at risk for the development of secondary malignant neoplasms. The same holds true for patient 2; it is likely that the chemotherapy, total-body irradiation, and immunosuppression after his stem cell transplantation made him more susceptible to developing secondary malignant neoplasms. For survivors of childhood cancer, the risk of developing a second cancer can be up to 35 times greater than in the general population, occurring at an incidence of 4%. Melanoma after childhood cancer has been reported after treatment of primary hematologic malignant neoplasms. Guérin et al found a trend toward increased risk of melanoma as a second malignant neoplasm after treatment with a combination of alkylating agents and mitotic spindle inhibitors, although these data were not statistically significant. Patient 2 was treated with cyclophosphamide, an alkylating agent, and 2 doses of vincristine, a mitotic spindle inhibitor. Interestingly, carboplatin and paclitaxel, the chemotherapy agents that were used to treat mucoepidermoid carcinoma in case 1, have been investigated as a possible treatment for metastatic melanoma.

Total-body irradiation, as was used in case 2, has been associated with a 2.7- to 4.4-fold higher risk of second neoplasms, with a positive dose relationship. The latency period from time of radiation treatment to the development of the second neoplasm may be up to 50 years after exposure. Guérin et al demonstrated that the risk of melanoma was found to be linked to the local radiation dose, with an increased risk noted specifically for local radiation doses of more than 1500 rad. Patient 1 received a dose of 6600 rad to the left parotid gland and cervical field, while patient 2 received 1200 rad of total-body irradiation plus 4860 rad to a cervical spine field. A considerable number of secondary malignant neoplasms that occur after radiotherapy do not occur within the irradiated field.

A genetic basis for disease could also be considered in patient 2, given his multiple atypical-appearing nevi and the family history of melanoma in his mother. Four melanoma-susceptibility genes have been characterized, including cyclin-dependent kinase inhibitor 2A (CDKN2A, also called p16), alternate reading frame (ARF), also called p14), cyclin-dependent kinase 4 (CDK4), and melanocortin 1 receptor (MC1R). Approximately 20% to 40% of families with melanoma carry a mutation in p16/ARF, and only 1% to 2% of families carry a mutation of CDK4 or ARF-only genes. Genetic studies have not been performed in these cases but will be considered in the future.

Some familial melanoma syndromes are associated with other cancers, including pancreatic cancer and neural tumors. The melanoma–neural system tumor syndrome is a familial syndrome that is composed of multiple primary melanomas as well as tumors of neural origin, including acoustic neuromas, meningiomas, astrocytomas, medulloblastomas, glioblastoma multiforme, and others. Mutations involving ARF alone or a region of chromosome 9p21 encompassing CDKN2A, CDKN2B (also called p15), and ARF genes have been identified in the melanoma–neural system tumor syndrome.

We have described 2 patients with a diagnosis of HHD, multiple primary melanomas, and other cancers. We hope to draw awareness to this association of HHD and cancer, and if similar cases are recognized, then additional genetic and molecular studies may be performed to elucidate the mechanism of carcinogenicity in this patient population.

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