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Response of recalcitrant generalized morphea to intravenous immunoglobulins (IVIg): three cases and a review of the literature

Background: Generalized morphea and eosinophilic fasciitis are difficult-to-treat inflammatory and sclerosing skin diseases. Few cases have been reported in which intravenous immunoglobulins were of benefit, possibly owing to their immunomodulatory and antifibrotic properties. *Objectives*: We present three new patients with generalized morphea treated with intravenous immunoglobulins as well as a review of the literature. *Materials & Methods*: Three hospitalized patients (two men, age 66 and 65 years, respectively, and a 67-year-old woman) with generalized morphea who received therapy for the first time are described. *Results:* The three patients were treated with intravenous immunoglobulins (1.5-2 g/kg body weight over three to four consecutive days every four weeks). This was combined with corticosteroid pulse therapy in all patients, methotrexate in two patients and mycophenolate mofetil in one patient, respectively. Marked and steady improvement of skin sclerosis was evident in all patients, one to five months after treatment initiation. No adverse events were observed. To date, there are 12 reports of 16 patients with generalized morphea or eosinophilic fasciitis treated with intravenous immunoglobulins. The treatment was highly effective in the majority of patients (9/16) and yielded a favourable risk profile. *Conclusion:* Our cases add to the hitherto limited evidence that the administration of intravenous immunoglobulins in combination with glucocorticoids and conventional immunosuppressive agents is a safe and effective therapy against morphea. It seems appropriate to verify these results in future high-quality studies.

Key words: localized scleroderma, IVIg, eosinophilic fasciitis, Shulman's syndrome

Circumscribed scleroderma, also called localized scleroderma or morphea, is a spectrum of rare sclerotic skin diseases with possible involvement of adjacent structures such as fatty tissue, muscles, joints and bones, depending on the subtype and localization [1]. The generalized variant of circumscribed scleroderma is diagnosed if at least three anatomical localizations are affected. The most common localizations are the trunk, the thighs and the lumbosacral region. Disabling pansclerotic morphea and eosinophilic fasciitis (EF; Shulman's syndrome) presents with extraordinary variants of scleroderma, which are associated with significant impairment in activities of daily life and quality of life [1-3]. Long-standing morphea also carries an increased risk of development of cutaneous squamous cell carcinoma [4]. Treatment of generalized morphea is challenging due to the rarity of the disease, the heterogeneous clinical spectrum and the variable course of disease [2]. There are no approved therapies. The German guidelines recommend treatment with methotrexate and/or systemic glucocorticoids (particularly as intravenous steroid pulse therapy) for generalized morphea. Mycophenolate mofetil can be considered as a treatment alternative to methotrexate [1]. Intravenous immunoglobulins (IVIg) are applied for dermatological autoimmune diseases and have been reported as an alternative treatment approach compared to conventional therapeutic measures for morphea/EF in a few case reports and one small case series [2, 5].

Materials and methods

Patients with generalized morphea who were treated with IVIg at the Dermatology Department of the University Medical Center Göttingen for the first time in 2018 and 2019 were identified retrospectively and their medical records were reviewed. Patients with evidence of systemic sclerosis according to ACR/EULAR criteria were

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not included. Data were extracted from medical records with regard to age, gender, disease duration, autoantibody status, laboratory and histological results, previous therapies, concomitant treatment, and clinical outcome. A literature search on PubMed was carried out to compile published cases of generalized morphea/EF treated with intravenous immunoglobulins, using the search string ((morphea) OR (eosinophilic fasciitis)) AND ((IVIG) OR (intravenous immunoglobulin*)). This search strategy was complemented by backward and forward reference searching of relevant publications. The study was performed according to the principles of the Declaration of Helsinki and was approved by the local ethics committee [6].

