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Case Report

Successful management of bullous pemphigoid with dimethyl fumarate therapy: A case report☆,☆☆,★★★

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ABSTRACT

A 69-year-old woman affected by multiple sclerosis for 35 years was diagnosed with bullous pemphigoid (BP) and treated successfully with dimethyl fumarate (DMF) at a dose of 120 mg twice per day for 7 days and then increased to 240 mg twice per day after first-line therapies of BP. DMF is now under evaluation with an investigator-initiated prospective controlled trial in patients with BP to determine the efficacy and safety of adjuvant DMF. To our knowledge, this is the first case of BP successfully treated with DMF in the literature.

Report

A wheelchair-bound 69-year-old woman affected by multiple sclerosis (MS) for 35 years presented to our clinic in April 2016 with a 2-month history of pruritus and an erythematous rash. She had also developed blisters on the arms, legs, and trunk (Fig. 1A). She was diagnosed with bullous pemphigoid (BP) with typical histology and direct immunofluorescence studies. She had a Bullous Pemphigoid Disease Area Index (BPDAI) activity score of 50, damage score of 8, and Autoimmune Bullous Skin Disorder Intensity Score (ABSIS) of 52.75.

The patient was treated with prednisolone 25 mg/day, doxycycline 100 mg twice per day (BD), and nicotinamide 500 mg/BD. The dose of prednisolone was tapered over 9 months and then ceased, while treatment with doxycycline and nicotinamide remained. At that point, the patient still had significant residual erythema but did not want to resume oral steroids. Therefore, we obtained permission from the Therapeutic Goods Administration to use dimethyl fumarate (DMF), provided by compassionate supply for BP because DMF does not work for permanent damage from MS.

DMF was added to her treatment, starting at a dose of 120 mg/BD for 7 days and then increased to 240 mg/BD (Fig. 1B). Her BPDAI activity score was 0, but her BP pruritus score was 12/30 and BPDAI damage score was 8; her ABSIS score was 14.5. In April 2017, her other medications for BP were ceased, and the patient continued to use DMF alone for 12 months without relapse of BP (Fig. 1C; BPDAI: 0; ABSIS: 0; BP pruritus: 0/30). Between April and July 2018, the patient did not use DMF for 3 months because she ran out of the medication. She had a mild BP relapse during this period, which then quickly resolved after restarting the DMF treatment. Her BP and MS are now in complete remission again (BPDAI: 0; ABSIS: 0), with only DMF 240 mg/BD.

BP is the most common type of AIBD, especially in developed countries, with a variable incidence of between 7 to 42.8 cases per million person-years (Hubner et al., 2016; Wertenteil et al., 2019). In the last decade, patients with BP have shown an increased association with neurological diseases, which may increase mortality (Milani-Nejad et al., 2017).

MS, one of the most common neurological concomitant diseases seen in patients with BP, is an autoimmune inflammatory disorder of the central nervous system. It results in demyelination and neurodegeneration due to chronic inflammation and dysregulation in the balance and can cause several clinical symptoms, such as sensory loss, muscle weakness and/or spasticity, blurred vision, and decline in cognitive symptoms. No cure has been found for this disease to date (Montes Diaz et al., 2018). Patients with BP have at least five times higher risk of developing MS than patients in age- and sex-

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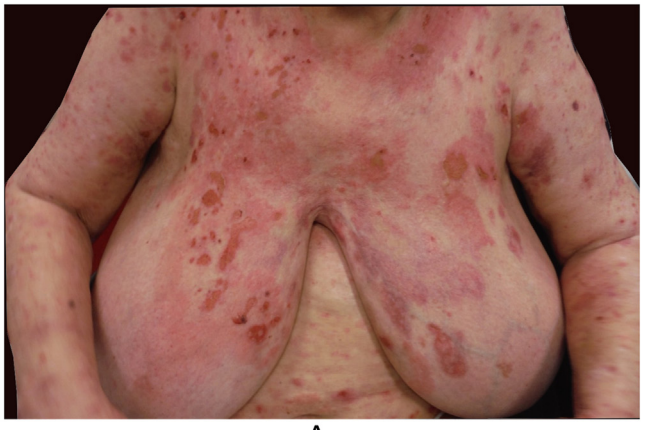

