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High-dose immunoglobulines and extracorporeal photochemotherapy in the treatment of febrile ulceronecrotic Mucha-Habermann disease

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ABSTRACT: Febrile ulcero-necrotic Mucha-Habermann disease (FUMHD) is a rare subtype of pityriasis lichenoides et varioliformis acuta (only 41 cases described to date), characterized by an acute onset of ulcero-necrotic papules accompanied by high fever and severe constitutional symptoms.We report a case of a 23-year-old man with a steroid-resistant FUMHD treated by intravenous immunoglobulins (IVIG) combined with methotrexate. Only one case of FUMHD treated by IVIG has been reported to date in literature. Also in our case, IVIG proved to be effective in inducing a dramatic improvement of ulceration and in arresting the appearance of new lesions. Moreover, in our experience we decided to perform a maintenance treatment with extracorporeal photochemotherapy (ECP), to the best of our knowledge not previously used in the treatment of pityriasis lichenoides et varioliformis acuta. ECP, which involves extracorporeal exposure of peripheral blood mononuclear cells to photo-activated 8-methoxypsoralen, induces an immunological reaction against auto-reactive T cell clones, without immune-depression and thus could potentially be useful particularly in FUMHD avoiding the risk o an infective reactivation.

KEYWORDS: extracorporeal photochemotherapy, FUMHD, IVIG

Febrile ulcero-necrotic Mucha-Habermann disease (FUMHD) is a rare subtype of pityriasis lichenoides et varioliformis acuta (PLEVA), first described by Degos et al. in 1966 (1). FUMHD is characterized by an acute onset of ulcero-necrotic papules rapidly coalescing into large ulcers with necrotic crusts, accompanied by high fever and severe constitutional symptoms (2). To the best of our knowledge, only 41 cases have been described (3,4), nine of those with fatal outcome (3). A 23-year-old Caucasian patient was referred to our institution for the appearance of diffused ulcero-necrotic lesions. Physical examination revealed disseminated erythematous scaly papules with sparse vesicles and pustules, round erosions and necrotic ulcers from few millimetres to 1 cmin diameter (FIG. 1a–c). Oral and genital mucosa were also involved with small and painful ulcers. Patient reported pruritus, fever, and malaise. The skin biopsy showed focal parakeratosis with vacuolar degeneration and necrosis of basal layer keratinocytes; edema of papillary dermis was present, associated with a peri-vascular lympho-histiocytic infiltrate and exocytosis. Immunohistochemistry did not disclose phenotypic abnormalities; molecular biology failed to reveal a T-cell receptor (TCR) clonal rearrangement. These clinical and histological findings suggested a diagnosis of FUMHD. Patient denied taking any medications and having drug or food allergies. Screening for Varicella-Zoster virus, herpes simplex virus, hepatitis B and C virus, HIV, Epstein-Barr virus, cytomegalovirus, parvovirus B19, toxoplasma, adenovirus, and enterovirus were negative, as well as treponema pallidum hemagglutination test. Screening for autoimmunity was also negative. Patient was treated with prednisone 1 mg/kg daily, without improvement. Considering the persistent appearance of new elements, steroid therapy was progressively tapered to 5 mg on alternating days, and treatment with intravenous immunoglobulins (IVIG) at 400 mg/kg/die for 5 days monthly was initiated, associated with methotrexate (MTX) 10 mg/m2 weekly. A progressive improvement of cutaneous lesions was observed since the second course and a complete remission with mild residual sclero-atrophic lesions and hyper-pigmentation was obtained after five courses (FIG. 2a–c). Thereafter, extracorporeal photochemotherapy (ECP) was started as

maintenance treatment; 6 months after the beginning of ECP, the patient was still in remission so MTX and steroids were discontinued. However, 1 month later, new lesions developed despite the ongoing ECP treatment: the reintroduction of low dose MTX induced a rapid improvement with complete clearing of all cutaneous lesions, that still continues at the time of writing.

Traditionally, two major clinical variants of pityriasis lichenoides (PL) are described (2). The acute form is represented by PLEVA, whereas PL chronica shows a much more indolent behavior.PLEVA is characterized by acute onset of scaly erythematous papules that become vesicles and pustules, and finally develop hemorrhagic necrosis nd ulceration. FUMHD differentiates from PLEVA by a rapid progression of necrotic papules to large coalescent ulcers with necrotic crusts, hemorrhagic bullae and pustules, and by the presence of severe systemic manifestations (fever, gastrointestinal, neurological, cardiologic and pulmonary involvement, sepsis, rheumatologic manifestations, conjunctival ulcers) (2,3). To date, nine fatalities have been reported in literature, all limited to adults (3,5). Some authors consider the disease as a hypersensitive reaction to an infectious agent; others suggest it can represent a T cell dyscrasia, based on the observation of a monoclonal T cell population in many cases (6).

