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CASE REPORT

Generalized morphea treated with Intravenous Immunoglobulin. A case report and systematic review of literature

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Abstract
Generalized Morphea (GM) is a subtype of localized scleroderma with a very rare incidence. Cases that are unresponsive to standard medication represent a difficulty in finding a suitable treatment plan. This case report presents a 35 year old female with a long history of disease (16 years) that is clinically characterized by extensive cutaneous sclerosis and limited joint movement . Multiple therapeutic approaches have been implemented, with modest response regarding disease progression. She associates essential thrombocythemia, that is kept under normal range with hematology specific treatment . The patient begins high-dose intravenous immunoglobulin therapy (IVIg) associated with Methotrexate, which shows a promising response.
Keywords: generalized morphea, intravenous immunoglobulin, essential thrombocythemia.

Introduction

Generalized Morphea (GM) is a subtype of localized scleroderma, which represents a rare inflammatory skin disease that can also affect the subcutaneous tissues [1]. In general, it is characterized by spot-like lesions on the head and neck area, trunk and extremities, the upper and lower limbs being the most severely damaged [2]. However, it may progress to widespread indurated plaques, growth deficiency, muscle atrophy and even to flexion deformities or ulcers that heal poorly, but most importantly, it does not affect the internal organs [3].

Morphea is a rare disease, with an annual incidence of 2.7 per 100,000 population. It is predominantly manifested in women with a ratio of 2.6:1 and it is prevalent in the Caucasian population, although it can affect all ethnicities. It occurs in people aged between 20 and 50 years in about 80% of patients [4].

According to Kreuter et al (2012), Morphea can be classified into 5 main types: limited, generalized, linear, deep and mixed. Several subtypes have also been described (Figure 1).

Morphea type	Morphea subtype
Limited	Plaque Morphea
	Guttate Morphea
	Atrophoderma of Pasini and Pierini
Generalized	Generalized Morphea
	Disabling Pansclerotic Morphea
	Eosinophilic Fasciitis (Schulman syndrome)
Linear	Morphea of the extremities
	Morphea *en coup de sabre*
	Progressive facial hemiatrophy (Parry-Romberg syndrome)
Deep	
Mixed	Combination of the above-mentioned types

Figure 1. Morphea classification (Kreuter et al, 2012).

There are several systemic therapeutic approaches available, such as Methotrexate (MTX), Mycophenolate Mofetil (MPM), typically in

association with corticosteroids, which have been proven efficient for their immunomodulatory effect [5]. However, there are cases in which their efficacy is limited or the patient cannot undergo the therapy due to contraindications. Therefore, providing evidence for new treatment options is an important effort that will grant the clinician better chances at treating severe cases.

Intravenous Immunoglobulin (IVIg) is a biological agent used for several conditions, including autoimmune diseases [6]. It can be administered in combination with an immunosuppressant drug, such as MTX and MPM.

Case Report

A 35 year old female diagnosed with GM, presented with severe skin induration on the upper, lower limbs and abdomen. The extensive lesions limited her mobility, especially in the lower limbs (associating bilateral calf muscle atrophy). Occupational history showed a potentially toxic exposure to hazardous substances used in industrial laundry.

Her history of disease begins at 18 years old (2007), when she presented an erythematous lesion on the right inner thigh. The skin biopsy diagnosis was cutaneous-limited scleroderma. However, the scleroderma autoimmunity screening was negative (anti-Scl70 antibody, anti-centromere antibody). She received MTX 20mg/week, therapy which is discontinued in 2009 due to severe digestive side effects (nausea, vomiting). The disease course is stationary between 2009 and 2017, period in which she does not attend any physician. In 2017 the patient develops aggravating symptoms of the disease. New cutaneous lesions appeared and thickening of the skin is predominantly observed in upper, lower limbs and abdomen, causing decreased articular mobility. Skin biopsy reveals Pansclerotic Morphea (PM). She receives MTX 20mg/week and methylprednisolone (MP) 32mg/day (which is gradually tapered down). In October 2017, the unfavorable evolution prompts to a therapeutic switch from MTX to Ciclosporin (for 3 months, until December 2017), which didn't improve the disease course. In January 2018, MPM 1000mg/day is introduced, but the treatment is administered for a short period of time (2 months). Vasodilator treatments were also administered (Pentoxifilin, Ilomedin). The patient moves to Italy, where she continues the treatment with Ilomedin (intravenous administration) and receives Bosentan. MTX 20mg/week is reintroduced.

