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Immunological Characteristics of The Useful Biomarker Siglec-1 For the Differential Diagnosis of Systemic Scleroderma

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Annotation: Systemic scleroderma (SS) is a clinically heterogeneous disease that involves increased production of type I interferons (IFN). The purpose of this study was to study the IFN-regulated sialic acid binding protein Lactic 1 (SIGLEC-1) in CC. The expression levels of SIGLEC-1 on the monocytes of 203 patients with CC were determined in a transverse and longitudinal analysis compared with 119 patients with other rheumatic diseases and 13 healthy patients. In the examined patients with CC, the expression of SIGLEC-1 on monocytes was higher (2097.94 = 2134.39) than in the control group (1167.45 = 380.93; p = 0.49). Thus, the study of the SIGLEC-1 level is suitable for the differential diagnosis of SS from other rheumatologically diseases.

Keywords: Systemic scleroderma; SIGLEC-1; biomarker; interferon; treatment; cytokines.

1. Introduction

Systemic scleroderma (SS) is a rare connective tissue disease characterized by a triad of microangiopathy, fibrous complications and immunological disorders, including both innate and adaptive immunity [1-5]. One of the autoimmune phenomena is the production of characteristic and various serum autoantibodies found in most patients, as well as the presence of inflammatory cells with a noticeable type I interferon (IFN) signature in circulating and infiltrating immune cells [4-13]. Activation of the type I IFN pathway is present in several rheumatic diseases, including systemic lupus erythematosus (SLE), primary Sjogren's syndrome (PSS), rheumatoid arthritis (RA) and others. It is known that sialic acid binding Ig like lectin 1 (SIGLEC-1), an IFN-induced adhesion molecule on monocytes [14], is one of the most prominent IFN-regulated type I genes, it has so far been the most promising marker. In PSH, SIGLEC-1 expression on peripheral blood monocytes may characterize patients with extra glandular lesion and high disease activity [15]. For myositis, SIGLEC-1 has been found to be a candidate biomarker for evaluating type I IFN activity. It has proved useful for monitoring disease activity and response to treatment in juvenile and adult dermatomycosis's [16,17]. In addition, SIGLEC-1 has been shown to be elevated in RA [18], autoimmune thyroiditis [19] and primary biliary cholangitis (PHC).
The most extensive data on the reliability of SIGLEC-1 as a biomarker of disease activity still exist for SLE [21]. Biased et al. We were able to show that the frequency of SIGLEC-1-producing monocytes correlates with disease activity and inversely correlates with levels of complement factors. At the same time, treatment with glucocorticoids led to a decrease in the expression of SIGLEC-1 in the cells of adult patients with active SLE [22]. There is little data for CC, but there are data from the authors York M.R. and co-authors, IFN can induce the expression of SIGLEC-1 in monocytes in CC. In addition, a link was found for IFNa and interferon-induced protein-10 (IP-10) in the sera of patients with heart disease with CC. However, York M.R. and co-authors [10] previously could not demonstrate any differences in relation to skin lesions or organ complications in patients with CC for the expression of SIGLEC-1 on monocytes or soluble SIGLEC-1 in the patient's serum, respectively [13,26].
An additional complication in CC is that activity estimates are poorly validated or can only be applied to specific subgroups. Accordingly, it was difficult to find the appropriate biomarkers. Ideally, biomarkers that indicate

general disease activity or specific organ manifestations or that predict a therapeutic response will also be widely used in clinical practice.
The purpose of this study was to evaluate the effect of SIGLEC-1 expression on CD14+ cells using flow cytometry, serving as a useful biomarker for the manifestation of the disease, including pulmonary or vascular complications, as well as the therapeutic response in CC.

2. Materials and Methods

For the study, patients and a control group were recruited in the Department of cardio rheumatology of the central hospital of the City Medical Association (CB GMO) of the city of Samarkand, as well as in the department of first therapy of the multidisciplinary clinic No. 1 of the Samarkand State Medical University (SamSMU). Patients with the following rheumatological diseases were included for the study: SS, SLE, PSH, mixed connective tissue disease (MHSD), idiopathic inflammatory myositis (IVM), undifferentiated connective tissue dysplasia (NDST), RA, as well as the control group (KG).
The diagnostic and classification criteria of ACR/EULAR 2013 for CC [37], the classification criteria of EULAR/ACR 2019 for SLE [42] and the classification criteria of ACR-EULAR 2016 for PSH [49] were used. MHSD was diagnosed in accordance with Alarcon-Segovia and co-authors. [50], 2017 EULAR/ACR for IVM [44] and 2010 ACR/EULAR criteria for RA [40]. Demographic, clinical and serological data were collected in accordance with the standards of the study. The inclusion criteria for patients with SS were skin changes, the time of onset of symptoms of SS together with Raynaud's syndrome, the time of onset of symptoms of SSD unrelated to Raynaud's syndrome, the duration of the disease, changes in other organs, as well as the effectiveness of immunosuppressive therapy, during blood sampling. The exclusion criteria were a history of smoking, gastric ulcers, calcification, hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction, angina pectoris, stroke, transient ischemic attack (TIA), peripheral arterial disease (PZA), interstitial lung disease (ILE), scleroderma renal crisis (PCOS), heart damage and myositis.
Laboratory tests (C-reactive protein [CRP], neutrophil count, hemoglobin and tumor necrosis factor-α [α-TNF]) were determined from peripheral blood during clinical procedures.
To determine SIGLEC-1 on CD14 monocytes, EDTA-anticoagulated whole blood was incubated with a 10 ml cocktail of mouse-anti-human antibody containing phycoerythrin-labeled (PE) anti-CD169 monoclonal antibody (mAb) (labeled with a fluorochrome/protein 1 ratio:1) labeled with alloficocyanin (APC) anti-CD14 mAb and Krome Orange-labeled anti-CD45 mAb (all antibodies from Beckman Coulter, Krefeld, Germany). It was determined that the reference range of SIGLEC-1 expression in healthy controls is less than 2,400 SIGLEC1 molecules/monocytes. SIGLEC-1 expression was evaluated using flow cytometry with a detection limit of 1200 molecules/monocytes. Values below the detection limit (LOD) are shown as follows LOD/√2.