Results

Case 1

A 66-year-old man presented with progressive skin sclerosis on the trunk and extremities, pruritus, erythema and oedema, all of which had manifested approximately five months earlier (*figure 1A*). The patient also suffered from hemiparesis after a stroke and subarachnoid haemorrhage 20 and 8 years ago, respectively. Histopathology revealed a pan-dermal and epidermotropic CD8-dominated T-cell infiltrate with sclerotic collagenous fibre bundles, while the fascia was unremarkable. In the peripheral blood, inflammatory parameters were elevated and there was eosinophilia (933/μL, normal: <500/μL) and mild hypergammaglobulinaemia. Antibody diagnostics were inconspicuous except for positivity of Ro-52 antibodies. MRI of the shoulder belt showed an inflammatory affection of the superficial fascia of the shoulder and trunk muscles on the left side without affection of deep fascias. Pulmonary function test was unremarkable. Based on clinical and histopathological findings, generalized morphea was diagnosed. Corticosteroid pulse therapy (dexamethasone at 100 mg/day for three days) and treatment with IVIg (1.6 g/kg body weight administered over three consecutive days) every four weeks was initiated. In addition, the patient received lymphatic drainage treatment, physiotherapy and compression of the lower legs. In the interval between intravenous treatments, he was treated with prednisolone starting with 0.5 mg/kg body weight day tapered and weekly subcutaneous injections of methotrexate (15 mg). Under therapy, the patient's skin condition showed a rapid and marked improvement with significant softening of the skin after a month (*figure 1B*). Thus, treatment with intravenous dexamethasone was reduced and discontinued after a total of 10 cycles, and oral prednisolone was gradually reduced and discontinued after 17 months. Methotrexate was reduced to 7.5 mg/week. IVIg were administered at the same dosage over the entire observation period (22 months). The interval was gradually extended to eight weeks. Treatment with IVIg was well tolerated without any adverse events.

Case 2

A 67-year-old woman presented with a two-year history of progressive sclerosis on her trunk and extremities (*figure 2A, B*). She also experienced hair loss on the forearms and lower legs (*figure 2C*). Apart from an elevated ANA titre (1:1.280), there were no laboratory abnormalities. Histopathology was compatible with scleroderma. Pulmonary function test was unremarkable. Generalized morphea was diagnosed. Weekly subcutaneous injections

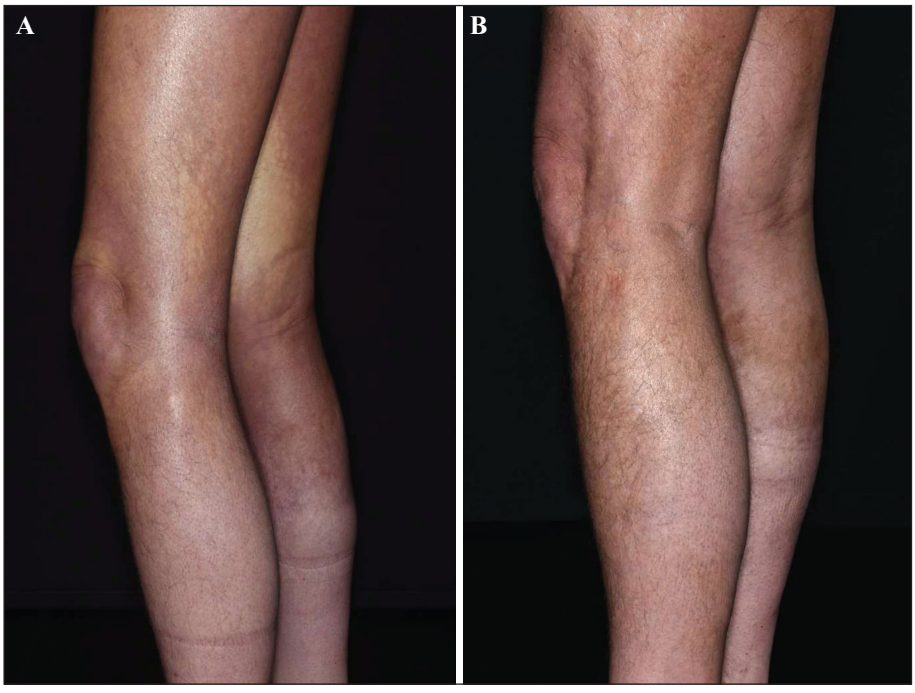

Figure 1. Clinical presentation of Patient 1. **A**) At initial presentation, there was marked inflammation of the legs, accompanied by sclerosis which restrained the patient's flexibility of the joints (incomplete extension of the knees). **B**) Treatment with intravenous immunoglobulins resulted in marked improvement of sclerosis and joint flexibility (observation period: 22 months).

