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Original Article

Plasma exchange in progressive systemic sclerosis

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Abstract. Systemic sclerosis (SSc) is an autoimmune systemic disease of unknown etiology. Present treatment modalities have limited impact on clinical/ laboratory outcomes. For the first time in our center, we used plasma exchange (PEx) in a rather young woman with recent onset but progressive SSc. She is a 39-year-old woman with a recent history of skin stiffness, Raynaud's phenomenon, nail fold capillary changes and newly diagnosis of SSc presented to us due to worsening her clinical symptoms even after initiation of routine remedies such as low dose oral prednisolone, Ca-channel blockers, azathioprine and pentoxyfylline. After obtaining written consent, interdisciplinary discussion with experts in this field and agreement we started a series of plasma exchange with FFP replacement for her. A dramatic clinical response was observed in respect to Raynaud's phenomenon, skin stiffness, tendon rub after three sessions of PEx. Her modified Rodnan skin score *(*MRSS*)* dropped from 36 (before commencement of therapy) to 28 in day 4 and 18 in day 20 after 15 sessions of PEx. In conclusion PEx could significantly modify the course of SSc as observed in our case study. Elimination of culprit immune mediators/cytokines/autoantibodies could be the possible mechanism of action of PEx.

Keywords: Systemic sclerosis, plasma exchange, therapy, plasmapheresis, treatment

Introduction

Systemic sclerosis (SSc) is one of the most devastating and chronic rheumatic diseases with disappointing results despite explosive discoveries of new treatment options in recent era.

Progressive organ fibrosis and obliterative vasculopathy are two major pillars of SSc pathophysiology. Skin, lungs and kidneys are the major organs involved in the process of SSc. But other organs like gastrointestinal and conductive system of heart may also be damaged during disease pathology [1].

SSc usually attacks young women of reproductive age with many physical, social and emotional consequences. Besides, current therapies are of very limited value in acceptable control or quenching disease. Actually most of observed dramatic improvements in SSc could be due to spontaneous regression rather than therapeutic intervention per se.

Innate and adaptive immunity also cellular and humoral mediators are involved in the pathogenesis of SSc resulting auto-antibody formation and cell-medicated tissue injury [2]. Genetic susceptibility along with environmental factors is shown to be important [3]. Circulatory autoantibodies or immune mediators which are more than simple epiphenomena are shown to play an effective role in disease activity in SSc [4]. Some antibodies are associated with specific organ involvement and others like autoantibodies against angiotensin II receptor and anti-endothelin1 receptor are associated with more severe disease [5, 6]. Other kinds of autoantibodies such as anti-RNA polymerase III antibody are associated with underlying malignancies [7].

Current pharmacologic therapies are based on immunomodulation, vasodilators, anti-platelet agents. Tyrosine kinase inhibitors (imatinib) are rather new agents used in SSc in order to regulate growth, differentiation and apoptosis of aberrant cell function. Considering the abundant circulatory factors (known and unknown) in sera of patients with SSc, inhibiting acting mediators could be a solution for systemic sclerosis. This could be achieved by using intravenous immunoglobulin (IvIG) to neutralize autoantibodies. We hypothesized that removing these culprit soluble mediators besides autoantibodies could be more efficacious than common strategies in immunomodulations. So here we report for the first time in our center and country a woman successfully treated with plasma exchange.

Case study

We report a 39-year-old woman with skin stiffness, Raynaud's phenomenon, nail fold capillary abnormalities for about 6 months before newly diagnosed with SSc referred to us due to worsening her clinical symptoms even after initiation of routine remedies such as low dose oral

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Fig. 1 Plasma exchange in the present patient.

prednisolone, calcium-channel blockers, azathioprine and pentoxyfylline. She had not significant positive medical history neither she nor her immediate family. Physical examination revealed blood pressure of 145/85 mmHg and otherwise normal vitals. She had puffy and shiny face with some erythema, tethered and reduced oral aperture, pale and cold hand and foot digits with marked nail fold capillary abnormalities on both fingers and toes. Tendon rub was audible in her right ankle movement. Her echocardiographic study showed normal EF with normal pulmonary artery pressure. Her chest X-ray was normal. HRCT revealed dilated esophagus with prominent interalveolar septa. Laboratory investigations showed negative RF, CRP= 26.2 mg/dl (reference range (RR) <6), ANA (Elisa) = 5.8 (RR <1.2), negative anti-ds DNA, negative anti-CCP, normal hemoglobin, ESR and urine analysis.

