Sclerosing diseases of the skin, clinical presentation, epidemiology and pathogenesis

PhD Thesis

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Introduction

Morphea (localized scleroderma) is a rare fibrosing disorder of the skin and underlying tissues. Localized scleroderma represents a unique entity among the sclerosing diseases and differs from systemic sclerosis (SSc), which is a systemic autoimmune disorder with fibrosis of the internal organs as well. Sclerodactyly, Raynaud phenomenon and nailfold capillary changes are absent in localized scleroderma.

Localized scleroderma is considered to be an autoimmune disorder because it is usually coupled with other autoimmune diseases. Furthermore, patients with morphea are often positive for antinuclear antibodies and frequently have a positive family history for other autoimmune diseases. Autoimmune comorbidities are present most of all in the generalized and linear subtypes.

Because of the similar fibrotic process, we have focused in the spectrum of the autoimmune diseases on the primary biliary cholangitis (PBC). PBC is an intrahepatic cholestatic disease which leads to the destruction of the intrahepatic bile ducts and therefore ends in liver cirrhosis. Similarly to morphea, PBC is often coupled with autoimmune disorders. However, most of the publications documented the coexistence of PBC and systemic sclerosis but not localized scleroderma.

The serological hallmark of PBC is the presence of antimitochondrial antibodies (AMA). AMAs can be detected in 80-96.5% of patients with PBC. AMA is highly PBC specific, however, the titer does not show correlation with disease activity. The diagnosis PBC can be made if

two of the three following objective criteria are present: (1) AMA positivity, (2) elevated level of serum alkaline phosphatase (ALP) (>1.5 times the upper limit of normal), (3) liver histology characterized by non-suppurative cholangitis and interlobular bile duct destruction.

The development of autoimmune diseases is thought to be the result of the interaction between genetic predisposition and environmental factors. Many predisposing or protecting genes of the major histocompatibility complex (MHC) have been identified in several autoimmune diseases. Possible predisposing alleles both for morphea and PBC have been detected in the HLA DRB1 subgroup. Common predisposing alleles can explain the coexistence of the diseases.

Literature on the quality of life in morphea is limited. Publications employed different tools to determine life quality. Taking into account the former studies, approximately 400 patients with morphea have been investigated for life quality worldwide. This sample size is much lower compared with studies in other dermatological diseases.

Treatment of severe forms of morphea remains a particular challenge. The currently used treatments have a low evidence level and follow different schemes. In Europe, infectious agents such as Borrelia burgdorferi are thought to be possible contributors to the pathogenesis, therefore antibiotics are often employed by dermatologists. Topical steroids are also frequently prescribed, although their efficacy is not proven by well-designed clinical trials. Extensive forms of localized scleroderma are also commonly treated with light therapy. On the other hand,

pediatric rheumatologists prefer immunosuppressive drugs because of the autoimmune origin of the disease. Accordingly, treatment is highly determined by the specialty of the provider. In 2017, the EDF (European Dermatology Forum) published the new S1 guidelines on the sclerosing diseases of the skin. This raises the question of how patients with morphea are treated in Hungary.

In the treatment of morphea, the best available (but low) evidence exists for the use of MTX (methotrexate), systemic steroids and light therapy. However, none of the mentioned treatments are licensed for localized scleroderma. Because of the narrow therapeutic spectrum there is a high need for further drugs in the treatment of severe forms in this disease. CyA (cyclosporine) is a well-known immunosuppressive drug. Only 5 case reports documented its use in morphea. The similar fibrotic process both in localized scleroderma and graft versus host disease makes interesting the use of this drug in morphea.

Aims

Primary aims

1. Prevalence of AMA positivity and PBC in localized scleroderma.
2. Impact of localized scleroderma on life quality.
3. Evaluation of diagnostic and therapeutic decisions of dermatologists in morphea in Hungary
4. Efficacy and safety of CyA in localized scleroderma.

Secondary aims

1. Search for common clinical parameters in AMA positive patients. Identification of possible explanations of the association of PBC and morphea.
2. Investigation of the relationship between DLQI (Dermatology Life Quality Index) and LoSCAT (Localized Scleroderma Cutaneous Assessment Tool). Association between DLQI and age, gender and other parameters (morphea subtype, localization of lesions, duration of the disease, dermatological and autoimmune comorbidities).
3. Discrepancies between the European morphea guidelines and the current practice of patient care in Hungary.
4. Long-term effect of CyA on morphea.

Methods

AMA positivity

Between 2015 and 2017 a prospective monocentric cross-sectional clinical trial was conducted in the Semmelweis University, Department of Dermatology, Venereology and Dermatooncology. Male and female patients with morphea over the age of 18 years were eligible to enter the study. We used the classification criteria of the EDF guidelines. The patients' gender, age, disease onset, current treatments, dermatological and autoimmune comorbidities were documented.