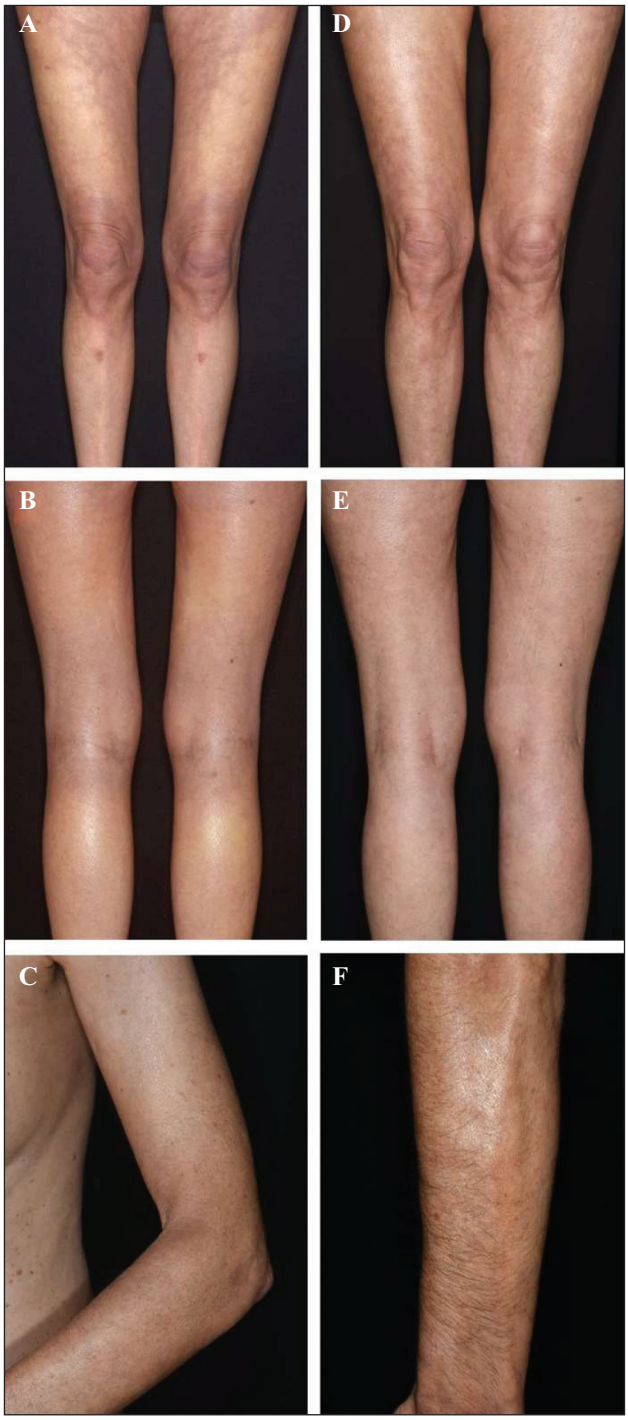

Figure 2. Clinical presentation of Patient 2. Sclerosis of the legs (**A**, **B**) and alopecia of the forearms (**C**) before treatment with intravenous immunoglobulins. Nine months after initiation of therapy with intravenous immunoglobulins, dramatic regression of sclerosis (**D**, **E**) and resumption of hair growth (**F**) was visible.

of methotrexate at 15 mg had been initiated five months prior to presentation at our hospital. We started treatment with corticosteroid pulses (dexamethasone at 80 mg/day for three days every four weeks) and continued the therapy with methotrexate. In addition, the patient received lymphatic drainage and physiotherapy. There was no significant clinical improvement after four cycles of dexamethasone pulse therapy. Therefore, we switched immunosuppressive therapy from methotrexate to mycophenolate mofetil (2 g/day) and prednisolone (5 mg/day). In addition, we initiated treatment with IVIg (2 g/kg body weight) parallel to the dexamethasone doses every four weeks. After approximately five months, the skin condition began to improve with significant softening of the skin and resumption of hair growth on the forearms and lower legs (*figure 2D-F*). No adverse events were reported. Continued improvement of skin symptoms was reported at 13 months after initiation of IVIg therapy.