3. Results and Discussions

203 patients with SS, 32 with SLE, 16 with PSH, 8 with MHSD, 26 with IVM, 14 with NDST, 23 with RA and 13 KG were examined. Our cohort of SS represented a distorted proportion between women and men (84%/16%), as well as the proportions of patients with limited or diffuse skin CC and age profile (46.67±14.80 years at the time of diagnosis) [28]. A total of 115 patients with SSD (56.7%) received immunosuppression, while 88 patients with SSD were without immunosuppressive therapy. In addition, 28.9% of patients with SSD receiving immunosuppressive therapy received hydroxychloroquine (in combination or separately). Comprehensive laboratory results were available for 97% of all patients with SSD, pulmonary function test results were available for 83% and echocardiography results for 60%.
As expected, patients with SLE were slightly younger, and patients with PSH were slightly older, which corresponds to the expected age at the onset of the disease for these conditions. Similarly, the duration of the disease in patients with NDT is short, since many of them will later develop a distinct connective tissue disease (Table 1).

Table 1. Clinical and serological characteristics of patients with SSD

	All patients c CCD (n=203)	**Negative SIGLEC-1 indicator (n=158)**	**Positive SIGLEC-1 indicator (n=45)**	**Level *p***
The skin subgroup - n (%)				
Generalized (GSSSD)	64 (31.5)	47 (29.7)	17 (37.8)	0.306
Focal (OCHSSD)	122 (60.1)	99 (62.7)	23 (51.1)	0.163

Without skin damage (SSDBpC)	17 (8.4)	12 (7.6)	5 (11.1)	0.453
Immunological parameters				
Antinuclear antibodies (ANA)	186 (94.4)	147 (93.0)	39 (86.7)	0.825
Anticentromeric antibodies (ACA)	71 (35.0)	58 (36.7)	13 (18.3)	0.332
Antibodies to topoisomerase I (TO-1)	76 (37.4)	58 (36.7)	18 (28.9)	0.687
Antibodies to RNA polymerase III (RP 3)	16 (7.9)	11 (7.0)	5 (11.1)	0.339
Internal organ damage in SSD, n (%)				
Raynaud's syndrome	181 (89,2)	144 (91,1)	37 (82,2)	0,090
IZL	91 (44.8)	70 (44.3)	21 (46.7)	0.779
LAG	19 (9.4)	15 (9.5)	4 (8.9)	0.902
Dysphagia	97 (47.8)	76 (48.1)	21 (46.7)	0.865
CVD	12 (5.9)	7 (4.4)	5 (11.1)	0.094
SEC	8 (3.9)	5 (3.2)	3 (6.7)	0.287
Myositis	10 (4.9)	8 (5.1)	2 (4.4)	0.866
Laboratory indicators				
SRB	4.36 ± 9.70	4.00 ± 9.72	5.78 ± 9.60	0.279
Hb	88.10 ± 1.62	88.10 ± 1.62	89.15 ± 166	0.815
Neutrophils	5.54 ± 2.63	5.66 ± 2.67	5.15 ± 2.46	0.275
Cardiopulmonary parameters				
FZHEL—%/ozhd	89.27 ± 20.16	91.34 ± 20.10	81.40 ± 18.70	0.007
OFV1—	86.30 ± 20.78	87.20 ± 21.53	83.00 ± 17.66	0.283
%/ojd	57.29 ± 18.91	58.29 ± 19.49	53.49 ± 16.19	0.195
DLCO —%/ojd	62.27 ± 9.63	63.03 ± 9.08	59.44 ± 11.22	0.098

CRP - C is a reactive protein; DLCO is the diffusion capacity of carbon monoxide; OFV1 is the volume of forced exhalation per second; FVC is the forced vital capacity; Hb is hemoglobin; IZL is interstitial lung disease; LVL is the ejection fraction of the left ventricle; n is the number; LAG is pulmonary arterial hypertension; SPC is a sclerodermic renal crisis; %/ojd-the expected percentage.

