Response of eosinophilic fasciitis associated with Waldenström macroglobulinemia to rituximab

Christian Kromer[1] MD, Silke S Matzke1[1,2] MD, Annalen Bleckmann[3,4] MD, Tobias Overbeck[3] MD, Undine Lippert[1] MD, Michael P Schön[1,5] MD, Rotraut Mössner[1] MD

Affiliations: [1]Department of Dermatology, Venereology and Allergology, University Medical Center, Göttingen, Germany, [2]Hautarztpraxis Dr Matzke, Bremen, Germany, [3]Department of Hematology and Medical Oncology, University Medical Center, Göttingen, Germany, [4]Department of Medicine A, Hematology, Oncology, and Pneumology, University Hospital, Münster, Germany, [5]Lower Saxony Institute of Occupational Dermatology, University Medical Center, Göttingen, Germany

Corresponding Author: Prof Dr R Mössner MD, Department of Dermatology, University Medical Center Göttingen, Robert Koch Strasse 40, 37075 Göttingen, Germany, Tel: 49-551-39-66401, Fax: 49-551-39-22047, Email: rmoessn@gwdg.de

Abstract

Eosinophilic fasciitis (EF) and generalized morphea (GM) are rare and difficult-to-treat sclerosing skin diseases which may occur in association with hematologic disorders. We present a 66-year-old man with EF and associated Waldenström macroglobulinemia who received combination therapy with rituximab (375mg/m^2 every other week, gradually extended to every eight weeks), prednisolone (1.25-30mg/d), and methotrexate (7.5-15mg/w). Three months after rituximab initiation, his skin condition improved steadily accompanied by a significant improvement in joint mobility with only mild and transitory flares (observation period: 59 months under treatment with rituximab). To date, there are five case reports on rituximab treatment of EF/GM with an association to hypergammaglobulinemia in three of those cases. Therapy effected significant improvement in four patients. Our case adds to the hitherto limited evidence that rituximab may be a promising therapeutic strategy for EF/GM in association with hypergammaglobulinemia.

Keywords: biologic, localized scleroderma, rituximab, Shulman's syndrome

Introduction

Eosinophilic fasciitis (EF; Shulman syndrome) and morphea belong to the spectrum of sclerosing skin diseases, presenting with erythematous to violaceous lesions that evolve into sclerotic plaques with postinflammatory hyperpigmentation [1]. Whether EF should be considered a separate entity or part of the morphea spectrum remains controversial [1-3]. Eosinophilic fasciitis can be diagnosed by its typical clinical presentation, peripheral eosinophilia, eosinophilia and thickened fascia in full-thickness biopsy specimens, and fasciitis in MRI or PET [1]. Owing to considerable functional limitations, EF may cause significant impairment of quality of life [1-3]. Generalized morphea (GM) is diagnosed if at least three anatomical sites are affected by scleroderma. Sclerosing skin diseases have been reported to rarely be associated with hematologic diseases, including plasma cell dyscrasia, and less commonly with solid tumors [4]. In addition, sclerotic lesions may give rise to the development of skin tumors [5].

Treatment of GM/EF is challenging owing to the rarity of the diseases, the heterogeneous clinical spectrum, and the variable course of diseases [2]. There are no approved therapies. Currently, German guidelines recommend systemically administered corticosteroids, methotrexate, and mycophenolate mofetil as treatment options for severe disease [1]. Evidence on therapy with other immunosuppressive agents is scarce and largely based on case reports and small case series [2]. Only very few reports exist regarding treatment of GM/EF with rituximab, a chimeric monoclonal antibody targeting CD20 on B lymphocytes [6-10]. Herein, we report a patient with severe EF associated with Waldenström

