Vitiligo-like lesions following imiquimod 5% application for condyloma acuminata: An additional case

Sir,

Among the many methods used in the treatment of condylomata acuminata, imiquimod 5% cream is the sole medication that is approved by the United States Food and Drug Administration.[1,2] Since 2005, ten patients with condyloma acuminata have been reported to develop vitiligo or vitiligo-like depigmentation following the use of imiquimod.[3-11] Vitiligo is an acquired skin disorder characterized by the appearance of depigmented macules due to a reduction in the number and function of melanocytes. Although several hypotheses have been proposed, the mechanism of depigmentation remains uncertain and is thought to be due to an immune-mediated attack by auto-reactive cytotoxic T-cells on melanocytes. Like other autoimmune disorders, cytokines play a role in the recruitment of auto-reactive T cells to the skin, which in turn may be influenced by imiquimod.[12] An additional case of vitiligo-like lesions induced by imiquimod in a 26-year-old man is presented here with a short review of literature.

A 26-year-old Lebanese man presented with hypopigmented lesions on the penis. He had applied imiquimod 5% cream on three condyloma acuminata lesions on his penis, three months prior to presentation. He used to apply the cream at night and wash it off in the morning, once a week for 3 weeks. Although he noticed some irritation and excoriation in the treated areas, he continued the application. After stopping the application of imiquimod, he observed some hypopigmented lesions in the treated areas which did not expand in size; however, they did not repigment in the following 2 months. He and his family members had no history of skin disorders such as vitiligo, other depigmented dermatoses or autoimmune diseases. He denied use of any other topical treatment.

Clinical examination revealed the hypopigmented macules on the penile region [Figure 1] that were accentuated on Wood's light examination. Laboratory tests (blood counts, liver and kidney function tests, thyroid function tests, human immunodeficiency virus (HIV) and syphilis serologies, hepatitis B and C serologies) were completely normal and a skin biopsy was recommended but refused by the patient. He was clinically diagnosed with imiquimod-induced localized vitiligo-like lesions.

Figure 1: Hypopigmented macules on the sites of application of imiquimod for condyloma acuminata

Imiquimod is an immune-response modifier that is generally well tolerated but has minor side effects like erythema, burning, blistering and excoriation.[13] Its mechanism of action in human papilloma virus (HPV) infection is by enhancing the host's innate and cellular immune response against the virus; it also stimulates peripheral blood monocytes, macrophages and dendritic cells to produce certain cytokines (interferon alfa, interleukins 12, 6 and 8, tumor necrosis factor alfa, nitric oxide).[14,15]

We found 10 previous reports in English of Imiquimod-induced hypopigmented macules [Table 1]. There appear to be no specific criteria to differentiate among "depigmentation," "hypopigmentation," "vitiligo" or "vitiligo-like lesions" and these names were chosen at will by authors of the respective reports. Moreover, among the 10 patients previously reported, only one had agreed for a biopsy and the histopathologic examination findings were consistent with vitiligo.[14] Besides, family history of vitiligo or other autoimmune disorders was reported in only one case. Thus, the reported hypopigmented macules were most probably secondary to imiquimod application. For this reason, we feel "imiquimod-induced hypopigmented macules" would be a better name for this side effect.

Table 1: Summary of all reported cases of vitiligo-like lesions following imiquimod application

Case	Author	Age/gender	Site	Histopathology	Family history	References
2005	Brown *et al*.	25/male	Scrotum	No	Not mentioned	[3]
2006	Stefanaki *et al*.	32/male	Penis Scrotum Pubic area	No	Vitiligo	[4]
2007	Senel and Seckin	32/male	Glans Penile shaft Scrotum	No	No	[6]
2007	Al-Dujaili and Hsu	21/male	Penile shaft Scrotum	No	No	[5]
2008	Serrão *et al*.	26/male	Penile shaft	No	Not mentioned	[7]
2011	Zhang and Zhu	25/male	Coronoid sulcus Penis	No	Not mentioned	[8]
		22/male	Penis	No	Not mentioned	
2013	Wang *et al*.	36/female	Perineum Perianal	No	No	[9]
2014	Li *et al*.	28/male	Penis Penile shaft Scrotum	Absence of melanocytes and melanin granules in the basal layer	No	[10]
2014	Serra *et al*.	25/female	Vulvar Hypomelanotichalo around trunk nevi	No	No	[11]

Concerning the pathomechanism of this side effect, many hypotheses were suggested. Imiquimod application induces antigen presentation that activates Langerhans cells. Consequently, destruction and apoptosis of the melanocytes can occur and this was confirmed by TUNEL assay.[16] Moreover, vitiligo pathogenesis involves pro-inflammatory cytokines such as interferon alfa, interleukin 6 and 8, tumor necrosis factor alfa and nitric oxide.[12] These cytokines can be induced by imiquimod application and may play a role in the development of hypopigmentation.[17] Third, the occurrence of these hypopigmented imiquimod-induced lesions has been exclusively reported in the genital area that has thin skin and this may also contribute to its development.

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Conflicts of interest
There are no conflicts of interest.

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