Patient sera were screened for AMAs with an indirect immunofluorescence assay (NOVA Lite® ANA KSL Kit) in the first 91 cases. Fixed mouse kidney stomach and liver sections were used as substrates. Positivity was confirmed with a line immunoassay for AMA M2, Sp 100 and gp210 (IMTEC-Liver-LIA S).

In case of AMA positivity, low resolution genotyping of the HLA DRB1 allele was confirmed by PCR-SSP (polymerase chain reaction by sequence specific primers) and PCCR-SSO (polymerase chain reaction by sequence specific oligonucleotide probes; Labtype, One Lambda). In case of relevant alleles high resolution genotyping was conducted. DNA was extracted from peripheral blood sample.

Quality of life in morphea

Skin-specific health-related quality of life was measured by the Dermatology Life Quality Index (DLQI). Disease activity and damage were applied. The Localized

Scleroderma Cutaneous Assessment Tool (LoSCAT) was applied to evaluate disease activity and damage. DLQI and LoSCAT were determined in all 101 patients entered the study.

The study was approved by the institutional review board of the Semmelweis University (licence No.: 144/2015).

Survey about management of morphea

800 questionnaires were sent out to dermatologists based on the mailing list of the Hungarian Dermatology Society. Treatment-specific questions were the following: local treatment, light therapy, use of systemic antibiotics and systemic immunosuppressive drugs. Investigation-specific questions were the following: use of histology, autoimmune serology, post infectious serology especially for Borrelia, search for foci, judgement of treatment efficacy (severity index, body surface area, patient-reported outcome), factors of treatment choice (severity, results of investigation), occupational data (qualification, number of patients treated per year).

Use of CyA in morphea

Efficacy and safety of CyA was investigated in a retrospective clinical trial based on the patients treated between 2002 and 2014 on the Medical University of Graz, Department of Dermatology and Venereology. This study was approved by the institutional review board of the Medical University of Graz (licence No.: 27-225 ex 14/15).

Patients were classified according to the German guidelines of the AWMF (Arbeitsgemeinschaft der

Wissenschaftlichen Medizinischen Fachgesellschaften). Using patients' documentation and photo documentation, extension of morphea was confirmed by body surface area (BSA). Efficacy of treatment was measured by the reduction of BSA. Extension, shape, number and localization of lesions were documented using digital photographs. Dose, treatment interval, side effects, use of concomitant immunosuppressive drugs, course of disease were registered by using patients' medical history.

Results

AMA positivity, incidence of PBC, clinical characteristics

AMA was confirmed in the first 91 patients. Six (6.6%) patients showed positivity for AMA and 4 (4.39%) had PBC. Female gender, generalized subset, tendency for remission were common in all AMA positive patients. Four of 6 patients showed spontaneous remission of morphea.

Out of 6 AMA positive patients, common predisposing alleles (HLA DRB1*15:01 and HLA DRB1*08) were detectable in 2 patients. One patient had predisposing alleles for both diseases (HLA DRB1*03:01 and HLA DRB1*14). One patient had only a PBC conferring allele. In one patient we have not found any predisposing alleles in the DRB1 subgroup.

Quality of life in morphea

A total of 101 patients (84 female, 17 male) entered the study. The mean age of patients was 56,8±14,8 years.

In the total sample, the median of DLQI was 2. Distribution of the DLQI medians within the subgroups was the following: generalized 4 (mean±SD 4,7±5,0), plaque type 1 (mean±SD 2,8±4,0), deep morphea 8 (mean±SD 8,0±9,9). Two patients presenting with en coup de sabre had 0 points on the DLQI. One patient with eosinophilic fasciitis had a DLQI score of 5, one with

disabling pansclerotic morphea had 11, and yet another with mixed morphea had 15.

More than half of the patients (53%) answered to feel at least a little embarrassed due to their skin disease. Overall, 46% of them reported at least minor symptoms (sensitive, itching or painful skin). Similarly, 43% of patients reported problems with clothing. One third (35%) of patients stated that their social activities were affected to some extent. Difficulties in interpersonal relationships were reported by 24%.

Female patients demonstrated significantly higher DLQI scores compared to male patients (p=0,047). Patients with generalized subtype presented significantly worse DLQI scores compared to other subtypes (p=0,031). One-point increase in PGA-A score was associated with a 0.043 point increase in the DLQI score. Involvement of hands and feet had a significant negative impact on DLQI (p=0,044). Patients treated by systemic therapy had lower DLQI scores compared with those receiving other treatments (p<0.001).

