Case report

Combination treatment of dupilumab with bortezomib in a patient with IgG kappa gammopathy of renal significance, uremic pruritus and chronic lichenoid dermatitis

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Abstract. Chronic pruritus (CP) is one of the most frequent symptoms among dermatological conditions, capable of reducing the quality of life (QoL). CP may be induced by atopic dermatitis or other dermatological and/or non-dermatological conditions. In this article, we report the case of a patient affected by generalized CP, characterised by multiple papulo-nodular and escoriatic lesions, developed after the onset of an immunoglobulin G (IgG) kappa monoclonal gammopathy of renal significance (MGRS), associated with renal insufficiency. Therefore, a combined treatment with dupilumab for CP and bortezomib for the hematologic malignancy was administered to the patient. The present case report highlights the efficacy of dupilumab for the treatment of CP. Moreover, no relevant side effects were recorded during the treatment in combination with other systemic biological drugs for other systemic pathologies. (www.actabiomedica.it)

Key words: chronic itchy skin, combined treatment, dupilumab, itch, monoclonal antibody

Introduction

Chronic pruritus (CP) is one of the most frequent symptoms among dermatologic conditions, showing a significant impact on patient's quality of life (QoL) (1). Atopic dermatitis (AD) is one of the main diseases that may induce CP (2). Pruritus may be induced also by non-dermatologic conditions, such as renal insufficiency, cholestasis, Hodgkin's lymphoma, polycythemia vera and solid tumors. When multiple conditions coexist, the distress increases, as well as the difficulties in their management.

Dupilumab is a monoclonal antibody that blocks the shared receptor component for interleukin (IL) 4 and IL-13, key drivers of type 2 inflammation in diseases such as AD, asthma, allergic rhinitis, and food allergies. These conditions are often associated as comorbidities (3). Common adverse events (≥5%) during treatment with Dupilumab for moderate-to-severe atopic sermatitis included nasopharyngitis, upper respiratory tract infection, oral herpes, conjunctivitis, injection-site reaction, and headache (4). In addition to AD, Dupilumab showed good response rates also in CP induced by other conditions, such as prurigo nodularis, uremic pruritus (UP), chronic idiopathic pruritus, lichen planus and eosinophilic dermatosis of hematologic malignancy (5). In these cases, Dupilumab also showed a safety profile in the long term, remaining a good candidate for patients with multifactorial pruritus.

Case report

A 55-years-old Philippine was admitted to our hospital for a 3-month-old history of generalized prurigo, with multiple papulo-nodular and escoriatic lesions associated with secondary hyperpigmented discoloration (Figures 1A-1B).

Oral and genital mucosa did not show any alteration. Peak pruritus numerical rating score (PP-NRS) was 9 (ranging between 0-10); Dermatology Life Quality Index (DLQI) induced by the cutaneous symptoms was 28. The cutaneous lesions began to arise 6 months after the onset of an immunoglobulin G (IgG) kappa monoclonal gammopathy of renal significance (MGRS), associated with renal insufficiency. The patient's personal medical history was positive for atopy and asthma (occasionally treated with fluticasone proprionate/formoterol fumarate); accordingly, a cutaneous biopsy was performed. Dermoscopy showed a central hypopigmented area, with a scar-like appearance and a peripheral hyperpigmentation with mild peppering, and a general aspect of dermatofibroma-like appearance (Figure 2A). As expected, reflectance confocal microscopy (RCM) did not show specific identifiable alterations, except for the presence of hyper-reflective edge papillae and general alteration of the epidermis, with unrecognizable spiny and granular layer and some multiple single hyper-reflective cells in the epidermis, corresponding in histology to exocytosis of lymphocytes (Figure 2B).

The cutaneous biopsy showed a hyperplastic epidermis with an underlying lichenoid infiltrate, resulting in a diagnosis of dermo-epidermal lichenoid interface dermatitis in atopic and uremic patient (Figure 2C).

Since local and systemic treatments with steroids and antihistamines did not improve the cutaneous conditions, a treatment with Dupilumab (initial dose 600 mg, subsequently 300 mg every two weeks) was

Figure 1. (A) Multiple papulo-nodular and escoriatic lesions associated with secondary hyperpigmented discoloration in the chest. (B) Multiple papulo-nodular and escoriatic lesions associated with secondary hyperpigmented discoloration in the back.