In August 2023, she presents at "Sfânta Maria" Clinical Hospital in Bucharest, Romania. Clinical examination revealed profoundly indurated, discolored skin patches in the upper, lower limbs and chest. The lower limbs were the most affected, associating flexion deformity of the tibiofemoral joint and calf muscle atrophy. The fingers were spared and Raynaud's phenomena was not present (Figure 2).

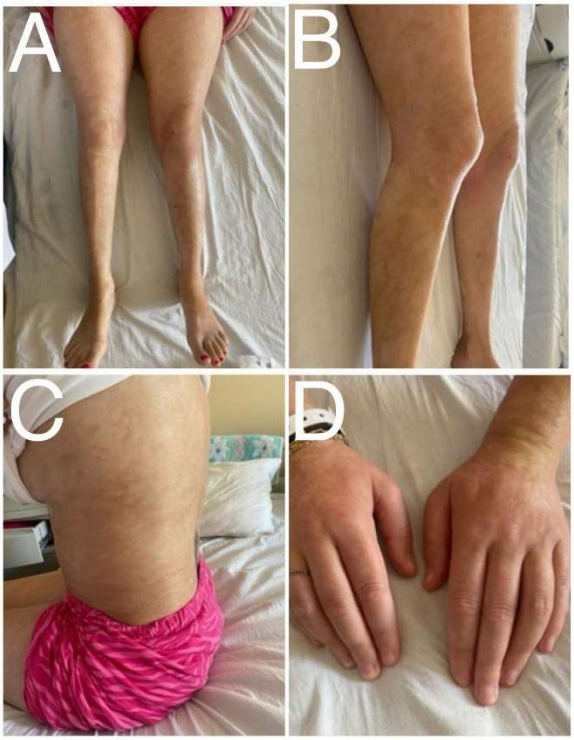

Figure 2. Clinical aspects (2023). Tibiofemoral joint flexion deformity, calf muscle atrophy (A, B); discolored, indurated patch-like skin lesions on the upper, lower limbs (A, B, D) and lateral abdomen (C); swelling of the hand (D).

She accused severe orthostatic dizziness. Routine blood tests revealed thrombocytosis (796,000/mm3), increased ESR (33mm/h), raised C-reactive protein levels (10.58mg/L). Further investigations show hypergammaglobulinemia (1900 mg/dL) and positive anti-nuclear antibodies. Scleroderma specific autoimmunity test were negative (anti-Scl70 antibody, anti-centromere antibody). Another skin biopsy was performed and the diagnosis was eosinophilic fasciitis (EF), another subtype of GM (Figure 3).