The small number of cases and the uncertain etiology could not lead to guidelines for treatment and management of these patients. Many cases reported in literature received in fact multiple drugs ranging from systemic steroids, MTX, psoralen + ultraviolet A, ultraviolet B, to antibiotics, antiviral agents, and dapsone, because of the inhibitory function of these molecules on lymphocytes (3,6). Only one case of FUMHD successfully treated by IVIG has been reported in literature (7). Also in our case, IVIG proved to be effective in inducing a dramatic improvement of the clinical picture. Moreover, we decided to perform in addition to IVIG and MTX a maintenance treatment with ECP, not previously reported in PLEVA. ECP involves extracorporeal exposure of peripheral blood mononuclear cells to photoactivated 8-methoxypsoralen, followed by reinfusion of the treated cells. ECP induces an up-regulation of T cell subsets with immunosuppressive properties (regulatory T cells, Treg); thus, leading to a down-regulation of auto-reactive immune responses (8,9). Thanks to this mechanism, ECP is effective not only for cutaneous T cell lymphoma, but also for a wide spectrum of dermatological and not dermatological immune mediated or autoimmune diseases (graft versus host disease, scleroderma, lupus, atopic dermatitis, multiple sclerosis, inflammatory bowel disease, and type 1 diabetes) (10). The downregulation of immune responses renders ECP potentially useful in FUMHD, since it does not induce immune-depression thus avoiding the isk of an infective reactivation. In our patient, ECP may have been effective in maintaining disease remission, even if it was not able to prevent disease relapse after MTX discontinuation.

Therefore, ECP could play a role as an adjunctive therapeutic tool in association with IVIG/MTX.

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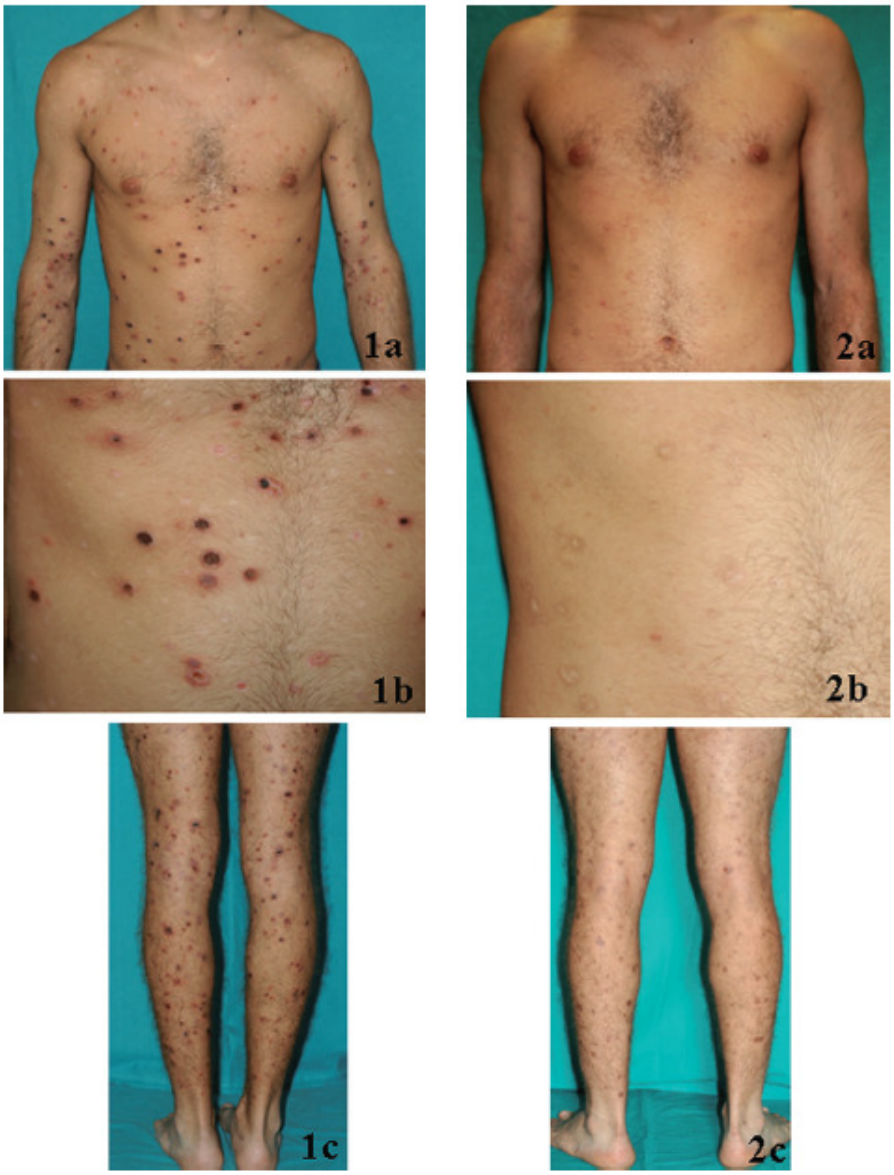

FIG. 1. The clinical picture before treatment on the lower limbs (a) and trunk (b,c). Disseminated erythematous scaly papules associated with vescico-pustules, round erosions and necrotic ulcers from few millimetres to 1 cm in diameter.

FIG. 2. The clinical picture after 5 IVIG courses. Complete remission of the disease, with residual hyper-pigmentation on the lower limbs (a) and sclero-atrophic lesions on the trunk (b,c).