Letters to the Editor

Dose-dependent effect because it usually occurs when using unfractionated heparin or low-molecular-weight heparin at therapeutic doses. Bullous hemorrhagic dermatosis usually appears some days after heparin injection although, rarely, it may occur weeks later. Clinically, it is characterised by tense hemorrhagic bullae distant from the heparin injection sites without any inflammatory signs in the adjacent skin. There are no other symptoms or signs. The key histopathological features of this entity are intraepidermal bullae with lack of thrombosis, vasculitis or inflammatory changes in vessels or dermis. These features are essential to exclude other cutaneous side effects of heparin injection.

Treatment for this condition is not necessary since the prognosis is usually favorable with spontaneous remission. Treatment with enoxaparin can be continued despite the eruption of hemorrhagic bullae. In conclusion, this case adds to the evidence from other reports that these drugs can probably cause skin reactions at sites distant from subcutaneous injections.

Till date, there are less than 20 cases reported in the literature. This disease is usually self-limited despite continuing the offending medication; hence, it may be an under-diagnosed phenomenon. Since enoxaparin is a drug frequently used in medical practice, dermatologists should be aware of these side effects so that their patients can be appropriately informed.

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There are no conflicts of interest.

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REFERENCES
1. Maldonado Cid P , Alonso de Celada RM, Noguera Morel L, Feito-Rodríguez M, Gómez-Fernández C, Herranz Pinto P . Cutaneous adverse events associated with heparin. Clin Exp Dermatol 2012;37:707-11.
2. Schindewolf M, Lindhoff-Last E, Ludwig RJ, Boehncke WH. Heparin-induced skin lesions. Lancet 2012;380:1867-79.
3. Maldonado Cid P , Moreno Alonso de Celada R, Herranz Pinto P , Noguera Morel L, Feltes Ochoa R, Beato Merino MJ, et al. Bullous hemorrhagic dermatosis at sites distant from subcutaneous injections of heparin: A report of 5 cases. J Am Acad Dermatol 2012;67:e220-2.
4. Peña ZG, Suszko JW , Morrison LH. Hemorrhagic bullae in a 73-year-old man. Bullous hemorrhagic dermatosis related to enoxaparin use. JAMA Dermatol 2013;149:871-2.
5. Concha-Garzon M, Sotomayor-Lopez E, Solano-Lopez G, Fraga J, De Argila D. Bullous hemorrhagic dermatosis distant from the site of heparin injection. Dermatol Online J 2014;20. pii: 13030/qt10w3j0ss.

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Basal cell carcinoma overlying vitiligo attributable to phototherapy

Sir,

A 54-year-old man with a 7 year history of vitiligo vulgaris presented with three pigmented plaques over pre-existing vitiliginous patches on his left shoulder and forehead [Figures 1 and 2]. Five years prior to this presentation, he had received treatment with oral psoralen and ultraviolet-A radiation three times a week for 5 months for his vitiligo. The cumulative dose of psoralen plus ultraviolet-A could not be calculated as he had lost his medical records. One year following the psoralen and ultraviolet-A therapy, he developed an asymptomatic pigmented nodule on his left shoulder over a vitiligo patch [Figure 1]. Three years later, he developed two similar lesions overlying pre-existing vitiliginous patches on the forehead [Figure 2]. There was no history of
prolonged sun-exposure, immunosuppression or occupational exposure to any carcinogenic agents such as arsenic. There was no family history of skin cancer.

A clinical diagnosis of pigmented basal cell carcinoma was made and was confirmed on skin biopsies which showed nodular aggregates of basaloid cells in the papillary dermis and the presence of melanophages in the aggregates as well as in the dermis [Figure 3a]. For treatment, radioactive Re-188 patches were applied over the lesions on 5 alternate days for 80 minutes each. This was followed by erosion and crusting over the plaques which healed over 10 weeks. A hyperpigmented rim persisted. A follow-up biopsy at 12 weeks showed no evidence of malignancy [Figure 3b]. The hyperpigmented area showed marked pigment incontinence. For the vitiligo, he was advised topical steroids with some improvement. There was no clinical recurrence of basal cell carcinoma at 1 year follow-up.