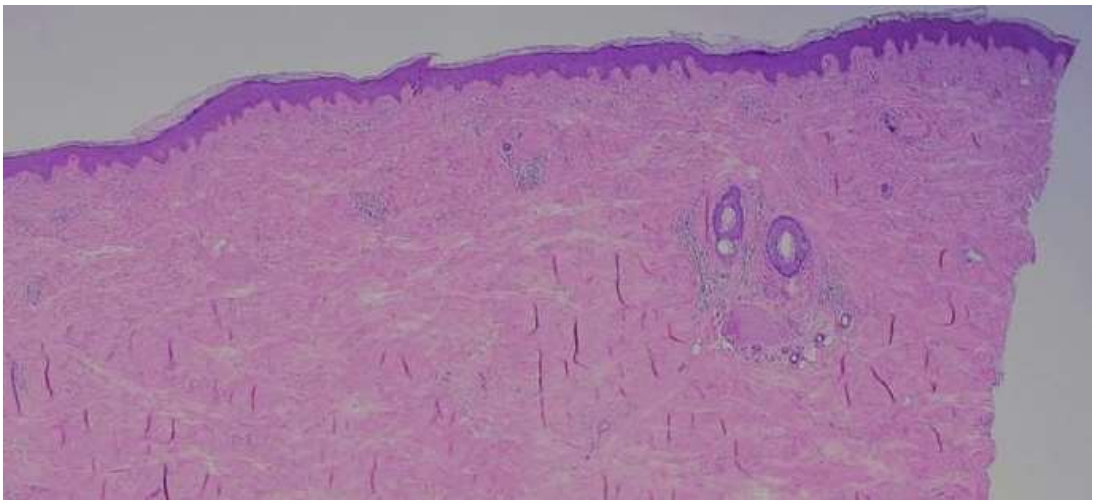

Figure 3. Histology diagnosis - EF (2023). Chronic inflammatory infiltrate (lymphocytes, plasma cells) present in all cutaneous strata, with presence of eosinophils in fascia tissue (eosinophilic fasciitis EF).

The 3 biopsy exams the patient took throughout the years have dissimilar results (cutaneous-limited scleroderma, PM, EF), it can thus, be concluded that the disease has an overlap character within the generalized subtype of Morphea.

Since Morphea is associated with hematologic disorders in multiple cases and the patient also had thrombocytosis, a hematology consult has been conducted. The osteo-medular biopsy diagnosis was Essential Thrombocytemia (ET). Moreover, molecular testing of blood detected JAK2 (V617F) mutation, which is present in 23-57% of ET cases [9]. She receives anagrelid e (Tromboreductin) 1,5mg/day, which keeps thrombocyte levels within normal range (395.000/mm3).

Based on all the clinical and paraclinical information presented, the final diagnosis was GM, with EF-like elements, associated with JAK2 positive ET and transient neurological symptoms (ameliorated by anagrelid).

Taking into consideration the lack of response on MTX as primary therapy, it is discontinued and switched to MPM 2g/day and a high dose of corticotherapy (0,75mg/kg/day).

In July 2024 she presents for Rheumatology re-evaluation. Clinical examination revealed a slight amelioration of the cutaneous symptoms, joint mobility being improved minimally (Figure 4).

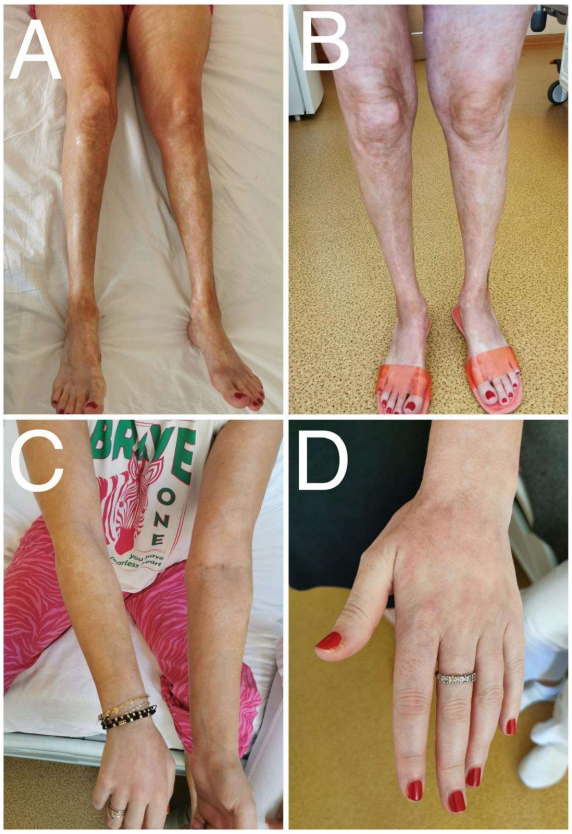

Figure 4. Clinical aspects (2024). Joint mobility, cutaneous manifestation slightly improved (A, B, C), reduced swelling and amelioration of the hand lesions (D).

