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Review

Serum free light chains of immunoglobulins as biomarkers for systemic sclerosis characteristics, activity and severity

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ABSTRACT

Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease. Humoral immunity and B cells are thought to play an important role in the pathophysiology of the disease. B cells are activated, produce specific autoantibodies and profibrotic cytokines. One way to assess B cell activation is to measure serum free light chains of immunoglobulins (sFLC) levels. We assess here sFLC levels in patients with systemic sclerosis (SSc) and their correlation with the disease characteristics, activity and severity. One hundred and thirty-four SSc patients were prospectively enrolled and compared to 401 age- and sex-matched healthy controls. sFLC levels were measured by a new quantitative immunoassay. sFLC levels were significantly higher in SSc patients than in healthy controls. sFLC levels correlated with modified Rodnan skin score and were independently associated with the presence of interstitial lung disease and its severity. In univariate analysis, sFLC levels correlated with SSc activity, as measured by the European Scleroderma Study Group activity index, and severity, as measured by the Medsger's total severity score. In multivariate analysis, beta2-microglobulin levels correlated with disease activity, BAFF levels with severity and sFLC with neither of these. Other B-cell activation biomarkers (IgG, IgA, beta2-microglobulin and BAFF) were independently correlated with sFLC. sFLC levels are elevated in SSc and are independently associated with lung disease and its severity. B-cell activation biomarkers, including sFLC, beta2-microglobulin and BAFF, correlate with disease severity and activity. These results further support the role of B cell activation in the pathophysiology of SSc.

Contents

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1. Introduction

Systemic sclerosis (SSc) is a chronic connective tissue disorder characterized by vascular involvement, fibrosis and autoimmunity [1,2]. The clinical heterogeneity of SSc is a major issue to identify and validate robust biomarkers for disease severity and activity, which are crucial to optimize the management of this disease [3,4]. The majority of these biomarkers are collagenous or non-collagenous extracellular matrix constituents [5,6]. Besides cellular immunity abnormalities [7], humoral immunity is increasingly thought to play a significant role in the pathophysiology of this disease [8–13]. Hypergammaglobulinemia is associated with a more severe disease with pulmonary involvement [14,15]. SSc patients have abnormal blood B-cell compartments with an expansion of naive B cells and activated memory B cells [16]. B cells can secrete proinflammatory and/or profibrotic cytokines such as IL-6 and TGF-β leading to collagen secretion by fibroblasts [17]. B-cell activating factor (BAFF) is crucial for B-cell survival [18] and is elevated both in serum and skin of SSc patients and correlates with the skin score [19]. Finally, anti-CD20 treatment has yielded promising results in patients with severe SSc with or without interstitial lung disease (ILD) [20–23]. Taken together, these data suggest that B cells and their activation are likely to play an important role in SSc pathophysiology.

B-cell activation is associated with an exaggerated polyclonal synthesis of immunoglobulins. Immunoglobulin light chains and heavy chains are combined together during this synthesis. However, free light chains are physiologically produced in excess to heavy chains [24] and are released into the serum, from which they are rapidly excreted by the kidneys with a half-life of 2–6 h. A new automated latex-enhanced single turbidimetric assay for simultaneous measurement of both kappa and lambda free light chains is now available to readily measure both kappa and lambda serum free light chain of immunoglobulins (sFLC) levels [25]. sFLC are mainly used in monitoring plasma-cell dyscrasia [26]. However, a growing body of studies suggests that sFLC could be useful biomarkers in several immunopathological conditions by reflecting B-cell polyclonal activation. As an example, sFLC levels are elevated in lupus [27], rheumatoid arthritis and Sjögren syndrome [28,29] and are associated with the disease activity.

To our knowledge, no study has yet focused on sFLC in SSc. We designed the following prospective and controlled study to address the role of sFLC as a biomarker for disease activity and severity in SSc.

2. Methods

2.1. Patients

All consecutive patients with SSc followed in the scleroderma outpatient clinic of Lille University Hospital were prospectively included between October 2012 and October 2013 if they fulfilled the following inclusion criteria: (1) age over 18 years; (2) American College of Rheumatology (ACR) criteria for SSc [30] and/or the LeRoy's classification system (limited cutaneous or diffuse cutaneous SSc) [31]. There were no exclusion criteria. Sex- and age-matched healthy blood donors served as controls with 3 healthy controls (HC) for 1 SSc patient.

Prospective assessment at the time of blood sample collection for SSc patients gathered data on age, weight, the presence of digital ulcers, gastro-esophageal reflux disease (GERD), New York Heart Association (NYHA) functional class and distance on a non-encouraged 6-minute walk test (6MWD). Modified Rodnan skin score (mRSS) was measured in all patients. All patients underwent pulmonary functional tests. Forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) were expressed as percentages of the predicted values. Muscle involvement was diagnosed if there was muscle weakness associated with raised creatine phosphokinase (CPK) level and electromyographic, muscle MRI or muscle biopsy abnormalities [32,33]. Joint involvement was defined by either synovitis or inflammatory arthralgia. Disease duration was measured from: onset of Raynaud's phenomenon (RP), onset of first non-RP symptom and diagnosis of SSc.

We collected from the patients' medical records: history of renal crisis, presence of ILD on high-resolution CT scan of the chest and presence of pulmonary arterial hypertension (PAH) diagnosed on right heart catheterization.

At the time of blood sample collection, we also prospectively assessed disease activity scored using the European Scleroderma Study Group activity index (EScSG-AI) [34]. The severity of organ involvement was evaluated using Medsger's severity scale for each organ as well as a total Medsger's severity score summing each scale for a maximum score of 36 [35]. Physician global assessment (PGA) was measured on a visual scale ranging from 0 mm (no active disease) to 100 mm (highly active disease). Disability was assessed by the health assessment questionnaire disability index (HAQ-DI). Patients were considered to have a history of immunosuppressive drugs if they had received an immunosuppressive treatment within 6 months before inclusion. We also collected information on the use of more than 10 mg/day of prednisone or equivalent within the 6 months before inclusion.

In accordance with French legislation, written information was provided and consent was obtained from each patient. The study was conducted in accordance with the recommendations of the Helsinki Declaration and complied with the requirements of the French Commission Nationale Informatique et Libertés (No. DC-2008-642).

2.2. Laboratory analyses

Serum was collected at the time of clinical assessment and stored at −80 °C until assayed. sFLC levels were measured both in patients and HC using Combylite® (The Binding Site, Birmingham, UK) according to the manufacturer's recommendations. Combylite® is a single assay that measures the combined level of free kappa and free lambda immunoglobulin light chains in serum using a SPA PLUS turbidimeter [25].

The specificity of antinuclear autoantibodies was identified as part of routine clinical care using both specific immunofluorescence patterns on HEp-2 cells (Euroimmun, Lübeck, Germany) and the Luminex approach (Bio-Plex 2200, Bio-Rad® Laboratories Ltd., CA, USA) for anti-topoisomerase I antibodies (ATA) and anti-centromere antibodies (ACA) identification. Rheumatoid factor and serum beta2-microglobulin were measured in each patient. Serum BAFF level was also measured in each patient in duplicate using a microplate EIA assay (R&D Systems, Minneapolis, MN, USA). Serum electrophoresis and serum and urine immunofixation were performed in all patients to assess the presence of a monoclonal component.

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