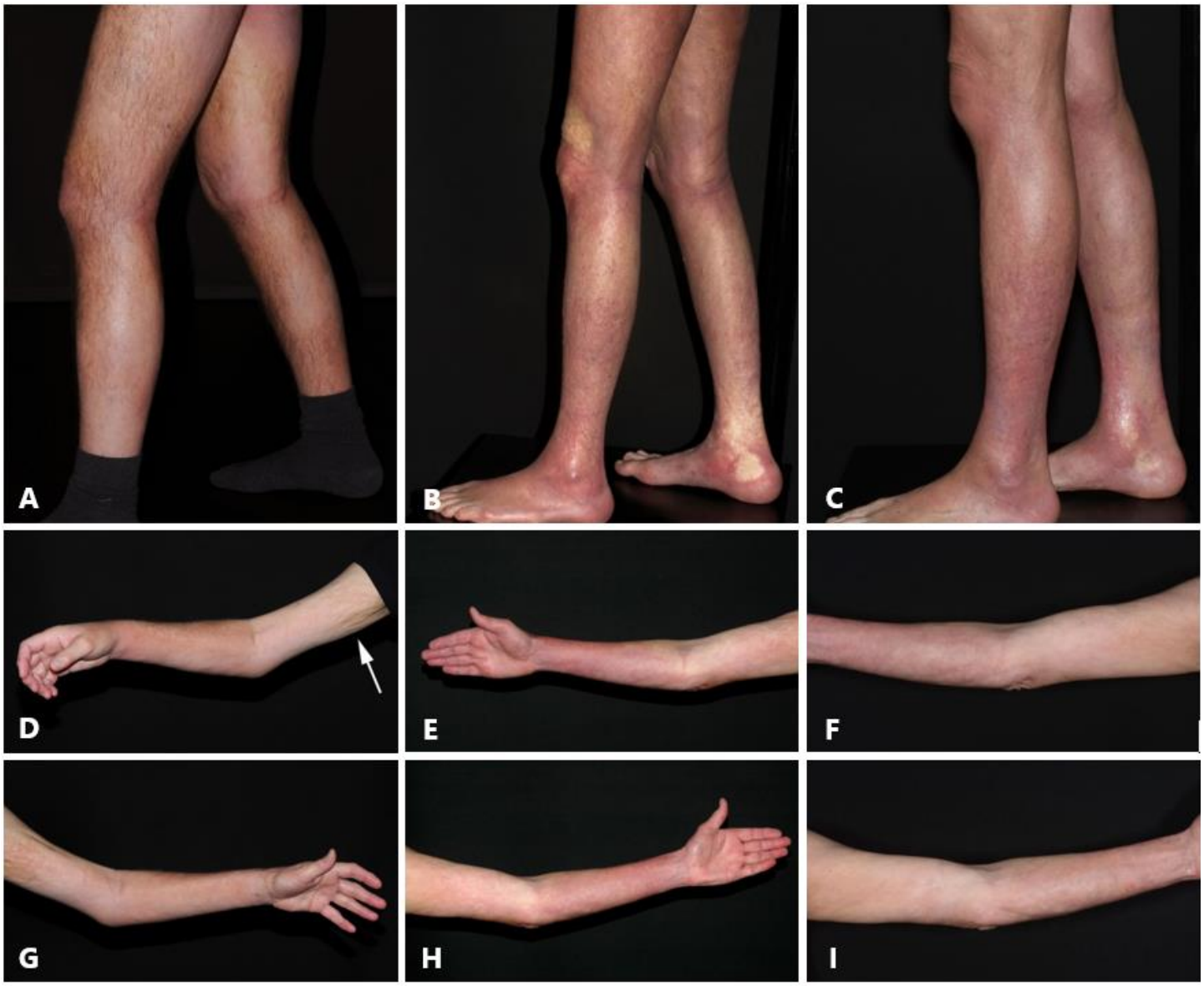

Figure 1. *Clinical presentation of the patient.* ***A***, ***D***, ***G)*** *At initial presentation, there was marked inflammation of extremities, accompanied by sclerosis which diminished the patient's joint mobility (incomplete extension in knees and elbows). The white arrow shows the typical dimpled peau d'orange aspect of the skin. Combination treatment with rituximab, methotrexate (dosage: 7.5-15mg weekly), prednisolone (dosage: 1.25-30mg/day), and two courses of UVA-1 phototherapy led to marked in improvement of sclerosis and joint flexibility,* ***B)*** *after 12 months;* ***C)*** *after 52 months;* ***E***, ***H)*** *after 17 months;* ***F***, ***I****) after 26 months. Overall observation period was 59 months.*

macroglobulinemia with marked and sustained response to a combination therapy of rituximab, systemic corticosteroids, and methotrexate.