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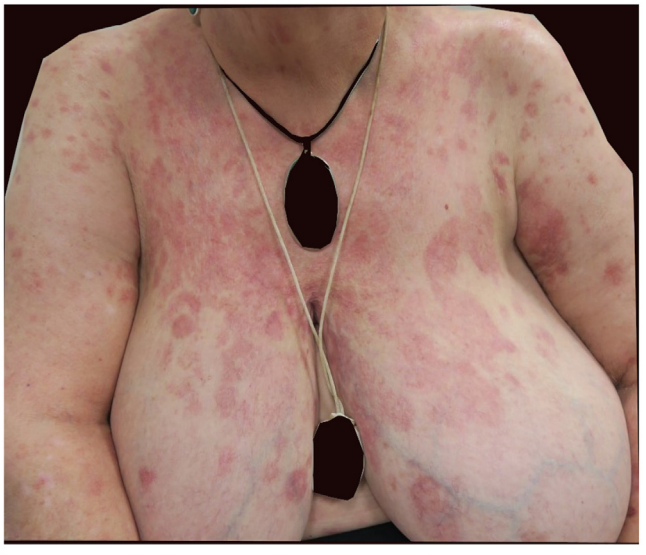

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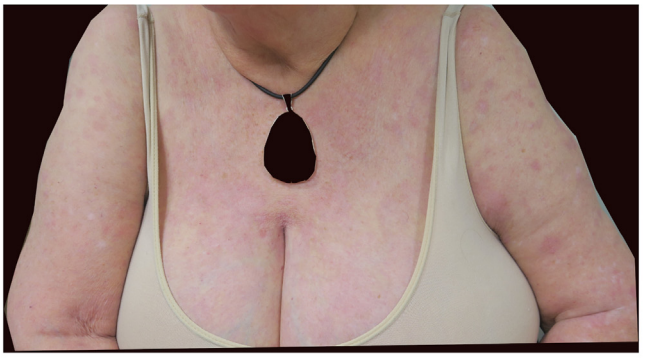

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Fig. 1. (A) Erythematous urticarial plaques with erosions and bullae on the chest during first visit. (B) Some erythematous plaques and post inflammatory changes on the chest before Dimethyl fumarate therapy. (C) Complete remission of BP lesions after dimethyl fumarate therapy for 1 year.

matched background populations, as shown in a recent Danish study (Kibsgaard et al., 2017).

MS is strongly associated with BP; therefore, we reasoned that DMF could be used as treatment for both conditions in our patient. BP treatment involves medications that reduce inflammation, such as corticosteroids (CS) as the first-line treatment. However, patients with BP usually need adjuvant therapies (e.g., azathioprine, tetracycline, and nicotinamide) to lower the dose of CS because CSs have detrimental side effects, especially in elderly patients in the long term (Feliciani et al., 2015). The common effect of all adjuvant therapies is suppression of the immune system to provide sustainable remission in BP, which is also the suggested mechanism for DMF.

DMF has been licensed to treat psoriasis and MS in the last few decades and has recently been shown to be effective in treating epidermolysis bullosa acquisita (subepidermal blistering AIBD like BP) in a murine model (Müller et al., 2016). DMF has been shown to reduce inflammation by activating Nrf2 protein, which regulates antioxidant genes involved in protecting cells from damage, and to create a stimulus-dependent inhibitory activity via its inhibiting effects on PI3K/Akt- and p38 MAPK signaling pathways (Müller et al., 2016). DMF is now under evaluation in an investigator-initiated, prospective, controlled trial in patients with BP to determine the efficacy and safety of adjuvant DMF (ERA-Net E-Rare, 2018). In the study, DMF is expected to reduce blisters and other symptoms by reducing the inflammation process in BP, which can help control the disease (Müller et al., 2016).

To our knowledge, this is the first case in the literature of BP that was successfully treated with DMF. Our patient had sustained remission with only DMF therapy after ceasing other established drugs. Further studies and larger case reports could provide more evidence with regard to its optimal use for BP and AIBD.

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