Survey on the management of morphea

101 questionnaires were eligible for the study. Local steroids are used by 87.12% of dermatologists. Systemic antibiotics are frequently employed. One third (32.67%) of dermatologists prescribe penicillin, 22.77% recommend doxycycline for the treatment of morphea. MTX is used only in 6.93%. Borrelia serology is obtained by 80.19% respondents. Search for autoantibodies was recommended by 53,46%of physicians.

Cyclosporine in morphea

Twelve patients (7 male, 5 female) were enrolled in the study. Mean age of patients was 52.66 years (10–72, median 61.50). The mean duration of morphea was 10.72 years (6–16, median 10). The distribution of the subtypes was the following: generalized (n=9, 75%), linear morphea of the extremities (n=2, 16.66%), Parry-Romberg syndrome (n=1, 8.33%).

Five of 12 patients (41.66%) showed partial and 6 (50%) showed complete remission at the end of treatment. One patient with Parry-Romberg syndrome did not respond to treatment with CyA. The affected average BSA fell from 50% (2-80, median 65) to 17% (0-40, median 18). Patients responded to the treatment in a short time (1-2 months). The duration of the treatment ranged from 9 to 46 months (mean 18.66, median 14). The dose of CyA varied from 1.2 to 3.0mg/kg (mean 2.40, median 2.50). CyA was combined with systemic steroids in 3 cases.

Two patients experienced recurrence after treatment. In one patient disseminated lichen sclerosus et atrophicus occurred during treatment. Four patients came to long-term remission. CyA was resumed because of disease activity. Contractures in different extension persisted in some patients.

Side effects occurred in half of the cases in form of elevated blood pressure (n=3), transaminase elevation(n=2), weight gain (n=2), creatinine elevation (n=1), hypercholesterinaemia (n=1) and muscle cramps (n=1).

Conclusions

PBC occurs in morphea more frequently than in the general population. Typically, elderly female patients with generalized morphea are affected, spontaneous remission is common. We recommend AMA screening in elderly female patients with generalized morphea before the initiation of MTX to exclude concomitant PBC.

Morphea has a moderate impact on life quality, however, active stage and generalized subtype are coupled with poor life quality. Involvement of functionally sensitive area (hands and feet) needs more intensive treatment. It should be mentioned that many patients with morphea report also subjective symptoms.

Most of the Hungarian dermatologists do not follow the current guidelines in the treatment and management of morphea. We recommend a more intensive medical education in this field. Furthermore, the treatment of patients with severe morphea would be reasonable in specialized experienced university departments.

CyA could be a possible agent among the poor therapeutic regimen of localized scleroderma. Morphea shows a slow response with classical treatments, CyA leads to rapid amelioration. Due to the retrospective design our results should be carefully interpreted. Further prospective randomized double-blind clinical trials could help to find the correct position of CyA in the treatment of morphea.

Literature

Publications related to this work

Bali G, Fruhauf J, Wutte N, Aberer E. (2016) Cyclosporine Reduces Sclerosis in Morphea: A Retrospective Study in 12 Patients and a Literature Review. Dermatology, 232(4): p. 503-510. (IF 1.598)

2. Knobler R, Moinzadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, Cutolo M, Rongioletti F, Denton CP, Rudnicka L, Frasin LA, Smith V, Gabrielli A, Aberer E, Bagot M, **Bali G**, Bouaziz J, Braae Olesen A, Foeldvari I, Frances C, Jalili A, Just U, Kahari V, Karpati S, Kofoed K, Krasowska D, Olszewska M, Orteu C, Panelius J, Parodi A, Petit A, Quaglino P, Ranki A, Sanchez Schmidt JM, Seneschal J, Skrok A, Sticherling M, Sunderkotter C, Taieb A, Tanew A, Wolf P, Worm M, Wutte NJ, Krieg T. (2017) European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: localized scleroderma, systemic sclerosis and overlap syndromes. J Eur Acad Dermatol Venereol, 31(9): p. 1401-1424.
3. Knobler R, Moinzadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, Cutolo M, Rongioletti F, Denton CP, Rudnicka L, Frasin LA, Smith V, Gabrielli A, Aberer E, Bagot M, **Bali G**, Bouaziz J, Braae Olesen A, Foeldvari I, Frances C, Jalili A, Just U, Kahari V, Karpati S, Kofoed K, Krasowska D, Olszewska M, Orteu C, Panelius J, Parodi A, Petit A, Quaglino P, Ranki A, Sanchez Schmidt

JM, Seneschal J, Skrok A, Sticherling M, Sunderkotter C, Taieb A, Tanew A, Wolf P, Worm M, Wutte NJ, Krieg T. (2017) European dermatology forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 2: Scleromyxedema, scleredema and nephrogenic systemic fibrosis. J Eur Acad Dermatol Venereol. 31(10): p. 1581-1594.

