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What's Your Diagnosis?

Familial Dyspigmentation on the Dorsal Hands and Feet

Mohammed I. AlJasser, Nina MacDonald, Harvey Lui

ABSTRACT: Patients often present with clinical skin features that may resemble a variety of similar but distinct conditions. A 41-year-old Asian woman was referred to the dermatology clinic for evaluation of dyspigmentation on the hands and feet that was first noted at the age of 6 years. Physical examination revealed a combination of hyper- and hypopigmented macules involving the dorsal aspects of her distal extremities.

Key words: Acropigmentation of Dohi, Dyspigmentation, Nevus, Nevus Depigmentosus, Nevus Spilus, Postinflammatory Dyspigmentation, Postinflammatory Response, Vitiligo

An otherwise healthy 41-year-old Asian woman was referred to the dermatology clinic for evaluation of dyspigmentation on the hands and feet that was first noted at the age of 6 years. Eight family members on her maternal side, going back at least four generations, had similar pigmentary changes. Physical examination revealed a combination of hyper- and hypopigmented macules involving the dorsal aspects of the distal extremities (Figures 1 and 2). The knees showed several scattered small dark brown macules (Figure 3). There were no pigmentary changes on other sites of the body. The hypopigmented macules showed accentuation by fluorescence under Wood's light examination (Figure 4).

WHAT'S YOUR DIAGNOSIS?

1. Vitiligo
2. Nevus depigmentosus
3. Postinflammatory dyspigmentation
4. Acropigmentation of Dohi
5. Nevus spilus

Vitiligo is a chronic acquired disease characterized by well-defined white, depigmented macules and patches affecting the skin and mucous membranes. Mucocutaneous lesions develop secondary to selective autoimmune destruction of melanocytes. Vitiligo may appear at any age with an estimated worldwide prevalence of 0.5%–1% (Taieb & Picardo, 2007) and is the most common skin disorder causing light-colored skin. The etiology of vitiligo is largely unknown but is likely thought to be multifactorial. A family history of vitiligo is positive in up to 20% of cases (Alkhateeb, Fain, Thody, Bennett, & Spritz, 2003; Nath, Majumder, & Nordlund, 1994). There are

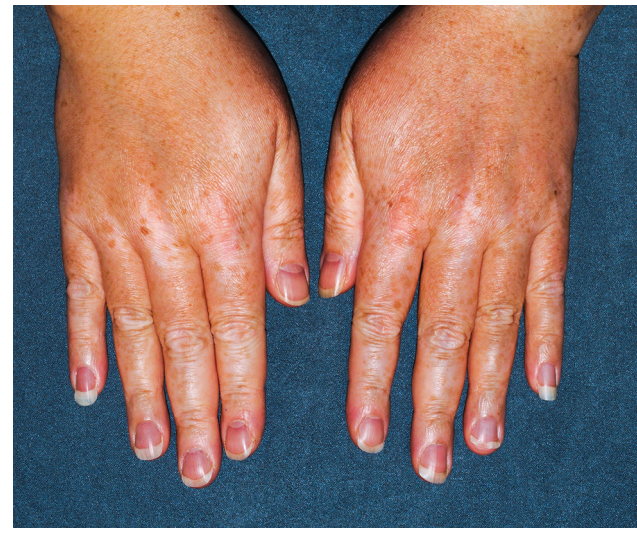

FIGURE 1. A combination of hyper- and hypopigmented macules involving the dorsal hands.

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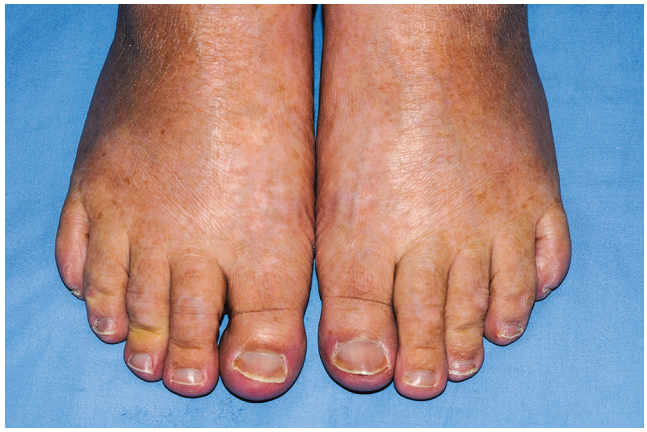

FIGURE 2. A combination of hyper- and hypopigmented macules involving the dorsal feet.