Case 3

A 65-year-old man presented with pruritus and progressive sclerosis of the trunk and extremities. The symptoms had developed in the past year. Antibody diagnostics and laboratory examination were inconspicuous. Pulmonary function test was unremarkable. Oesophagogastroduodenoscopy and oesophageal manometry were without relevant findings. Doxycycline, initially administered based on the suspected clinical diagnosis of chronic cutaneous Lyme disease, did not improve symptoms. A skin sample was taken, and the histological changes were compatible with generalized morphea. Treatment with intravenous penicillin and prednisolone at 20 mg/d were initiated and mobility in the knees and elbows improved slightly as the skin had softened. Upon presentation at our clinic, an MRI of the left forearm did not show evidence of fasciitis. We initiated corticosteroid pulse therapy (dexamethasone at 100 mg/d for three days every four weeks) and weekly subcutaneous injections of methotrexate (10 mg). Treatment with prednisolone (20 mg/d) was continued. The incidental diagnosis of a pleomorphic adenoma of the parotid gland prompted the cessation of methotrexate therapy. After resection of the tumour, therapy with IVIg (1.5 g/kg body weight every four weeks) and mycophenolate mofetil (2 g/day) was initiated due to progression of sclerosis. Up to the present day (observation period: nine months under treatment with IVIg), the skin condition has improved steadily, accompanied by a significant improvement in joint mobility. Thus, the dosage of dexamethasone and prednisolone was gradually reduced. No adverse events were reported.

Discussion

Our cases extend the growing evidence that IVIg in combination with glucocorticosteroids and/or steroid-sparing agents are an effective and safe treatment for generalized morphea. We identified only case reports and one small case series on the use of IVIg for generalized morphea und eosinophilic fasciitis (*table 1*) [7-18]. Most patients had received previous therapy for morphea/EF, particularly with systemic corticosteroids. IVIg were mostly administered in monthly cycles at a dosage of 2 g/kg body weight over three to five consecutive days. Treatment was combined in almost all cases with corticosteroids and frequently with conventional immunosuppressive therapy. IVIg were usually given for at least six months. A significant improvement was

Table 1. Treatment of generalized morphea and eosinophilic fasciitis with intravenous immunoglobulins based on published reports and the patients presented in this study.

First author, year [Ref.]	Publication type	Sex, age (years)[a]	Skin disease	Disease duration (months)[b]	Previous therapy (dosage)	IVIg dosage	Concomitant therapy (dosage)	Treatment duration (months)	Clinical outcome	Follow-up data[c]	Adverse events
Bani-Sadr, 2000 [7]	Case report	M, 18	EF	4	2 MP pulses (240mg/d), Pred (0.7mg/kg/d)	2g/kg over 2 days monthly	Pred (8mg/d)	6	Remission	Relapse after 18 months, improvement under corticosteroids	N/S
Barrier, 2001 [8]	Case report	M, 48	EF	6	MP pulse (240mg/d for 3d), Pred (65-120mg/d)	1.2g/kg over 3 days monthly	Pred (1mg/kg/d tapered)	8	Significant improvement	NA	N/S
El-Jammal, 2019 [9]	Case report	M, 57	EF	48	-	N/S	MP pulse (240mg/d for 3d), Pred (1mg/kg/d)	N/S	Nonresponse	MP pulse (240mg/d for 3d), Pred (1mg/kg/d), MTX (0.3mg/kg/w), adalimumab (40mg/2w) for 7 months successful	None
Gutierrez, 2019 [10]	Case report	M, 70	EF	12	-	2g/kg over 3 days monthly	Pred (20mg/d)	7	Significant improvement in swelling, induration, and pain	NA	N/S
Küçükoğlu, 2018 [11]	Case report	F, 23	GM	168	Corticosteroids, MTX	2g/kg over 5 days monthly	MP (40mg/d), MMF (2g/d)	5	Marked regression of sclerosis, healing of acral ulcers	NA	N/S
Nahhas, 2018 [12]	Case report	M, 67	EF	1	MMF, MP pulses	N/S	N/S	N/S	Nonresponse	No response to hydroxychloro-quine, cyclophos-phamide; improvement under corticos-teroids + MTX + rituximab (1g day 0, 14; 2nd course after 5 months)	N/S
Odhav, 2014 [13]	Case report	M, 4	PM / EF	5	-	N/S	MP, MTX, MMF, imatinib	24	Slow improvement	Relapse, autologous stem cell transplantation with relapse after 3 months, improvement under corticos-teroids + abatacept	N/S

Table 1. (*Continued*).