The MPM therapy was interrupted because of the adverse effects, which the patient did not tolerate. IVIg was initiated and 0.5g/kg was administered within a period of 3 days, in which she was moved to the intensive care unit. Additionally, MTX 15mg/week was added as an immunosuppressant therapy, proven to be efficient in this combination, along with MP 0,5mg/kg/day (tapered to half the dose in 2 weeks). The patient tolerated the therapy well, no adverse effects being reported.

Discussion

IVIg, routinely used for more than 60 years in clinical practice, is a pooled antibody used in management of a plethora of conditions, including immunodeficiency, hyperimmune therapy against specific infectious agents and autoimmune disease (Kawasaki disease, Systemic Sclerosis, Anti-phospholipid syndrome etc.) [6,8]. It is a part of a modern set of therapeutic approaches. However, their application is off-label and different from their registered therapeutic indication [8]. It can be associated with an immunosuppressant, typically MTX or MPM. For many rheumatology patients, it can serve as a last resort in therapy, especially in cases which prove reluctant to most, if not all approved drugs. There are several cases documented in which patients with severe GM received this therapy, with significant positive outcomes.

IVIg is a biological agent isolated from pooled human plasma (1000-10,000 donors) [10]. It is mostly comprised of immunoglobulin G (IgG) (90%) [10]. In autoimmune disease, it acts as an non-specific immunomodulatory drug [11] and it is generally administered in a high dose (2g/kg) [10]. It regulates humoral immunity through autoantibody neutralization, lowering inflammatory cytokine levels (IFN-γ, IL-2, IL-1β), raising anti-inflammatory cytokine levels (IL-4, IL-13), prevention of complement-mediated damage, inhibition of antibody production by B-cell activity suppression (Fc receptor blocking, suppression of proliferation). It also affects cellular immunity, by dentritic cell maturation inhibition, cytotoxicity for neutrophils and eosinophils, macrophage action suppression, activation of regulatory T-cells (Figure 5) [6,13,14].