Case Synopsis

A 66-year-old man presented with rapidly progressive, severe, ubiquitous, and symmetrical skin sclerosis of extremities, erythema, and edema, which had manifested approximately two months earlier. The hands were largely spared. On first presentation, he could barely walk 10 meters, whereas before he could run 5 kilometers. The mobility of his joints was significantly reduced (**Figure 1A**, **D**, **G**). The patient also suffered from arterial hypertension. Histopathology revealed a dermal lymphocytic infiltrate with some macrophages and plasma cells and broad sclerotic

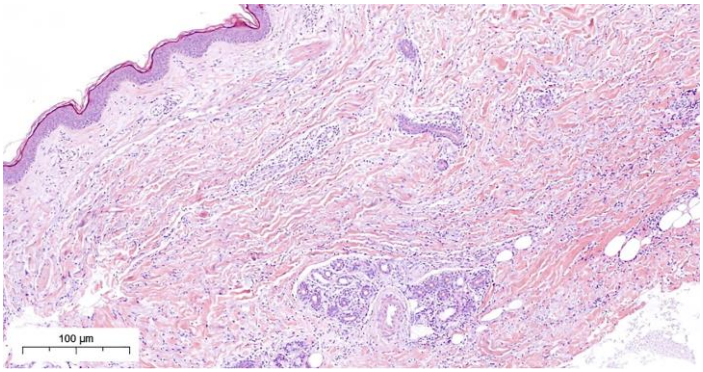

Figure 2. *Histopathologic results. H&E staining of skin sections. Unchanged epidermis and lymphoid infiltrates with some macrophages and plasma cells in the mid and deeper portions of the dermis are seen as well as broad sclerotic collagenous fiber bundles. Scale bar, 100µm.*

collagenous fiber bundles, consistent with the active inflammatory stage of scleroderma (**Figure 2**). The fascia was not represented in the biopsy. Laboratory analysis showed eosinophilia (629/µl, normal: <500/µl) whereas autoantibody diagnostics (ANA, ENA, ds-DNA) were unremarkable. MRI examination of the right upper arm showed a ubiquitous signal alteration of fascia (**Figure 3**). Pulmonary function was normal and nail fold capillaroscopy revealed only a slight decline of capillary density. We diagnosed EF according to German guidelines [1]. Additionally, the erythrocyte sedimentation rate was significantly increased (63mm/h) and an elevated IgM (7.17g/l; normal range: 0.22–2.93g/l) with kappa light chain restriction was found in peripheral blood; genetic analysis revealed a *MyD88* (c.794T>C, p.L265P) mutation. Bone marrow biopsy showed a diffuse infiltration with plasma cells, kappa light-chain restriction, and aggregation of CD20+ lymphocytes. Thus, results were compatible with Waldenström macroglobulinemia.

For treatment of EF, the patient received corticosteroid pulses (dexamethasone 100mg/day for three days monthly), prednisolone (50mg/day), and weekly subcutaneous injections of methotrexate (15mg). In addition, he received lymphatic drainage and physiotherapy. During the next eight weeks, the patient reported faster progression of sclerosis with manifestation of ulcers of the lower legs. Moreover, IgM increased to 12.32g/l. The treatment of Waldenström macroglobulinemia was initiated with rituximab (375mg/m^2 every two weeks), bortezomib (1.3mg/m^2 for three cycles), and dexamethasone (20mg/day). Methotrexate was discontinued because of this chemotherapy and the dosage of prednisolone was tapered to 30mg/day. Additionally, we administered UVA-1 phototherapy. Owing to sensory polyneuropathy, treatment with bortezomib and dexamethasone was discontinued after three cycles (6 weeks) and methotrexate (15mg/week subcutaneously) was restarted. Moreover, immunoglobulins (10-20g every other week) were substituted intravenously for treatment of secondary immunoglobulin deficiency.

Three months after initiation of rituximab treatment, the patient experienced a slight softening and