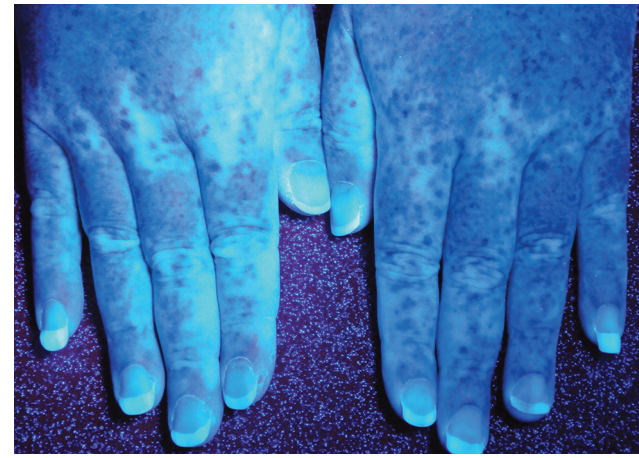

FIGURE 4. Wood's light illumination of the hands.

several hypotheses on the pathogenesis of vitiligo, including the autoimmune, neurohormonal, and autocytotoxic theories (Alikhan, Felsten, Daly, & Petronic-Rosic, 2011). The strongest evidence supports the autoimmune hypothesis of altered cellular immune response (Ongenae, Van Geel, & Naeyaert, 2003). Vitiligo presents with sharply demarcated depigmented macules and patches (Figure 5). It commonly affects the face, axillae, nipples, umbilicus, dorsal aspect of the hands, elbows, knees, digits, flexor wrists, sacrum, groin, and anogenital area. Trauma to unaffected skin might result in the development of new lesions, a phenomenon called koebnerization (Alikhan et al., 2011). Spontaneous repigmentation of vitiliginous patches is uncommon (seen in 10%–20% of patients) but can occur (Castanet & Ortonne, 1997; Yaghoobi, Omidian, & Bagherani, 2011). Repigmentation usually occurs in a perifollicular pattern, suggesting that the hair follicle functions as a reservoir for melanocytes (Castanet & Ortonne, 1997). On the basis of the general morphological pattern of the individual patches, vitiligo is broadly divided into two categories: segmental and nonsegmental (Taieb & Picardo, 2007). Segmental vitiligo is usually unilateral, occurring along a dermatome. Nonsegmental vitiligo is more common, generally has a symmetric distribution, and is more likely to be progressive. When vitiligo is classified according to the distribution of lesions, there are three types (Table 1): localized, generalized, and universal (Alikhan et al., 2011). Localized vitiligo is further subdivided into focal, segmental, and mucosal. Generalized vitiligo is classified into acrofacial, vulgaris, and mixed. Universal vitiligo affects more than 80% of body surface area. The diagnosis of vitiligo is usually made on clinical grounds based on the

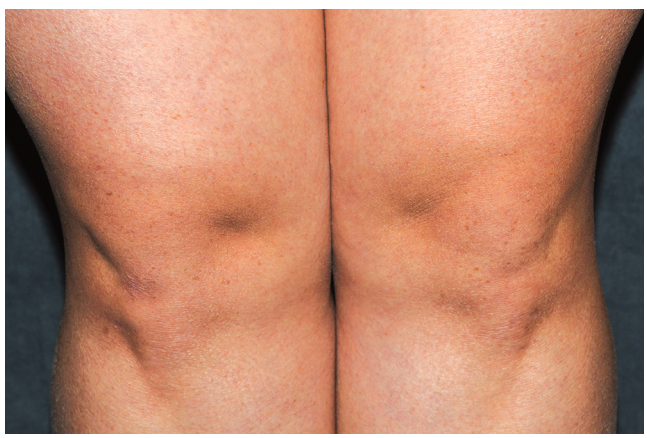

FIGURE 3. Several scattered small dark brown macules on both knees.