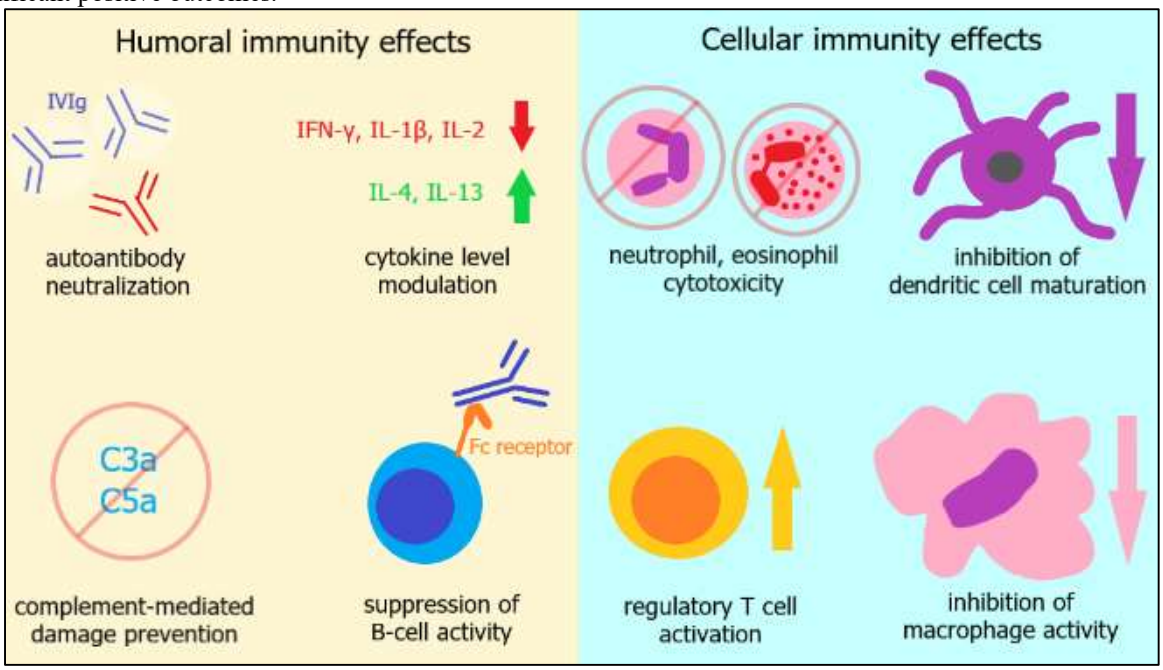

Figure 5. Immunomodulatory effects of IVIg.

Although progress has been made regarding classification of the Morphea subtypes, the clinical manifestation and biopsy findings tend to overlap, leading authors to draw the conclusion that GM, DM, EF and PM are more likely to comprise a spectrum of disease, rather than completely distinct clinical entities [7]. Therefore, the effects of IVIg have been studied on all the previously mentioned subtypes in this systematic review of literature. Using the Google Scholar search engine, all of the relevant cases have been documented and compiled in a database.

Information regarding the clinical response, additional immunosuppressant efficacy and treatment duration (with regard to efficacy) has been provided. A number of 42 patients have been analyzed, out of which 24 (57.14%) are diagnosed with EF [14-26], 13 (30.95%) with GM [26-29], 4 (9.52%) with PM [26, 30] and one (2.38%) with DM [16].

36 (85.71%) of the patients had a clinically relevant response (improved cutaneous lesions with regression of sclerosis, improved joint mobility), 28 (66.66%) presenting total response and 8 (19.04%) a partial response. 6 (14.28%) of the patients had clinically irrelevant response, out of which 3 (7.14%) had a modest response and 3 (7.14%) had no response (Figure 6).

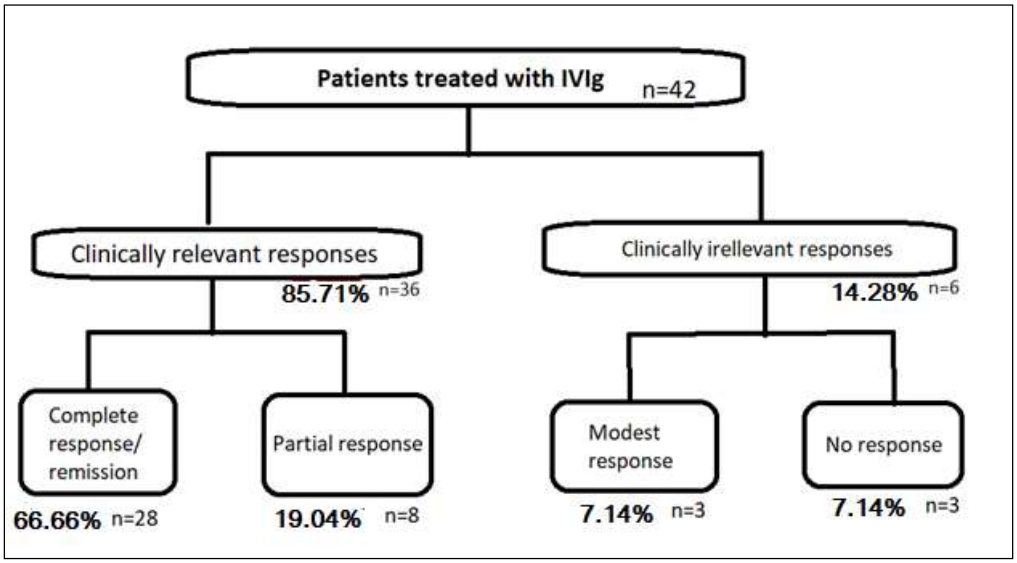

Figure 6. Clinical response to IVIg – systematic review of literature.