First author, year [Ref.]	Publication type	Sex, age (years)[a]	Skin disease	Disease duration (months)[b]	Previous therapy (dosage)	IVIg dosage	Concomitant therapy (dosage)	Treatment duration (months)	Clinical outcome	Follow-up data[c]	Adverse events
Pimenta, 2009 [14]	Case report	M, 39	EF	14	Pred (30mg/d), MTX (20mg/w)	1.5g/kg over 3 days monthly	Pred (20mg/d), MTX (20mg/w)	6	Improvement of induration	Remission (2 years) under Pred (2.5mg/d) + MTX (10mg/w)	N/S
Soh, 2019 [15]	Case report	M, 5	PM	9	Pred (1mg/kg/d), MTX (15 mg/m^2/w)	1g/kg monthly	MP pulse (30mg/kg/month), Pred (1mg/kg/d), MTX (15 mg/m^2/w), hydroxychloroquine (200mg every other day)	6	Incomplete response	Incomplete response to hydroxychloroquine (200mg every other day), MMF (600mg/d), MTX, rituximab, tocilizumab, ruxolitinib (20mg/d), autologous stem cell transplantation, MP pulses (30 mg/kg/month), Pred (10mg/d)	N/S
Tkachenko, 2019 [16]	Case series	M, 55	EF	40	Pred (60mg/d), MTX (25mg/w), MMF (1.5g/d)	2g/kg over 2 days monthly	MTX (12.5mg/w), MMF (1.5g/d)	48	Complete response	NA	None
		M, 60	EF	14	Pred (80mg/d), MTX (20mg/w)	2g/kg over 2 days monthly	MTX (17.5mg/w)	16	Complete response	NA	Headache
		M, 25	EF	10	Pred (60mg/d), MTX (25mg/w)	2g/kg over 2 days monthly	-	25	Complete response	NA	None
		M, 71	EF	8	Pred (20mg/d), sulfasalzine (N/S)	2g/kg over 2 days monthly	MTX (5mg/w)	18	Partial response	NA	None
		F, 56	EF	12	Pred (40mg/d), MTX (25mg/w)	2g/kg over 3 days monthly	MTX (25mg/w)	6	Partial response	NA	Headache
Vilchez-Oya, 2020 [17]	Case report	M, 60	EF	3	MP pulse, Pred (1mg/kg/d), MTX (20mg/w)	2g/kg monthly	Pred (0.5mg/kg/d), MTX (20mg/w)	6	Nonresponse	Partial remission under Pred (0.5mg/kg/d), MTX (20mg/w), tocilizumab (8mg/kg/month) for 10 months	N/S
Wollina, 1998 [18]	Case report	M, 7	PM	48	-	25g (=1.2g/kg) over 5 days monthly	-	>12	Marked improvement	NA	None

Table 1. (*Continued*).

First author, year [Ref.]	Publication type	Sex, age (years)[a]	Skin disease	Disease duration (months)[b]	Previous therapy (dosage)	IVIg dosage	Concomitant therapy (dosage)	Treatment duration (months)	Clinical outcome	Follow-up data[c]	Adverse events
This study	Case series	M, 66	GM	5	-	1.6g/kg over 3 days monthly	Dexamethasone pulse (100mg/d i.v. for 3 days monthly), Pred (0.5mg/kg/d), MTX (15mg/w s.c.)	22	Marked improvement	NA	None
		F, 65	GM	28	Dexamethasone pulse (80mg/d i.v. for 3 days monthly), MTX (15mg/w s.c.)	2g/kg over 3 days monthly	Dexamethasone pulse (80mg/d i.v. for 3 days monthly), Pred (5mg/d), MMF (2g/d)	13	Marked improvement	NA	None
		M, 64	GM	24	Penicillin (i.v.), Pred (20mg/d), dexamethasone pulse (100mg/d i.v. for 3 days monthly), MTX (10mg/w s.c.)	1.5g/kg over 3 days monthly	Dexamethasone pulse (100mg/d i.v. for 3 days monthly), Pred (20mg/d), MMF (2g/d)	9	Marked improvement	NA	None

