Extensive Verrucae over Healed Pemphigus Vulgaris Lesions in an Immunocompetent Female: A Rare Presentation of Wolf’s Isotopic Response

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Abstract
Wolf’s isotopic response refers to the occurrence of a skin disorder at the site of another unrelated and already healed skin disease. The cases described so far in the literature include herpes (simplex or zoster) as the primary disease in most cases and a myriad of skin diseases as the secondary disease. Here, we report a case where extensive verrucae developed over the sites of healed lesions of pemphigus vulgaris, in an immunocompetent female. Pemphigus vulgaris being the primary disease and absence of verrucae over normal skin makes this case, a rare presentation.

Key Words: Pemphigus vulgaris, isotopic response, verrucae

Introduction
The term “isotopic response” describes the occurrence of a skin disorder at the site of another unrelated and already healed skin disease. The term was coined by Wolf et al. in 1995.[1] However, the phenomenon was described in 1955 by Wyburn-Mason, who reported a series of 26 patients in whom malignant tumors developed at the site of previous herpes zoster or herpes simplex eruption.[2] The initially occurring disease in most cases is herpes zoster followed by herpes simplex. A variety of cutaneous diseases have been reported to occur at already healed site which include granulomatous disorders, malignant tumors, lichen planus, morphea, reactive perforating collagenosis, infections (viral, mycotic, and bacterial), and others.[3] Here, we report a case of an immunocompetent patient developing extensive verruca vulgaris confined to the site of healed pemphigus vulgaris lesions. To the best of our knowledge, no such case has been reported in the literature till date.

Case Report
A 28-year-old married female presented to our outpatient department with complaints of multiple fluid-filled lesions over the body since last 4 years associated with multiple painful raw areas in the mouth. The lesions used to rupture easily and heal in around 2–3 weeks, leaving behind areas of increased pigmentation. The patient also gave a history of raw areas in the mouth which led to difficulty in food intake. Since the last 4 months, the patient noticed development of firm, skin-colored growths with rough surface appearing at the sites of healed lesions which initially began as a small pea-sized lesion and slowly increased to cover whole of the pigmented area. There was no history of any prior drug intake, blood in the lesion, redness of eyes, hoarseness, or raw areas in genitalia. The patient had been treated at various places in the last 4 years with oral steroids and various immunosuppressants. She did not receive any treatment for the skin-colored growths during the last 4 months. The patient's husband was seropositive for HIV, but her investigations for detection of HIV, repeated multiple times over the last 4 years, showed a negative status.

On examination, the patient had multiple clear to turbid fluid-filled flaccid bullae over an erythematous base over the trunk and both lower limbs. Nikolsky sign was negative, and bulla spread sign was positive. There were multiple hyperpigmented macules of varying sizes present over trunk, both breasts, axillae, buttocks, and both the lower limbs suggestive of postinflammatory
hyperpigmentation. Multiple verrucous lesions of size ranging from 0.5 cm to 6 cm were present over these hyperpigmented macules in both axillae, breasts, back, and both lower limbs [Figure 1a and b]. Some of these lesions were sessile, while others were pedunculated. Mucosal examination revealed multiple well- to ill-defined erythematous erosions over the buccal mucosa and lateral borders of the tongue. There was a well-defined verrucous lesion over upper labial mucosa. A thorough examination of the husband did not reveal any verruca or mucosal wart.

Hematological investigations of the patient including complete blood count, liver and renal function tests, and blood sugar level were normal. Her HIV status was nonreactive. Histopathological evaluation was done, both from the bullous lesion and the verrucous growth. Biopsy of the bullous lesion showed intraepidermal split consistent with pemphigus vulgaris. An excision biopsy of a verrucous lesion showed hyperkeratosis and papillomatosis along with koilocytes and was suggestive of verruca vulgaris [Figure 2a and b].

We started the patient on dexamethasone-cyclophosphamide pulse (DCP) therapy in the form of 100 mg dexamethasone in 500 ml of 5% glucose for 3 days with 500 mg of cyclophosphamide added on day 2. The pulse was repeated after 28 days. In between the pulse, the patient was kept on low-dose corticosteroids and oral cyclophosphamide 100 mg daily. Over a span of 10 days, we removed the verrucae with the help of electrocautery and cryotherapy. The steroid dose was tapered gradually, and the DCP pulse was given for 6 months after which the patient was shifted to oral steroids and cyclophosphamide. The verrucae recurred over some sites and were managed with electrocautery. New pemphigus lesions stopped appearing and oral steroid was tapered off and stopped over the next 6 months.

**Discussion**

According to the literature, earliest report of isotopic response dates back to 1929, when Gougerot and Filliot[4] described a case of lichen planus that developed in a scar of a herpes zoster eruption of 2 months’ duration. The phenomenon was, however, made popular when in 1955 Wyburn-Mason for the first time studied a number of cases with the occurrence of a new skin disease at the site of the another skin disease that had already healed.[2] No specific name was given to these phenomenon till Wolf and Wolf[5] in 1985 coined a term “isoloci response,” which was later modified by them only to “isotopic response.”[1] Finally, the phenomenon was reframed as Wolf’s isotopic response by Ruocco et al. in recognition of Dr. Wolf’s invaluable contribution to the understanding of this topic.[6]

Various theories have been proposed to explain this phenomenon; however, the exact pathomechanism still remains elusive. Multiple hypotheses which have been put forward are viral, vascular, immunologic, and perhaps, the most acceptable, neural. Viral hypothesis suggests the presence of viral DNA at the healed site which causes some neurovascular alterations. In spite of the viral DNA being isolated initially in a few cases,[7] this theory is the least favored one because of the lack of reproducibility. Wolf et al., in their initial report, proposed a vascular hypothesis, which suggested damage to microcirculation by inflammation. This damage may be recalled if any insult occurs in future again and thus localize the inflammation to the healed site.[1] Immunologic hypothesis suggests changes in the regional immune system or formation of memory T-cells which when triggered at a later date may give rise to a new dermatosis.[8] Appearance of fixed drug eruptions at the same site supports this theory. Finally, we discuss the
neural hypothesis which has been explained in detail by Ruocco et al.\textsuperscript{(6)} and is currently the most favored one. It implicates the presence of various neurohumoral factors induced by primary insult which may contribute to the pathogenesis of a new disease either directly by release of neuropeptides or indirectly by aberrant activation of immune system. These theories were studied in detail by Mahajan et al.,\textsuperscript{(9)} who recently proposed a composite theory for occurrence of isotopic response. They suggested one or more, or in fact all the factors played role in the causation of a new disease along locus minoris resistentiae, that is, the area of lessened resistance.

**Conclusion**

Occurrence of such extensive verrucae over sites confined to healed pemphigus lesions has not yet been reported in the literature. We kept a possibility of pemphigus vegetans in mind; however, the histopathology report supported our diagnosis of verruca vulgaris. Although the patient’s spouse is seropositive, her immunity seemed to be intact as shown by repeated negative HIV status over 4 years and normal total blood count. In addition, there was absence of other symptoms such as fever, chronic diarrhea, or weight loss. The most baffling thing in our case was that the warts did not appear over the sites of lesions which healed after the patient was started on DCP therapy. Occasional recurrence of the warts occurred over previously cauterized lesions only.

Feature supporting our diagnosis of the case being that of isotopic phenomenon was complete absence of warts over the normal skin, even when the patient had such extensive lesions. We decided against the case being that of Koebner’s phenomenon as there were no verrucae over other traumatized sites. The purpose of reporting this case is to bring to knowledge a rare presentation of the isotopic phenomenon involving two common dermatological diseases in an immunocompetent person.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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