4. **Bali G**, Hidvegi B. (2018) Diagnostic and Treatment Strategies of Dermatologists for Treating Morphea in Hungary. Acta Dermatovenerol Croat, 26(1): p. 21-24. (IF 1.054)
5. **Bali G**, Szilvasi A, Inotai D, Varga A, Sardy M, Karpati S, Medvecz M, Szegedi A, Hidvegi B. (2018) Comorbidity of localized scleroderma and primary biliary cholangitis. J Dtsch Dermatol Ges, 16(11): p. 1323-1327. (IF 2.743)
6. **Bali G**, Karpati S, Sardy M, Brodszky V, Hidvegi B, Rencz F. (2018) Association between quality of life and clinical characteristics in patients with morphea. Qual Life Res. doi: 10.1007/s11136-018-1897-1 (IF 2.392)

Independent publications

1. **Bali G**, Aberer E. (2003) [Iloprost therapy in systemic sclerosis]. Hautarzt, 54(9): p. 845-851.
2. Sunderkotter C, Herrgott I, Bruckner C, Moinzadeh P, Pfeiffer C, Gerss J, Hunzelmann N, Bohm M, Krieg T, Muller-Ladner U, Genth E, Schulze-Lohoff E, Meurer M, Melchers I, Riemekasten G, Worm M, Klaus P, Rubbert A, Steinbrink K, Grundt B, Mierau R, Hein R,

Hinrichs R, Szeimies RM, Karrer S, Muller AM, Meyering R, Seitz C, Schmidt E, Lehmann P, Foeldvari I, Reichenberger F, Gross L, Kuhn A, Haust M, Reich K, Becker M, Saar P, Schmeiser T, Fierlbeck G, Kotter I, Lorenz HM, Blank N, Grafenstein K, Juche A, Aberer E, **Bali G**, Fiehn C, Stadler R, Bartels V, Buslau M, Distler J, Sticherling M. (2009) Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol, 160(4): p. 835-843. (IF 4.26)

3. Hanitsch LG, Burmester GR, Witt C, Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, Muller-Ladner U, Schulze-Lohoff E, Becker M, Sunderkoetter C, Worm M, Klaus P, Rubbert A, Steinbrink K, Grundt B, Hein R, Scharffetter-Kochanek K, Hinrichs R, Walker K, Szeimies RM, Karrer S, Müller A, Seitz C, Schmidt E, Lehmann P, Foeldvári I, Reichenberger F, Gross L, Kuhn A, Haust M, Reich K, Böhm M, Saar P, Fierlbeck G, Kötter I, Lorenz HM, Blank N, Gräfenstein K, Juche A, Aberer E, **Bali G**, Fiehn C, Stadler R, Bartels V, Buslau M, Distler J, Sticherling M., Riemekasten G. (2009) Skin sclerosis is only of limited value to identify SSc patients with severe manifestations--an analysis of a distinct patient subgroup of the German Systemic Sclerosis Network (DNSS) Register. Rheumatology (Oxford), 48(1): p. 70-73. (IF 4.236)

4. Hunzelmann N, Genth E, Krieg T, Lehmacher W, Melchers I, Meurer M, Moinzadeh P, Muller-

Ladner U, Pfeiffer C, Riemekasten G, Schulze-Lohoff E, Sunderkoetter C, Weber M, Worm M, Klaus P, Rubbert A, Steinbrink K, Grundt B, Hein R, Scharffetter-Kochanek K, Hinrichs R, Walker K, Szeimies RM, Karrer S, Muller A, Seitz C, Schmidt E, Lehmann P, Foeldvari I, Reichenberger F, Gross WL, Kuhn A, Haust M, Reich K, Bohm M, Saar P, Fierlbeck G, Kotter I, Lorenz HM, Blank N, Grafenstein K, Juche A, Aberer E, **Bali G**, Fiehn C, Stadler R, Bartels V, Registry of the German Network for Systemic S. (2008) The registry of the German Network for Systemic Scleroderma: frequency of disease subsets and patterns of organ involvement. Rheumatology (Oxford), 47(8): p. 1185-1192. (IF 4.136)

5. Gyulai R, Gaál M, Tabák R, **Bali G**, Kui R. (2009) Citokinek, kemokinek és terápiás befolyásolásuk lehetőségei psoriasisban. Bőrgyógyászati és Venerológiai Szemle. 85(2): p. 37-41.

6. **Bali G**, Gyulai R, Kemény L. (2009) Betesil tapasz használata psoriasis vulgarisban. Magyar Orvos, 7-8(1): p. 38-40.

7. **Bali G**, Schwantzer G, Aberer F, Kraenke B, Aberer E. (2011) Discontinuing long-term Iloprost treatment for Raynaud's Phenomenon and systemic sclerosis: a single-center, randomized, placebo-controlled, double-blind study. Acta Dermatovenerol Alp Pannonica Adriat, 20(1): p. 13-21.