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The dilemma of treating pyoderma gangrenosum associated with monoclonal gammopathy of undetermined significance

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Abstract

Pyoderma gangrenosum (PG) is a rare ulcerative skin condition. It can be associated with a number of systemic diseases. Association with monoclonal gammopathy of undetermined significance (MGUS) is uncommon, but prognosis may be different depending upon the type of MGUS. Cases of MGUS-related PG reported in the literature with data concerning evolution and treatment were identified through a PubMed search. A patient with recurrent PG in the setting of a MGUS-IgA-λ in our department was also included. In total, 10 cases were identified. Only the two cases with Ig populations other than IgA improved without recurrence after treatment of the PG. All the patients with MGUS-IgA showed recurrences. Early multiple myeloma was proposed for three patients with MGUS-IgA-related PG. Second or third line treatments were necessary in some cases.

Keywords: pyoderma gangrenosum, monoclonal gammopathy of undetermined significance, MGUS, MGUS-related PG

To the Editor:

A 62-year-old man, with a history of surgery for an inguinal hernia two months prior, was referred to our dermatology department for extensive ulceration of the abdominal wall, spreading from the surgical incision site. The patient reported initial wound healing with the onset of ulceration after an interval of a few weeks (**Figure 1A**). At the initial assessment, the lesions were extensive, violaceous, painful, and necrotic with purulent exudate at the base and raised, irregular purple borders.

A biopsy specimen taken from the erythematous border showed a dense neutrophilic infiltrate throughout the dermis, with epidermal extension. His serum immunoelectrophoresis revealed IgA-λ monoclonal gammopathy. Additional investigations confirmed the diagnosis of monoclonal gammopathy of undetermined significance (MGUS), IgA-λ, complicated with pyoderma gangrenosum (PG). He had no signs or symptoms of inflammatory bowel disease or rheumatoid arthritis. Blood cell count and blood chemistries were within normal limits.

The patient's lesions showed rapid improvement and complete involution on daily oral prednisolone at 60mg but resulted in cribriform scarring.

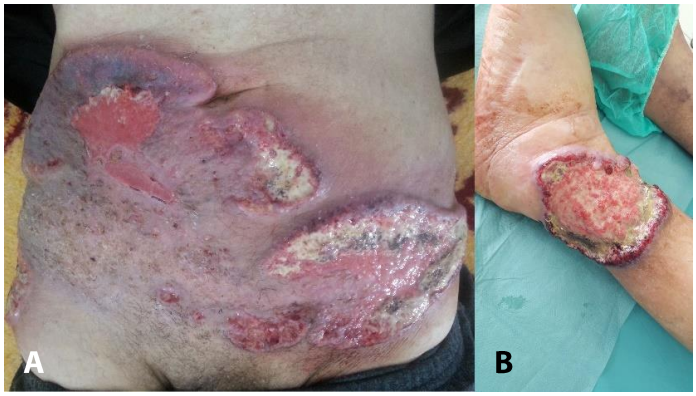

Figure 1. ***A)*** *Post-surgical pyoderma gangrenosum of the abdominal wall.* ***B)*** *A relapse of pyoderma gangrenosum on the left ankle.*

Corticosteroids were tapered gradually. A first relapse of PG emerged on the left ankle when a dose of 20mg was reached (**Figure 1B)**. Prednisolone was raised to 60mg daily with complete resolution of the ulceration within a few weeks.

Six months later, and upon reaching a dose of 12mg/day of oral prednisolone, the patient presented with a new ulceration of the wrist, which was again successfully managed by prednisolone 60mg. A last relapse occurred on the thighs after one year of withdrawal from prednisolone and was managed with the reintroduction of prednisolone 40mg daily, with rapid re-epithelialization.

Pyoderma gangrenosum is a rare ulcerative skin condition. It can be associated with a number of systemic diseases. Systemic corticosteroids, along with cyclosporine and anti-TNF agents, are actually considered the first-line treatment along with the treatment of the associated disease [1]. Monoclonal gammopathy of undetermined significance is associated with about 4.2% of cases of PG [2] and this condition affects the course of evolution of the latter. Monoclonal gammopathy of undetermined significance is defined as a plasma cell disorder characterized by a level of serum M-protein of <3g/dL with <10% plasma cell infiltration in the bone marrow and without CRAB (hypercalcemia, renal insufficiency, anemia, or bone lesions) or any other myeloma-defining event [3]. Nine cases of MGUS-related PG with data concerning evolution and treatment were identified in the medical literature (**Table 1**).