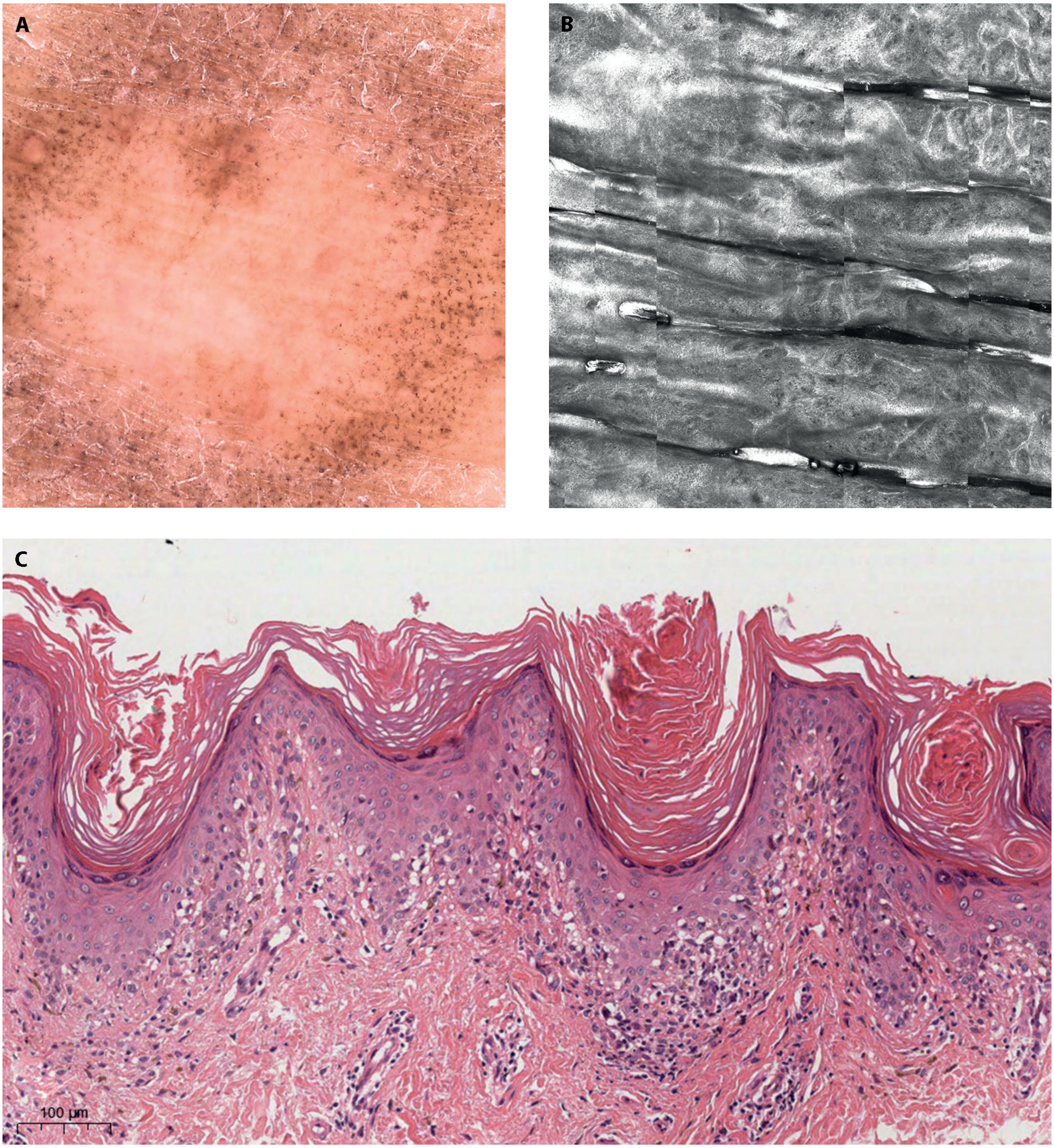

Figure 2. (A) Dermoscopy of the lesions showed a dermatofibroma-like appearance, with peripheral areas of hyperpigmentation, with peppering (15X). (B) Reflactance confocal microscopy did not give consistent results. (C) Hyperplastic epidermis with an underlying lichenoid infiltrate, performing a diagnosis of dermo-epidermal lichenoid interface dermatitis (Hematoxylin and Eosin, 200X).

started. Simultaneously, the patient started a treatment with bortezomib (1.3mg/m2 of the body surface area twice a week for two weeks over a 35-days treatment course) + 40 mg dexamethasone weekly for his underlying systemic disease.