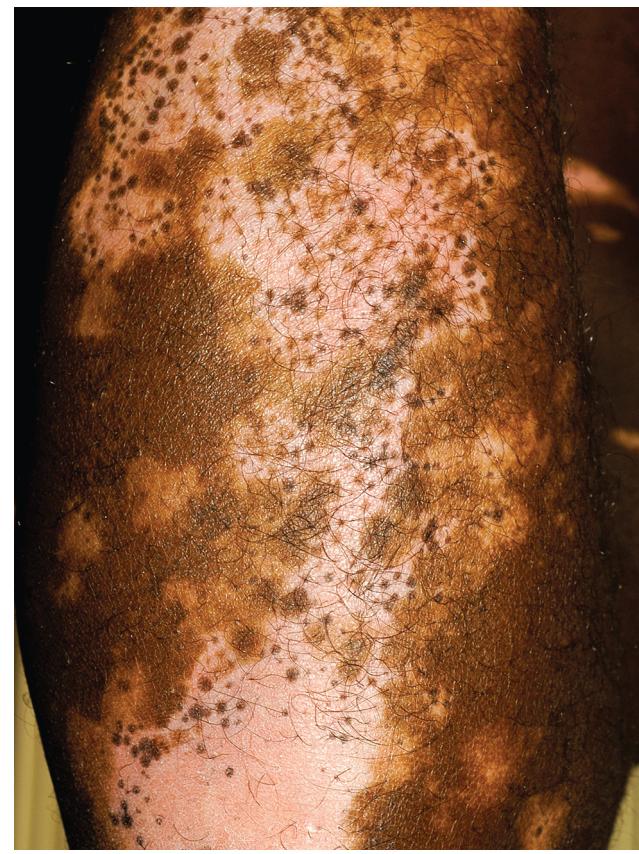

FIGURE 5. Vitiligo. Large depigmented patch with multiple areas of perifollicular repigmentation.

TABLE 1. Classification of Vitiligo Based on the Distribution of Lesions

Localized
• Focal
• Segmental
• Mucosal
Generalized
• Acrofacial
• Vulgaris
• Mixed
Universal: Affects more than 80% of the body surface area

presence of well-demarcated macules or patches of skin that are depigmented, that is, devoid of normal pigmentation. This can be confirmed with the use of Wood's lamp wherein the affected vitiligo skin typically appears chalky white. Wood's lamp examination is particularly useful for identifying vitiligo spots in lighter-colored patients, where the contrast between normal and affected skin is not as obvious as in darker-skinned patients. A skin biopsy is rarely needed for diagnosis; if done, it will typically show an absence of melanin in the epidermis with no or few melanocytes (Gokhale & Mehta, 1983). There are many treatment modalities available for vitiligo; however, none of them can cure the disease. These include topical treatments (including topical corticosteroids and calcineurin inhibitors), phototherapy, surgical therapy, and depigmentation therapy.

Nevus depigmentosus (ND) usually presents at birth as a hypopigmented macule or patch and remains stable throughout life. Some cases of ND develop later in life; however, approximately 74% of cases develop lesions before the age of 3 years. The lesions may have an irregular border and can be solitary or clustered (Figure 6). The trunk is the most commonly involved site, but the face, neck, and extremities can also be affected (Xu, Huang, Li, Wang, & Shen, 2008). Nevus depigmentosus has no familial tendency and usually occurs sporadically in families. The etiology of ND is unknown. However, it has been reported to be because of a defect in the transfer of melanosomes from melanocytes to keratinocytes (Kim, Kang, Lee, & Kim, 2006). Distinguishing ND from vitiligo is difficult. Clinicopathological features that favor the diagnosis of ND over vitiligo include early age of onset, stability throughout life, macules that are hypopigmented rather than depigmented, an off-white rather than a chalky white accentuation under Wood's light, and decreased melanin with normal melanocyte numbers on biopsy (Kim et al., 2006; Xu et al., 2008). Hypomelanotic macules similar to ND are seen in 97% of patients with tuberous sclerosis (TS). Tuberous sclerosis is an autosomal dominant neurocutaneous syndrome characterized by the development of tumors in several body organs. The ovoid

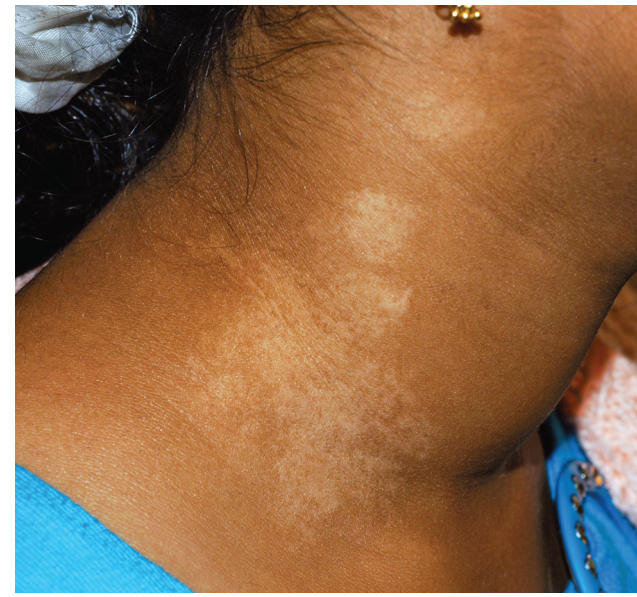

FIGURE 6. Nevus depigmentosus. An irregular hypopigmented patch involving the neck.