Among the 9 cases in the literature, in addition to the case reported above, an IgA monoclonal gammopathy was identified in 8 cases, with IgA-λ in 6 of them. In only the two cases with Ig populations other than IgA, did the cutaneous PG heal without recurrence after treatment. All the patients with MGUS-IgA showed recurrences of PG lesions after treatment. Two patients evolved into multiple myeloma (MM). Patients with MGUS do not necessarily require any treatment unless they have associated immunoglobulin deposition such as in monoclonal gammopathy of renal significance, POEMS syndrome, or light-chain amyloidosis [4]. The six cases with MGUS-IgA which did not evolve into MM were managed with different strategies. Four authors decided to continue managing each recurrence independently, using several treatments, including corticosteroids (oral, intravenous, intralesional, or topical), sulfones, cyclosporine, azathioprine, trimethoprim/sulfamethoxazole, and colchicine. A complete resolution without recurrence was never reached. As there is no treatment specific to MGUS, MGUS-IgA was treated as MM in the two remaining cases. One patient who evolved into MM responded initially to a first line treatment with 5 cycles of bortezomib–dexamethasone, leading to the resolution of PG lesions. These findings are in line with the data reported by Campbell et al., which postulated the superior efficacy of anti-MM therapy [4].

A strong association between IgA isotype and neutrophilic dermatoses has been shown to be in part related to the activation of neutrophils by the abundant IgA receptors on their surface [5]. According to this data, no durable remission of the PG can be expected as long as the MGUS persists, unless an Ig population other than IgA is present. A successful treatment of MGUS is generally associated with resolution of the PG, but MGUS is less responsive to treatment than MM and aggressive treatments may be needed to achieve the objective.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. *Monoclonal gammopathy of undetermined significance-related pyoderma gangrenosum cases reported in the literature.*

	Age	Gender	Ig type	Location	Post surgery	Associated diseases	Treatment	Evolution of PG before treatment of MGUS	Treatment of MGUS	Evolution of PG after treatment of MGUS
Chang, 2010 [6]	33	M	IgA-λ	Leg	No	None	Methylprednisolone pulse therapy	Short response	Thalidomide	Not effective
									VAD	Not effective
									Cyclophosphamide Autologous PBSCT Total body irradiation Melphalan	Free of PG lesions (18 months follow-up)
Shareef, 2012 [7]	53	M	IgA-λ	Abdomen Leg	No	None	Topical clobetasol propionate and tacrolimus Oral prednisolone Cyclosporin Mycophenolate mofetil Infliximab	Recurrences Evolution on MM	No treatment before evolution on MM	N/A
Mirkamali, 2007 [8]	57	M	IgA-λ	Lung Chest Shoulders Back	Yes	None	Oral prednisolone 60 mg daily IVIg Sulfone Cyclosporin Azathioprin	Recurrences	None	N/A
Matsubara, 2002 [9]	56	M	IgM-k	Perianal	No	PNH	Oral prednisolone 40 mg daily	Remission	None	N/A
Setterfield, 2001 [10]	54	M	IgA-λ	Lower limb Oropharynx Tongue	No	None	Oral prednisolone 25-40 mg Daily azathioprine cyclosporin Colchicine	Recurrences	Thalidomide prednisolone cyclophosphamide	Not effective
									Pulsed intravenous methyl prednisolone and cyclophosphamide	Improvement
Birnkrant, 2003 [11]	62	M	IgA-k	Legs	No	Acne conglobata	Oral prednisone, 60 mg daily Dapsone	Regression with AEs / New lesions continue	None	N/A

							Trimethoprim/ sulfamethoxazole		to develop		
							Intralesional corticosteroids Short courses of oral prednisone	Regres-sion			
							Colchicine Dapsone Topical clobetasol propionate	Regres-sion			
Chave, 2001 [12]	82	M	IgA-k	Legs	No	SPD	Oral prednisolone	Incomplet response		None	N/A
Simsek, 2004 [13]	61	M	IgG-k	Legs	Extension after surgery	None	Oral prednisolone 1 mg/kg	Improvement		None	N/A
Velasco-Tamariz, 2017 [14]	40	F	IgA-λ	Lower limb	No	None	Corticosteroid Cyclosporine Colchicine Mycophenolate Dapsone Etanercept	Incomplet response Evolution on mouldering MM		5 cycles of bortezomib–dexamethasone regimen	Free of PG lesions (6 months)
Machan et al., this study	62	M	IgA-λ	Abdo-men Ankle Wrist Thigh	Yes	None	Oral prednisolone 1 mg/kg	Recurrences		None	N/A