Comparing SIGLEC-1 expression on CD14+ monocytes in the peripheral blood of patients with CVD with KG, almost half of patients with CVD (47.8%) had SIGLEC-1 monocyte expression, which barely exceeded the level at KG. Statistically, the expression of SIGLEC-1 (molecules/monocytes) was not significantly increased in patients with SSD compared to KG (2097.94 ± 2134.39 vs. 1167.45 ± 380.93, p = 0.49;

Compared with other connective tissue diseases (CST), SIGLEC-1 expression was highest in SLE (8761.66±8325.74), followed by NDST (6414.50±1846.55) and PSH (4371.69±4227.89).

Patients with RA (1425.22±1312.69) and NDST (1826.00±1051.36) showed no increased expression of SIGLEC-1 compared with KG (1167.45±380.93).

When analyzing the comparison of SIGLEC-1 expression in patients with, in accordance with various clinical manifestations of internal organs of SSD, patients with positive SIGLEC-1 levels had a significant violation of the VVC (81.39±18.67 vs. 91.34±20.09; p = 0.007); however, no differences were found in the prevalence of ISL (46.7% vs. 44.3%; p = 0.779), and there was no difference in the absolute expression of SIGLEC-1 between patients with and without ISL (2068.89±1963.12 vs. 2129.13±2266.90; p = 0.427).

When analyzing various manifestations of SSD in accordance with the positive level of SIGLEC-1, it can be detected in 23/122 (18.9%) patients with HSSD; 17/64 (25.0%) patients with HSSD; 21/91 (19.8%) patients with ISL; 4/19 (21.1%) patients with PAH; 26/111 (22.5%) patients with vascular complications, including PAH, dysphagia and PCOS, 21/97 (20.6%); and 2/10 (20.0%) patients with myositis (Table 1). Patients with positive SILGEC-1 levels tended to have a higher prevalence of heart disease (11.1% vs. 4.4%; p = 0.094) and a reduced left ventricular ejection fraction (LVEF) (59.44 ± 11.22 vs. 63.03 ± 9.08; p = 0.098).

In our studies, specific autoantibodies in SSD showed that SSD patients with a positive RP3 index tended to increase SIGLEC-1 expression compared with other patients (3376.94±3821.81 vs. 1984.86 ± 1899.83, p = 0.136) (Table 1).
Interestingly, this group showed a significantly higher score on the modified Rodnan skin induration Assessment Scale (mSCIC) compared with other patients with SSD (13.38 ± 8.35 vs. 5.86 ± 6.70, p = 0.003).
SIGLEC-1 expression was significantly increased in patients with SLE and MHD in combination with SSD (8761.66±8325.74 vs. 2097.94±2134.39; p<0.0001 and 6414.50±1846.55 vs. 2097.94±2134.39; p = 0.0003).
Over the past few decades, more and more information has appeared indicating the activation of type I interferon and their pathways in the pathogenesis of SSD [5,29-32]. In particular, SIGLEC-1 has been shown to be activated both on monocytes in SSD and on tissue macrophages [10,22]. In our study, positive expression of SIGELC-1 was associated with reduced VVC; however, we did not observe an association with ISL. In addition, patients with positive SIGELC-1 tended to have a higher prevalence of heart disease along with a decrease in LVEF.
Evaluating the use of SIGLEC-1 as a marker of response to therapy, we found that the expression of SIGLEC-1 is largely independent of changes in immunosuppression in patients with SSD. This contrasts with previous data in SLE, where the effect of immunosuppressive therapy on SIGLEC-1 expression can be seen [15,22]. We did not see any differences in SIGLEC-1 levels between patients receiving immunosuppressive treatment and patients who did not, including patients receiving hydroxychloroquine. In fact, hydroxychloroquine blocks Toll-like receptors (TLR) 7 and 9 and has been shown to inhibit the production of type I IFN in SLE [34]. In our cohort, SIGLEC-1 expression remained largely constant over time in patients with SSD, even with an increase or decrease in immunosuppressive therapy, including hydroxychloroquine or other drugs such as glucocorticoids, methotrexate and rituximab, which are known to reduce the production of type I IFN.
Another potential role for SIGLEC-1 expression on monocytes is to facilitate differential diagnoses. There is the fact that patients with SLE or MHST showed significantly elevated levels of SIGLEC-1 compared to patients with SSD, which can be used in combination with clinical signs, as well as the autoantibody profile, to conduct an early differential diagnosis. The key results of our study are that the expression of SIGLEC-1 on monocytes is slightly, but slightly, increased compared to healthy controls. SIGLEC-1 expression may be valuable for differentiating SSDs from MHST and SLE.

4. Conclusion

Thus, in a large cohort, we demonstrated that patients with CVD showed slightly increased SIGLEC-1 expression on monocytes compared to healthy controls, but SIGLEC-1 expression was much lower compared to other CTFs such as SLE and MZST. SIGLEC-1 expression levels remained largely constant during disease progression and were not significantly affected by changes in therapy. However, we have found that SIGLEC-1 is valuable for early differential diagnosis of SDS and may be useful for differential diagnosis of SDS from SLE and MZST.

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