Due to a severe adverse events that occurred after the third cycle of combined therapy (nocturnal sphincter relaxation and paraesthesia) the patient stopped treatment with bortezomib and dexamethasone, but continued to take as home therapy: febuxostat, sodic warfarin, medoxomil olmesartan, nevibolol hydrochloride, amlodipine besylate, ezetimibe/simvastatin and furosemide. After a 10 month-period of follow-up, the patient experienced an optimal hematological response of MRGS, with disappearance both of monoclonal component and proteinuria (both clonal Bence Jones and global proteinuria, although renal failure remains with stable creatinine levels) and a significant reduction of prurigo, without the onset of new active cutaneous lesions. Furthermore, the patient experienced a reduction of the pre-existing secondary cutaneous lesions, including lichenoid pigmentation (Figures 3A-3B), without experiencing any side effect.

Discussion

CP strongly impacts the QoL of affected patients (6), even more when it is associated with an underlying systemic disease.

Among extra-cutaneous diseases, multiple myeloma (MM) and renal failure can exacerbate chronic prurigo; specifically, various cutaneous manifestations can be observed in MM patients (7). In a study involving 1.438 patients, cutaneous manifestations were present in 24.61% of cases and most of them presented

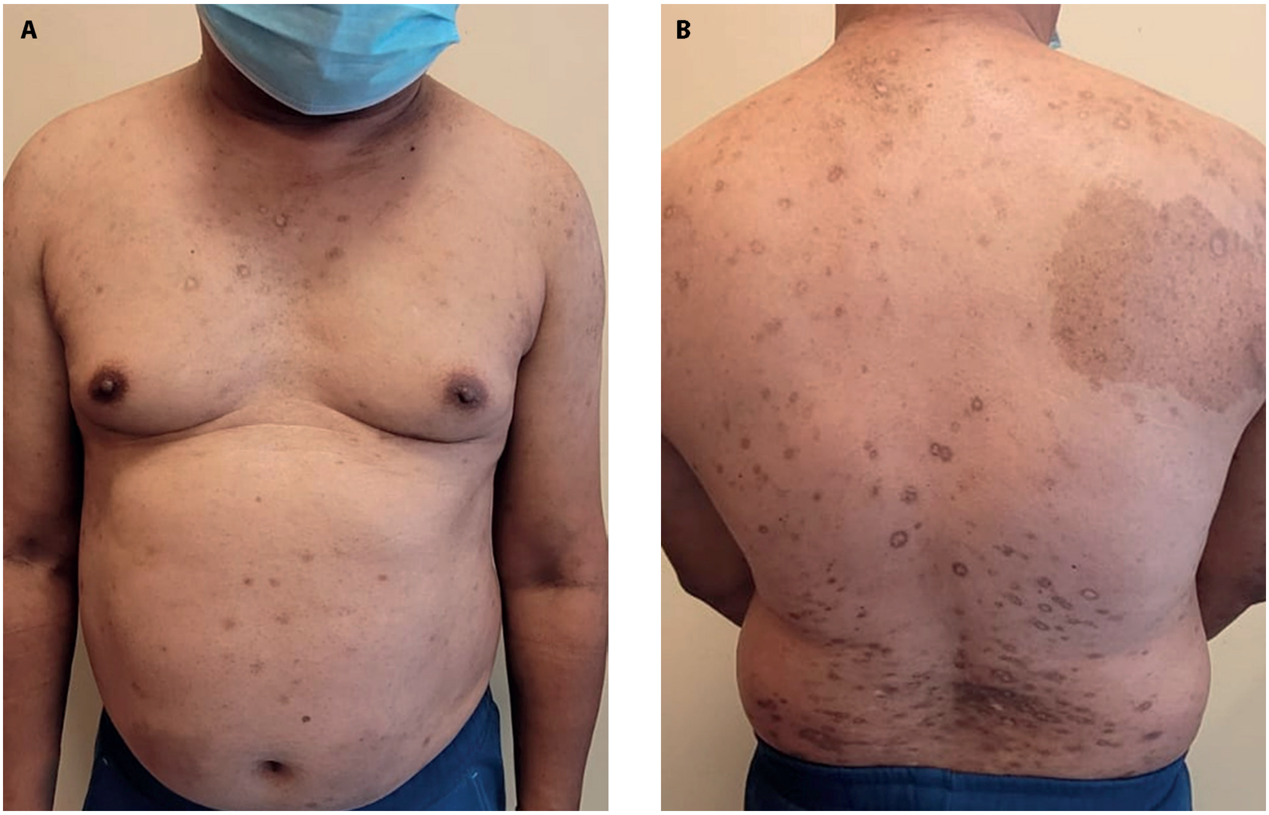

Figure 3. (A) Improvement of the cutaneous lesions after the treatment with dupilumab. (B) Improvement of the cutaneous lesions after the treatment with dupilumab, with also reduction of hyperkeratotic lesions, reduction in discromia and reduction of itching.

kappa light chain (57%), with general dermatosis and eczema as the main cutaneous diseases observed, respectively in 13.10% and 5.23% of cases (7).

The genesis of pruritus in our patient occurred following the concomitant presence of different factors, such as the underlying atopy, UP and MM. In atopic patients, several pathways are involved in the pathogenesis of itch; among them, IL-4 and IL-13 have multiple effects on epidermal and dermal cells as well as on sensory fibers (6). For these reasons, we selected dupilumab as treatment of choice for our patient. The pathogenesis of UP is not well elucidated, but studies have implicated IL-31, which is upregulated by Th2 cells (4). As also reported in the literature (8, 9), it's possible that dupilumab indirectly inhibits itch by decreasing production of IL-31 by T-helper 2 cells, justifying the improvement of symptoms in our patient.