hypomelanotic macules are classically given the name "ash leaf" macules (Schwartz, Fernandez, Kotulska, & Jóźwiak, 2007). The development of seizures in the presence of three or more hypomelanotic macules strongly suggests the diagnosis of TS (Schwartz et al., 2007). However, the prevalence of having two or less hypomelanotic macules in the general population is approximately 1% and does not in itself mandate a work-up for TS (Schwartz et al., 2007).

Postinflammatory dyspigmentation (PID) refers to cutaneous pigmentary changes secondary to inflammation. These changes are often localized to areas of previous inflammation. Hyperpigmentation, hypopigmentation, depigmentation, or a combination of all three (Figure 7) may occur. The term "dyspigmentation" or "dyschromatosis" refers to skin patches that have multiple colors as

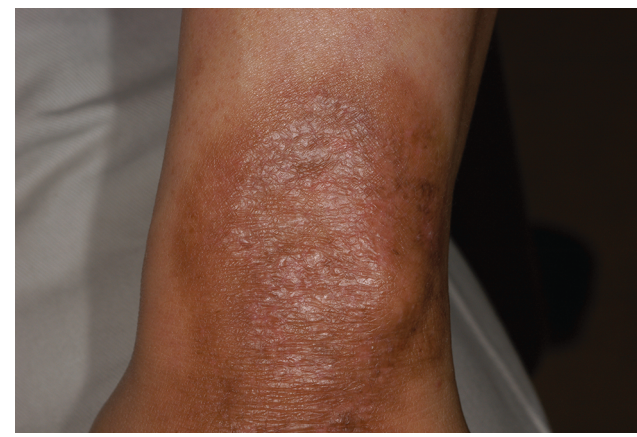

FIGURE 7. Postinflammatory hyperpigmentation secondary to topical psoralen and ultraviolet A treatment for psoriasis. The central scaly plaque represents psoriasis.

compared to the normal surrounding skin. Postinflammatory dyspigmentation occurs more frequently in patients with darker skin types. There are many causes of PID including inflammatory skin diseases, dermatologic procedures, physical trauma, burns, and chemical insults to the skin (Lamel, Rahvar, & Maibach, 2012). It is thought to be related to increased production and/or abnormal distribution of melanin (Ruiz-Maldonado & Orozco-Covarrubias, 1997). Key findings important in differentiating PID from other pigmentary disorders are a history of preceding trauma or inflammation and the presence of borders corresponding to the antecedent skin reaction. The two main aspects to consider in the management of PID are to treat the underlying cause of inflammation and sun protection to minimize further darkening. Medical treatment of established pigmentary changes include topical inhibitors of melanin synthesis such as hydroquinone, topical retinoids, chemical peels, and laser therapy, although the overall efficacy of these approaches is marginal at best. For the most part, PID will usually resolve spontaneously over time as long as the antecedent cause is eliminated.

Nevus spilus (also known as speckled lentiginous nevus) is characterized by a localized light brown patch studded with small dark brown macules or papules with no areas of hypopigmentation (Figure 8). Most lesions of nevus spilus develop during the first year of life (Leung, Kao, & Robson, 2006). Nevus spilus is usually an isolated finding but can be associated with other anomalies. The small dark lesions within the larger light brown patch represent melanocytic nevi. Development of melanoma within nevus spilus has been reported but is fortunately very rare (Rhodes, 1996).