Some patients experienced mild adverse reactions (headache, nausea), but it is hard to determine if adverse effects were due to IVIg or the associated immunosuppressant.

MTX is known for its efficacy in preventing skin sclerosis, so it is recommended as the adjuvant immunosuppressant of choice. Unfortunately, some patients cannot receive MTX. Instead, MPM is used in these instances. From the current study cluster of patients (n=42),14 (33.33%) of them received either MTX or MPM. Out of the 7 patients who received IVIg with MTX, 6 (85.71%) achieved clinically relevant response, out of which 4 (57.14%) achieved complete response, and 2 (28.57%) of them had a partial response. Out of the 7 patients who received IVIg with MPM, 6 (85.71%) patients achieved complete response and one (14.28%) had a modest response (Figure 7). This indicates that IVIg in combination with MPM is likely to show greater results than IVIg with MTX (Figure 7).

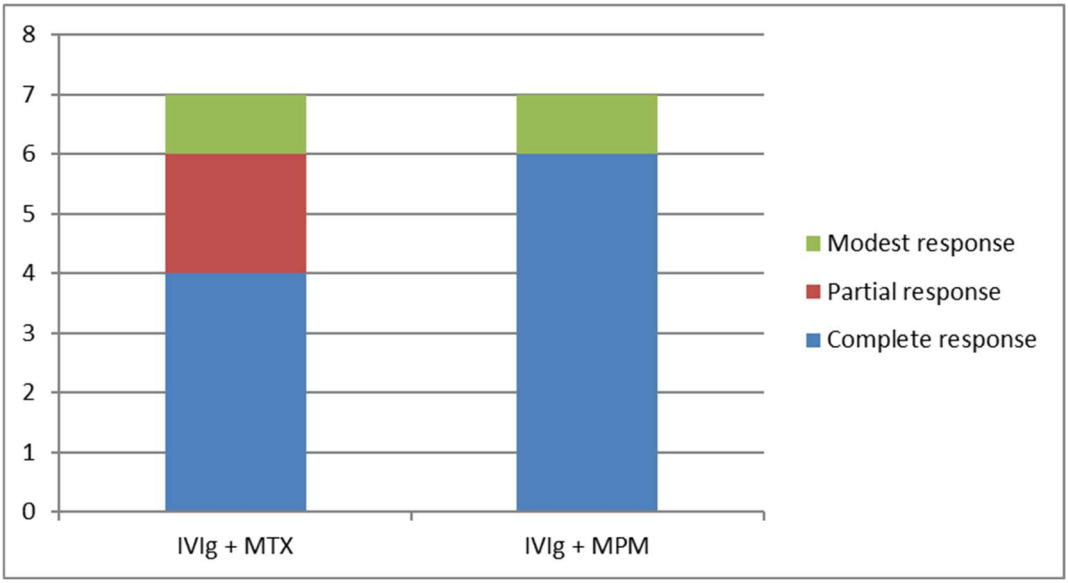

Figure 7. IVIg with MPM combination shows greater effect than IVIg with MTX.

Aditionally, there has been a reported case treated with both MTX (12.5g/week) and MPM (1.5g/day), which achieved complete clinical response.

IVIg is administered monthly and it generally takes several sessions in order to observe any effect on disease progression. From the current study cluster (n=42), in 26 of the cases the treatment duration has been documented. However, current data shows no direct correlation between treatment duration and clinical outcome.

Conclusions

GM is a rare clinical entity, which is difficult to

diagnose and treat. It can be associated with hematologic disorders. GM can have several overlap characteristics with EF. In this regard, the clinician should refer to the histopathology diagnosis. Some cases are reluctant to most therapeutic options. In this case, IVIg combined with an immunosuppressant shows promising results, especially in combination with MPM. For an early diagnosis, this treatment can improve clinical outcome and the patient's quality of life. A multidisciplinary approach (Rheumatology, Pathology, Hematology, Surgery) is crucial for the correct management of this disease.

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