After full explanation of our plan to initiate plasma exchange, possible unwanted events for getting vascular access, and PEx per se, she was hospitalized on 25 May 2015. Baseline Modified Rodnan Skin Score (MRSS) was 36. Daily PEx with 2 liters fresh frozen plasma replacement was instituted after getting a jugular venous access (Fig. 1). She tolerated PEx well and unexpectedly her MRSS dropped to 28 in day 4 and to 18 in day 20 after 15 sessions of PEx. Overall clinical problems improved after first sessions of PEx of them Raynaud's phenomenon and digital ischemia was more rapid and prominent. We are planning to repeat PEx every six months according to the ongoing nature of such rheumatic diseases.

Discussion

SSc is one of the most complex autoimmune disorders of unknown etiology. So, all therapeutic studies tried to find a way to combat the disease based on disease features and complications. Hitherto, 77 accomplished clinical trials are registered on ClinicalTrials.gov. Most of the studies are focused on specific organ involvement in SSc. This shows that SSc is a multi-facet and subtle disease that is shown to be not amenable to a single holistic treatment. Before new biologic agents, the only two most poorly controlled rheumatic conditions were "ankylosing spondylitis" and "systemic sclerosis". However after history-making achievements in biologicals, meaning TNF blockers, actually the last condition that seems not to be amenable to classic treatments is systemic sclerosis.

However, these new agents namely TNF blockers and B-cell depletion therapy have minimal evidence to support their clinical use in SSc. Thus any novel ideas other than conventional or new drugs may be a solution. It looks that in some instances, old weapon, meaning PEx, could fight old and complex diseases such as SSc more powerfully that the new ones. The superiority of PEx to other therapies in immunologic and rheumatic diseases is to "eliminate" rather than "neutralize" wandering obnoxious agents or particles. Because these neutralized pathogenic factors or immune complexes could still remain pathogen and make a potentially "new pathogen" itself. In most instances, IvIG and PEx are "liquid friends" and can be used interchangeably or even in combination in several clinical settings [8].

Both PEx and IvIG are costly and carry potential disadvantages. Several studies worked on IvIG on SSc with different results [9, 19]. However future results are needed to compare short term along with long term results. McCune was one of the first clinicians who used PEx in SSc as an off-label treatment and published his results in 1983 [11]. He believed that Subjective improvement ensued after PEx in respect to Raynaud's phenomenon and digital ulcer. There are less than 20 published articles dealing with PEx in classic features other than standard indications of PEx in SSc since then. The most number of patients studied in a single report belongs to Guillevin in 1990 by 40 cases [12]. He concluded that PEx has limited and short term results. However, we emphasize, this is fully expected that a chronic, complex and progressive disease like SSc needs a sustainable or sequential suppressive therapy and not a single course of treatment like what happens in thrombotic thrombocytopenic purpura as a standard indication for PEx. As our study showed, some other reports also showed early response of Raynaud's phenomenon to PEx within 3-4 days [13].

Guillevin et al. [12] state poor wound healing from vanous access is a problem in SSc patients, nevertheless, we propose that the best candidates of PEx are new cases of SSc who yet are in initial (edematous stage) phase of disease and not in late stages when irreversible skin stiffness has emerged. However, dramatic response of Raynaud's phenomenon and ischemic digits to PEx makes it a potentially powerful tool against refractory vasospastic, digital ischemia and ulcers.

In conclusion, PEx could significantly modify the course of SSc as observed in our case. Elimination of culprit immune mediators/cytokines/autoantibodies could be the possible mechanism of action of PEx.

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Conflict of interest

The author declares no conflicts of interest.

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