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The distribution of pemphigus vulgaris-IgG subclasses in patients with active disease

We have read with great interest the report of M. Ayatollahi and coworkers¹ on 'IgG4 as the predominant autoantibody in sera from patients with active state of pemphigus vulgaris' that appeared in the *Journal of the European Academy of Dermatology and Venereology* (2004) **18**, 221–224. The authors reported on elevated levels of IgG4 in patients with active disease and of IgG1 in patients in remission. It was concluded that IgG4 in patients with pemphigus vulgaris (PV) is pathogenic and its detection should be considered as a clinical marker.

Indeed, their results confirm some previous reports concerning the importance of PV-IgG4 in the pathogenesis of the disease.^{2,3} Actually, our group has found similar results by comparing the distribution of PV-IgG subclasses and their reactivity with desmoglein 3 and 1 in patients with PV, their unaffected first-degree relatives and healthy controls.⁴ By Western immunoblotting, circulating PV-IgG were found in 91%, 49% and 12%, respectively. The distribution of PV-IgG 1,2 and 3 was similar among patients and relatives. PV-IgG4 was found in 62% of the patients but only in 1.8% among relatives. This finding seems to be linked to the fact that they do not develop pemphigus.⁴

M. Ayatollahi *et al.* also concluded that the production of PV-IgG1 is within the repertoire of natural and non-pathogenic autoantibodies. However, to our opinion, this is not an evidence-based statement. Direct immunofluorescence studies have clearly demonstrated the presence

of complement-fixing PV-IgG1, 2 and 3 in patients with PV and with active disease as well as deposit of C3 in the perilesional skin. Moreover, the later correlated with the activity of the disease.⁵ These data correspond with the findings in the experimental model of pemphigus in mice in which complement activation enhanced the development of cutaneous lesions.⁶ Thus, we think that the non-complement-fixing PV-IgG4 and at least one complement-fixing PV-IgG subclass (IgG1) appear to be involved in the pathogenesis of the disease.

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Response of predominantly recalcitrant cutaneous warts to topical chemotherapy

Warts, particularly plantar warts, are often therapeutically challenging.¹ They may disappear when least expected or persist despite months of intensive treatment. The

fig. 1 Treatment of recalcitrant plantar warts. (a) Recalcitrant plantar warts in an immunosuppressed patient with acute lymphocytic leukaemia who was receiving chemotherapy. There had been no response to treatment with any of the following agents: salicylic acid for 2 months, liquid nitrogen for 3 months or cantharidin for 2 months. (b) Five months after starting treatment with a topical liquid formulation of salicylic acid, fluorouracil, levamisole and 2-deoxy-D-glucose.



objective of this preliminary study was to assess the response of recalcitrant warts to a topical liquid compound containing chemotherapeutic (antineoplastic) agents (Wart Film Formula 4, NuCara Pharmacy, Waterloo, Iowa) (fluorouracil,²⁻⁴ levamisole,⁵⁻⁷ aspirin^{8,9} and 2-deoxy-D-glucose¹⁰). Each component of this compound has been reported to be helpful separately in the treatment of warts.

With approval of the Mayo Foundation Institutional Review Board, we surveyed all adult patients (> 18 years old) who presented to the Department of Dermatology at Mayo Clinic between 2000 and 2002 with recalcitrant cutaneous warts, mostly involving the feet, and received a prescription for the compound. The survey was conducted by mail and, if no reply, by telephone.

The questionnaire was sent to 280 patients, and 221 (79%) completed it. Responses were analysed for the 188 patients (85%) who used the compound as prescribed. Of these 188 patients, 155 (83%) had tried other treatments unsuccessfully. In response to the survey, 77 patients (41%) reported that the warts were completely gone (fig. 1), 37 (20%) that the warts were almost gone, 52 (28%) that the warts were the same and 9 (5%) that the warts had increased in number. Eighty-six patients (46%) reported that they were very satisfied with the treatment. Mean duration of therapy was 10.3 weeks (range, 1–60 weeks). No serious adverse effects were reported.

Thus, we observed a high rate of therapeutic success treating predominantly recalcitrant warts with a topical liquid formulation containing chemotherapeutic agents. Use of a liquid preparation is more appealing than the destructive approaches frequently used (liquid nitrogen, electrodesiccation, curettage, excision, CO₂ laser), all of

which cause some degree of morbidity. Our patients reported infrequent adverse effects using this compound.

We conclude that this topical formulation, which incorporates two chemotherapeutic agents, is an effective treatment for warts. Although a survey study has limitations, we believe our results warrant further study.

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Spontaneous repigmentation of vitiligo in an untreated HIV-positive patient

Immunosuppression is a well-known phenomenon in individuals infected with human immunodeficiency virus (HIV). The development of autoimmune diseases in these individuals is intriguing, moreover, the number of such reports is increasing.¹ Viral-induced immune activation and molecular mimicry are the proposed mechanisms for the development of autoimmune diseases in HIV-infected individuals.² However, there is also a possibility of improvement of auto-immune diseases in these individuals because of HIV-related immune suppression. We report a 43-year-old man who had spontaneous improvement of vitiligo vulgaris after acquisition of HIV.

A 43-year-old man presented with genital ulceration that had been recurrent for the last two years. Over this period, he had multiple episodes of painful grouped ulcers over glans and prepuce, with increasing frequency and severity, which always responded to therapy with acyclovir. History of sexual promiscuity was present. Patient had seroconversion only 4 years back but the vitiligo was of 15 years duration. He had noticed spontaneous but significant repigmentation of the vitiligo lesions (30–40%) in the past one and half year without any specific therapy. His CD4⁺ T-cell count was 390/mm³ and he had not received antiretroviral therapy anytime in the past. There were no systemic complaints. Lesions of vitiligo were present widely over lips, trunk and limbs with evidence of follicular and marginal repigmentation in majority of them. For his herpetic lesions he was treated with tablet acyclovir 400 mg t.i.d. for 1 week and the lesions started healing at the end of 1 week.

In literature, there have been some reports of development of vitiligo in patients with HIV infection.^{3,4} Repigmentation of the pre-existing vitiligo lesions in HIV-infected

individuals, possibly caused by HIV-related immunosuppression, has not been reported previously. After HIV seroconversion in an untreated patient, the total number of CD4⁺ T lymphocytes declines gradually at the rate of 50 µL per year.⁵ Among the various mechanisms proposed in the etiopathogenesis of vitiligo, the autoimmune theory is considered to be most important. Development of antibodies against melanocytes leads to the initiation of vitiligo and this antibody activity is more pronounced in actively spreading vitiligo compared with the stable disease, almost confirming this aspect of etiopathogenesis.⁶ As increase in (number and percentage) peripheral CD4⁺ T lymphocytes and an elevated CD4⁺ : CD8⁺ ratio has been observed in stable vitiligo^{7,8} T-cell-mediated immunity seemingly plays a major role in the pathogenesis of long-standing stable vitiligo. So, repigmentation in our patient can be partially explained with the fall of CD4⁺ T-lymphocytes and reduced CD4⁺: CD8⁺ T-cell ratio (as a result of HIV) that might have led to the reactivation of functional melanocytes in the lesions. Furthermore, the excessive production of polyclonal antibodies by activated B-lymphocytes in HIV infection may competitively block the action of pathogenic antimelanocyte antibody facilitating repigmentation of vitiligo patches.

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