NA: not applicable (IVIg therapy not discontinued); N/S: not specified; F: female; M: male; GM: generalized morphea; PM: pansclerotic morphea; EF: eosinophilic fasciitis; MTX: methotrexate; MMF: mycophenolate mofetil; MP: methylprednisolone; Pred: prednisolone; d: day; i.v.: intravenously; s.c.: subcutaneously; Ref.: reference.

[a] *Age at onset of disease.*

[b] *Time between age at onset of disease and initiation of IVIg therapy.*

[c] *After IVIg discontinuation.*

noted in most patients (9/16 reported cases), while partial response (4/16) or non-response (3/16) were observed less frequently [7-18]. Adverse events were not stated conclusively in the majority of cases. Tkachenko and colleagues provide the largest cohort of patients with EF ($n = 5$) [16]. The authors report complete clinical response in three out of five patients and partial clinical response in the remaining two patients with improvement of functional limitation in all affected patients and good tolerability of treatment [16]. In line with published literature, treatment with IVIg in combination with glucocorticoids and immunosuppressive agents was effective and well tolerated without adverse events in our cohort. All patients were still on IVIg therapy at last observation with a therapy duration of 22, 13, and 9 months in Cases 1, 2, and 3 respectively.

The incidence of morphea has been reported to peak between 7 and 11 years for paediatric-onset disease (including pansclerotic morphea of childhood) and between 44 and 47 years for adult-onset disease [2]. Thus, our patients had a late onset of disease. Response of morphea/EF to IVIg seems to depend on the age at onset of disease. While therapy with IVIg was successful in a majority of treated adults, two out of three paediatric patients with pansclerotic morphea only showed slow and partial improvement and received extensive immunosuppressive comedication [13, 15].

Although the exact mode of action of IVIg is not fully understood, the anti-sclerotic effect seems to be mediated by the Fc part of IgG which modifies both innate and acquired immune system via a plethora of immune cell types. More specifically, administration of IVIg leads to an increase of regulatory T cells, interferes with autoantibody secretion of B cells, and suppresses dendritic cells and macrophage activation [19]. On a cytokine level, decreased collagen deposition and type I collagen expression may be mediated by diminished production of proinflammatory tumour necrosis factor (TNF)-α and the profibrotic cytokines, interleukin (IL)-4 and transforming growth factor (TGF)-β1 on the one hand, and upregulation of interferon (INF)-γ and IL-12 on the other hand [20-22]. Interestingly, IVIg have also been reported as an effective treatment option for the related disease, systemic sclerosis [19, 23].

The results of our study should be interpreted with caution: First, all patients were treated with a combination of IVIg, glucocorticosteroids, and steroid-sparing agents. It is likely that the marked improvement noted in all three cases was attributable to the combination therapy and not solely to IVIg. Second, objective measurement tools, such as the mLoSSI, were not documented conclusively. Thus, clinical outcome was assessed according to photographic evidence and descriptions in medical records. Third, a reporting bias of selective publication of positive results cannot be ruled out.

In conclusion, IVIg in combination with glucocorticosteroids and/or steroid-sparing agents appear to be an effective and safe therapeutic strategy for morphea/EF and thus should be considered in patients with insufficient response to, or adverse events under established therapy options such as systemic glucocorticosteroids, methotrexate, and mycophenolate mofetil. Although IVIg are well tolerated in general, possible adverse events such as immediate infusion reactions (headache, fever, fatigue, anaphylaxis), fluid overload, thromboembolic events, haemolytic reactions, and acute renal failure should be considered and monitored clinically and by laboratory testing [24]. Of course, high-quality studies with long observation periods must follow to firmly establish IVIg in the therapeutic armamentarium. ■

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