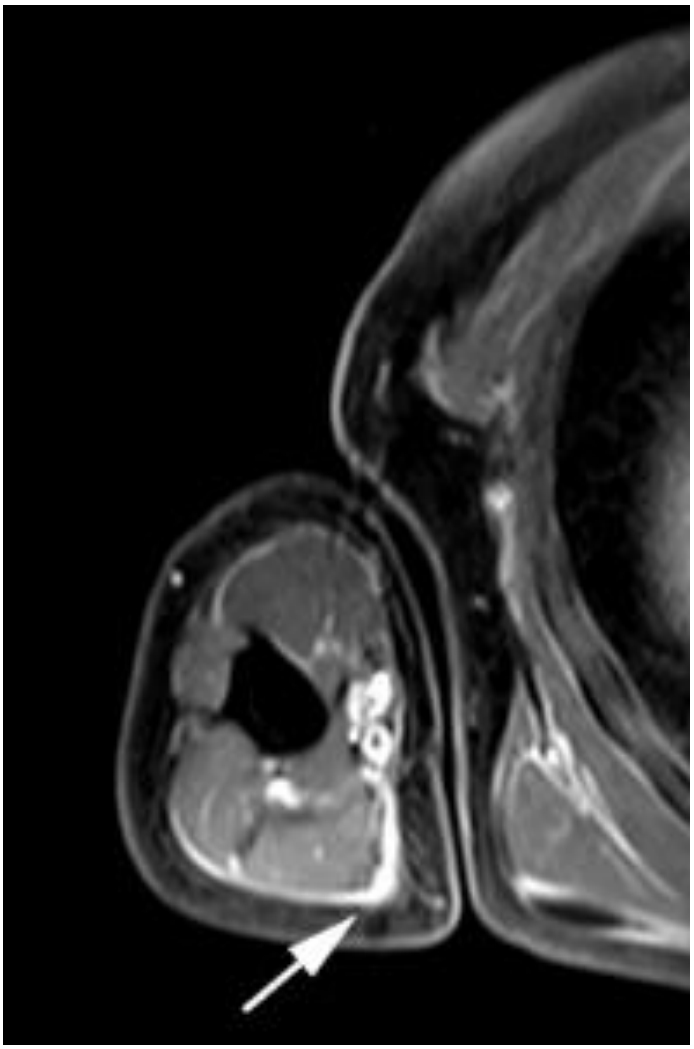

Figure 3. *MRI findings. Contrast-enhanced T1-weighted MRI of the right upper arm showed signal alterations (arrow), consistent with fasciitis.*

improvement of his functional limitation whereas the ulcers persisted. The interval between rituximab administrations could be gradually extended to eight weeks owing to normalization of the serological parameters of Waldenström macroglobulinemia (IgM: 0.27g/l at last observation) and clinical response of EF. Under combination therapy of rituximab, methotrexate (dosage: 7.5-15mg weekly), prednisolone (dosage: 1.25-30mg/day), intravenous immunoglobulins (10-20g every other week), and two courses of UVA-1 phototherapy, the skin condition improved steadily accompanied by a significant improvement of joint mobility. Up to the present day there have been only mild and transitory flares (observation period: 59 months under treatment with rituximab; **Figure 1C**, **F**, **I**). Importantly, the patient has been able to resume long-distance running (>5 km). Intravenous immunoglobulins were only given in a low dosage (10-20g every other week) for treatment of secondary immunoglobulin deficiency.

Case Discussion

Clinical findings of EF comprise erythema and edema which progress to deep sclerosis. Neck, trunk, and extremities are usually involved symmetrically with exclusion of hands and feet. General symptoms such as fatigue, myalgia, and weight loss may occur. Diagnosis is based on the typical clinical presentation, peripheral eosinophilia, eosinophilia and thickened fascia in full-thickness biopsy specimens, and fasciitis in MRI or PET [2]. Eosinophilic fasciitis has been reported to be associated with malignancy in 5-10% of patients including a variety of hematological diseases (aplastic anemia, thrombocytopenic purpura, myelodysplastic syndrome, myeloproliferative disorders, multiple myeloma, Hodgkin disease, chronic lymphocytic leukemia, and myelomonocytic leukemia). Solid organ neoplasms (prostate cancer, lung cancer, breast cancer) are much less common [3].