Patches of vitiligo are expected to be more vulnerable to ultraviolet light-induced phototoxicity and non-melanoma skin cancers due to the absence of melanin which protects against photodamage. However, this complication has been rarely noted even in long-standing cases. Overexpression of tumor suppressor gene P53 and its regulatory oncogene mouse double minute 2 (MDM2) homolog proteins in both normally pigmented and depigmented skin of patients with vitiligo is postulated to contribute to this protective effect.[1]

Squamous cell carcinoma and actinic keratosis have been previously reported on vitiliginous patches with prolonged sun-exposure. However, the development of basal cell carcinoma in these patches appears extremely rare; we were able to find only 3 previous reports.[2-4] In these patients, basal cell carcinomas appeared on vitiligo lesions over sun-exposed sites on the scalp, cheek and naso-labial fold. Two patients were Caucasian and one patient was Mexican-American. No specific predisposing factor could be demonstrated. Phototherapy was not given in any of these patients. Sun exposure or an unspecified spontaneous mutation were suspected as predisposing factors.

According to recent studies, psoralen and ultraviolet-A treatment is associated with a clearly dose-related increase in risk of non-melanoma skin cancer, mainly squamous cell carcinoma.[10] The risk of squamous cell carcinoma was significantly higher for patients exposed to high doses of psoralen plus ultraviolet-A (>200 sessions or 2000 J/cm²). This dose relationship could not be established for basal cell carcinoma because of its rare occurrence. Ultraviolet radiation is the most important risk factor in the development of basal cell carcinoma. Ultraviolet light leads to the formation of thymine dimers and cumulative DNA damage resulting in various mutations. It also depresses the local immune system decreasing immune surveillance for new tumor cells.[11] This mechanism may explain
phototherapy-induced basal cell carcinoma in vitiligo patients.

Multiple basal cell carcinomas are uncommon in the Indian population. In our patient, although inability to calculate the cumulative dose of psoralen plus ultraviolet-A makes its relationship with basal cell carcinomas speculative, localization of the tumour over vitiligo patches on sun exposed as well as non-sun exposed sites, the absence of any other known predisposing factor, as well as appearance 1 to 3 years after therapy raises the possibility that psoralen plus ultraviolet-A therapy was responsible. Other unknown factors such as spontaneous mutations may also play a role. Interestingly, the basal cell carcinomas in our patient were pigmented even though they developed over patches of vitiligo. Pigmented basal cell carcinoma contains melanin which is produced by melanocytes that colonize the tumor. These may have been derived from the mutation and proliferation of surviving epidermal melanocytes in the vitiligo patch and these tumor melanocytes may be resistant to the depigmenting factors present in that milieu.

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REFERENCES
1. Bakry OA, Hammam MA, Wahed MM. Immunohistochemical detection of P53 and Mdm2 in vitiligo. Indian Dermatol Online J 2012;3:171-6.
2. Rustemeyer J, Günther L, Deichert L. A rare association: Basal cell carcinoma in a vitiliginous macula. Oral Maxillofac Surg 2011;15:175-7.
3. Arnon O, Mamelak AJ, Goldberg LH. Basal cell carcinoma arising in a patient with vitiligo. J Drugs Dermatol 2008;7:1075-6.
4. Hessel CL, Edie MJ, Johnson CC, Krajenta R, Jacobsen G, Hamzavi I, et al. Incidence of nonmelanoma skin cancer in a cohort of patients with vitiligo. J Am Acad Dermatol 2009;60:929-33.
5. Situm M, Buljan M, Bulat V, Lugović Mihić L, Bolača Z, Simić D. The role of UV radiation in the development of basal cell carcinoma. Coll Antropol 2008;32 Suppl 2:167-70.

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