DIAGNOSIS

This patient's skin condition represents acropigmentation of Dohi (APD). Acropigmentation of Dohi (also known as dyschromatosis symmetrica hereditaria) is a rare, autosomal dominant genodermatosis with approximately 200 cases reported in the literature to date (Oyama, Shimizu, Ohata, Tajima, & Nishikawa, 1999). In some cases, it is inherited in an autosomal recessive fashion (Alfadley, Al Ajlan, Hainau, Pedersen, & Al Hoqail, 2000). Most of the cases were reported from Japan, and the onset of pigmentary changes is seen mainly before the age of 6 years (Oyama et al., 1999). Acropigmentation of Dohi has been recently found to be because of mutation in ADAR1 gene (Suzuki et al., 2005). The mechanism by which this mutation causes the cutaneous changes in APD is unknown. However, it is thought to be because of the defect in protection against stress-induced apoptosis that is normally provided by the ADAR1 gene. This might explain loss of color in trauma prone sites like the hands and feet (Suzuki et al., 2005).

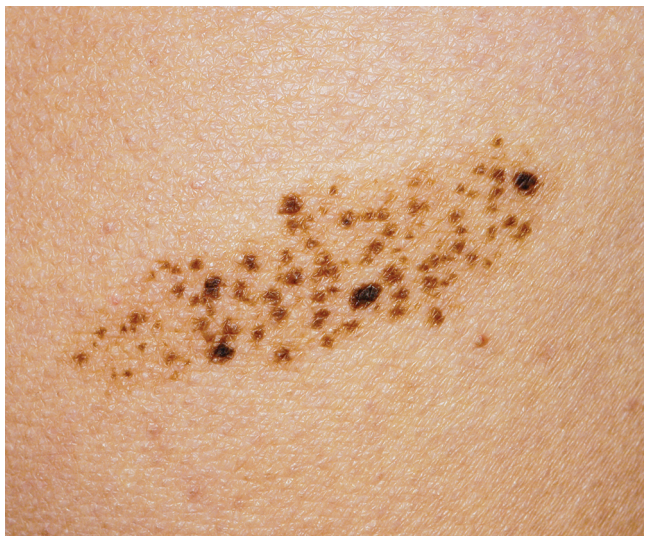

FIGURE 8. Nevus spilus. A well-demarcated light brown patch studded with multiple dark brown macules and papules.

The diagnosis of APD is made on clinical grounds based on the characteristic presentation. During infancy or early childhood, multiple hyperpigmented and hypopigmented macules develop on the dorsal aspects of the hands and feet. In addition, multiple small hyperpigmented macules can be seen on the face (Urabe & Hori, 1997). The lesions tend to progressively increase in number and size until adolescence and then remain stable for life (Oyama et al., 1999). There is typically sparing of the palms, soles, and mucous membranes. Acropigmentation of Dohi is often isolated and not associated with systemic abnormalities. Because of the reduction in melanocytes within the hypopigmented areas (Urabe & Hori, 1997), they may appear chalky white under Wood's light as seen in vitiligo. However, vitiligo is not usually associated with coexisting areas of hyperpigmentation within the affected skin sites, except when there is spontaneous repigmentation.

The hyperpigmented macules histologically show increased melanin in the stratum basale, whereas the hypopigmented areas show a reduction in melanocyte density (Urabe & Hori, 1997). The main entity in the differential diagnosis of APD is reticulate acropigmentation of Kitamura. Reticulate acropigmentation of Kitamura shares with APD the presence of hyperpigmented macules on distal extremities. Features that differentiate reticulate acropigmentation of Kitamura from APD include onset during the first two decades of life, reticulate pattern of hyperpigmentation, presence of atrophy, absence of hypopigmented macules, palmar pits, and breaks in the palmar epidermal rete ridge pattern (Sharma, Sharma, Radotra, & Kaur, 1989). Other diseases that should be considered in the differential diagnosis include dyschromatosis universalis hereditaria, mild xeroderma pigmentosum, dyspigmentation secondary to chemicals or radiation, and ephelides (Oyama et al., 1999; Urabe & Hori, 1997). Dyschromatosis universalis hereditaria is characterized by lesions similar to those seen in APD but in a more generalized distribution affecting the head and neck, trunk, and extremities including the palms and soles (Urabe & Hori, 1997).

There is no simple effective treatment that exists for the hypopigmented macules seen in APD. Treatments for vitiligo would not be expected to be effective for APD. Split thickness skin grafts have shown some efficacy in one case (Taki et al., 1986). The hyperpigmented macules can be effectively treated with different Q-switched lasers (Urabe & Hori, 1997). From the cosmetic standpoint, a camouflage make-up can be used to even out the skin tone. Sun avoidance and the use of sunscreens are recommended to decrease the visibility of the depigmented areas and avoid sunburns. The patient can be assured that this is not a condition that is known to be linked with other health issues. Reassurance can also be given that, after adolescence, the condition is generally stable. ■

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