Dermoscopy showed a dermatofibroma-like appearances, with also lichenoid features (peppering in the peripheral hyperpigmentation) and a central scar-like area. Contrariwise, as expected, RCM did not give consistent results, although some aspects were appraisable, such as hyper-riflective edge papillae (corresponding in dermatosocpy to peripheral pigmentation and in histology to pigmentation in basal layer), unrecognizable spiny and granular layers (in histology corresponding to thin epidermis, basal vacuolization) and multiple single hyperiflective cells, corresponding to exocytosis of lymphocytes. Histology allowed to perform a final diagnosis, excluding other differential diagnosis such as prurigo nodularis (absence of thickened granular layer, fibrosis and, crescendo-like epidermal hyperplasia, as well as the clinical aspects of the lesions) and lichen (focal hyperkeratosis, wedge-shaped thickening of the granular layer, acanthosis with saw-tooth pattern to rete ridges, subepidermal band-like lymphocytic infiltrate with occasional eosinophils).

An important point of the present case is the association of dupilumab with bortezomib (a reversible inhibitor of the 26S proteasome). This combination highlights how dupilumab is both effective and easy to handle for patients that perform also multiple systemic treatments. Besides, regarding MM patients, Owji et al. recently reported how dupilumab is an effective treatment for cutaneous reactions for immunomodulatory drugs (IMiDs), routinely used for the treatment of multiple myeloma and, that at the same time, by blocking IL-4 and IL-13, can improve the prognosis of MM patients, proposing it as an adjuvant treatment for MM (10).

Often, these patients underwent to numerous treatments and it is not always easy to find a treatment both effective and without negative interactions with other systemic treatments. In this regard, Dupilumab shows a general safety profile, drastically improving the symptoms in patients with multifactorial CP and under multiple therapies.

Ethic Committee: This study was conducted in accordance with the ethical standards of the Declaration of Helsinki. The patients provided written informed consent before treatment and also gave approval for the publication of his clinical data and photographs.

Conflict of Interest: none

Authors Contribution: Conceptualization: GP, MM; Writing – original draft preparation: GP, MRDN, MM, NR, VF; Writing – review and editing: GP, MRDN, MM, NR, VGB, VF, SRM. All authors approved the final version of the manuscript.

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