A literature search in PubMed using the search string ((morphea) OR (localized scleroderma) OR (eosinophilic fasciitis)) AND (rituximab) was complemented by backward and forward reference searching of relevant publications. Overall, we identified five case reports with associated hypergammaglobulinemia in three of those articles (**Table 1**), [6-10]. Scheinberg and colleagues reported a patient with EF and associated Waldenström macroglobulinemia who experienced remission associated with rituximab administration [9]. However, the treatment regimen was not clearly described. Traboulsi and colleagues reported on a 54-year-old woman with GM and previous unsuccessful therapy with prednisone, hydroxychloroquine, and methotrexate [10]. The patient was additionally diagnosed with primary biliary cirrhosis and Waldenström macroglobulinemia. For treatment of the latter, she received six monthly cycles of rituximab (375mg/m^2) and bendamustine (180mg/m^2) which resulted in improvement of skin tightness and induration two months after initiation and near complete clearance at the end of treatment. However, two months after treatment discontinuation, her skin disease relapsed. Thus, rituximab was restarted (maintenance dosage: 375mg/m^2/3 months) which again controlled the disease. As published by Chan et al. [6], GM/EF overlap with hypergammaglobulinemia manifested in a 20-year-old man after epoxy resins exposure. Among other immunosuppressive drugs, rituximab was administered with only minimal improvement. However, to our knowledge, it is still controversial whether scleroderma-like disorders occurring after exposure to organic solvents constitute a separate entity or at least differ substantially from "classic" GM/EF. Nahhas and colleagues described a 67-year-old patient with EF refractory to several immunosuppressive agents [8]. The combination therapy of oral corticosteroids, methotrexate, and rituximab (1g, two weeks apart, cycle repeated after 5 months) led to improvement of the skin disease. Finally, de Masson and colleagues reported four patients with EF and aplastic anemia [7]. One of these patients (male, 57 years) was treated with rituximab (375mg/m^2/w for four weeks, repeated after 6 months) in combination with cyclosporine (200mg/d tapered to 80mg/d). After the second course, the authors observed remission of the skin disease which was maintained until the time of last observation six months later.

Conclusion

Our case extends published reports that rituximab may be a reasonable therapeutic strategy for GM/EF in association with hypergammaglobulinemia. However, whether resolution of GM/EF occurs related to the successful treatment of the underlying hematologic disease or results from a genuine therapeutic effect of rituximab on the sclerosing skin disease is not clear. Further studies with high methodological quality are needed to determine the position of rituximab in the therapeutic algorithm.

Potential conflicts of interest

The authors declare no conflicts of interest.

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Table 1. *List of published reports on treatment of generalized morphea and eosinophilic fasciitis with rituximab and own patient.*

First author, year [Ref]	Sex, age (years)[a]	Skin disease	Hypergamma-globulinemia present	Comorbidity	Disease duration (months)[b]	Previous therapy (dosage)	Rituximab dosage	Concomitant therapy (dosage)	Treatment duration (months)	Clinical outcome
Own patient	M, 66	EF	Yes	Waldenström macro-globulinemia	4	Dexamethasone (100mg/d for 3 days monthly), prednisolone (50mg/d), methotrexate (15mg/d)	375mg/m^2 every 2 weeks (extended to every 8 weeks)	Prednisolone (up to 30mg/d), methotrexate (7.5-15mg/d), IVIG*	59	Marked improvement
Scheinberg, 2006 [9]	F, 20	EF	Yes	Waldenström macro-globulinemia	6	N/S	N/S (375mg/m^2/w x 4 or 1 g day 0, 14)	N/S	N/S	Remission
Traboulsi, 2018 [10]	F, 54	GM	Yes	Waldenström macro-globulinemia, primary biliary cirrhosis	N/S	Prednisone, hydroxychloroquine, and methotrexate	375mg/m^2/month (extended to every 3 months)	Bendamustine, 180mg/m^2/ month	>6	Near complete clearance
Chan, 2018 [6]	M, 17	EF/GM	Yes	N/S	>24	Prednisone (10mg/d), methotrexate (25mg/w), azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine	N/S	N/S	N/S	Minimal improvement
de Masson, 2013 [7]	M, 57	EF	No	Aplastic anemia	23	Prednisone (1mg/kg/d), cyclosporine (360mg)	375mg/m^2/w x 4, same protocol 6 months later	Cyclosporine 200mg/d tapered	6	Remission
Nahhas, 2018 [8]	M, 67	EF	No	Sarcoidosis, latent tuberculosis, testicular seminoma	3	Photopheresis, mycophenolate mofetil, prednisone, methylprednisolone pulse, IV immunoglobulin, hydroxychloroquine, cyclophosphamide	1g day 0, 14, same protocol 5 months later	Corticosteroids, methotrexate	5	Improvement

[a]Depicted is the age at onset of disease. [b]Depicted is the disease duration before initiation of rituximab.

IVIG*, intravenous immunoglobulins (10-20g every other week) as substitution treatment of secondary immunoglobulin deficiency. EF, eosinophilic fasciitis; F, female; GM, generalized morphea; M, male; N/S, not stated explicitly; Ref, Reference.