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Review

Systemic sclerosis and prevalence of monoclonal immunoglobulin ☆

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ABSTRACT

Introduction: The purpose of this study was to estimate the prevalence of monoclonal immunoglobulin (MIg) among patients with systemic sclerosis (SSc) according to the capillary electrophoresis or immunofixation method of detection and to search for any related clinical correlations.
Patients and methods: Retrospective multicenter comparison of capillary electrophoresis and immunofixation results in SSc patients and of the characteristics of patients with and without MIg.
Results: The study included 244 SSc patients (216 women and 28 men, mean age: 55 ± 14 years). Median time since SSc diagnosis was 51 months [0–320]; disease was diffuse in 48% of cases. Ten percent of patients had cancer, including Waldenström macroglobulinemia (n = 1) and multiple myeloma (n = 3).
Capillary electrophoresis showed a γ-globulin anomaly in 41% of cases, and immunofixation in 18%: MIg (13.5%) and restriction of heterogeneity (4.5%). Capillary electrophoresis failed to detect 60% of the 33 MIg patients. Measurable MIg concentrations were obtained from 7 patients.
MIg patients were significantly older at SSc diagnosis than those without MIg ($p = 0.002$), had a lower diffusing capacity ($p = 0.002$), a higher prevalence of pulmonary hypertension and cancer ($p = 0.002$) and were more frequently positive for anti-mitochondrial and anti-beta2-glycoprotein-I antibodies ($p = 0.03$ and $p = 0.02$, respectively). Multivariate analyses showed that only age at test [hazard ratio 1.03 (95% CI, 1.00–1.07, $p = 0.04$)] and presence of cancer [hazard ratio 4.46 (95% CI, 1.6–12.4, $p = 0.004$)] were associated with MIg.
Conclusion: Immunofixation detected a high prevalence of MIg among SSc patients especially in patients aged 50-years or older. MIg was not detected by the standard capillary electrophoresis in 60% of cases and was significantly associated with cancer.

Contents

Abbreviations: ACA, anti-centromere antibodies; ANA, anti-nuclear antibodies; CI, confidence interval; DLCO, diffusing capacity for carbon monoxide; dSSc, diffuse systemic sclerosis; FVC, forced vital capacity; Ig, immunoglobulin; ILD, interstitial lung disease; lSSc, limited systemic sclerosis; MGUS, monoclonal gammapathy of unknown significance; MIg, monoclonal immunoglobulin; PAH, pulmonary arterial hypertension; PBC, primary biliary cirrhosis; PFT, pulmonary function test; SD, standard deviation; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TLC, total lung capacity; anti-β2GP1, anti-beta2-glycoprotein I.

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1. Introduction

Although systemic sclerosis (SSc) can be easily diagnosed by physical examination alone, screening is routine after this diagnosis for "scleroderma-like" disorders associated with plasma cell dyscrasia and monoclonal gammopathy, such as scleromyxedema, Buschke scleredema (Type 2) and POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes) [1]. This determination of paraproteinemia status at SSc diagnosis is clearly justified by the higher risk to SSc patients of monoclonal gammopathy of unknown significance (MGUS) or of multiple myeloma; their respective age-adjusted relative risks (RR) are 4.21 (95% CI, 1.89–9.38) and 2.41 (95% CI, 1.08–5.36) [2]. In addition, MIg in SSc patients sporadically leads to atypical SSc or multiple myeloma (initial presentation or aggravation) [3,4].

Capillary electrophoresis and agarose-gel-electrophoresis are generally used to screen for monoclonal immunoglobulin (MIg). Compared with immunofixation, however, which is the reference technique, their sensitivity and specificity for detecting MIg components are less than optimal [5]. The purpose of this study was to estimate the prevalence of MIg among SSc patients by different methods of detection and to search for correlations between SSc phenotypes and MIg.

2. Patients and methods

2.1. Patients

This multicenter retrospective study included patients who between March 2000 and August 2008 were referred to and followed at three medical departments: internal medicine at Pitié-Salpêtrière (Paris, France), Huriez CHRU (Lille, France) and dermatology at Tenon (Paris, France). All patients met either the American College of Rheumatology criteria for SSc [6] or the criteria proposed by Leroy et al. [7,8]. Institutional review board (IRB) approval was not required, due to the retrospective purely observational nature of the study.

Antibody determination included antinuclear antibodies (ANA), assessed by indirect immunofluorescence on Hep-2 cell substrate, anti-SSA/B, anti-Scl70, and anti-centromere antibody (ACA), by immunodot or enzyme-linked immunosorbent assays.

Pulmonary function tests (PFT) included total lung capacity (TLC), forced vital capacity (FVC) and diffusing capacity for carbon monoxide corrected for anemia (DLCO), which were analyzed as the percentage of standardized predicted values. Interstitial lung disease (ILD) was suspected by the presence of crackling, an abnormal chest X-ray, or TLC or FVC values <80% of predicted. ILD diagnosis was confirmed by high resolution computed tomography of the lungs, routinely performed on all patients with DLCO ≤50% of normal. Pulmonary arterial hypertension (PAH) was assessed by tricuspid gradient detected on echocardiography with a threshold of pulmonary arterial systolic pressure (PASP) ≥45 mm Hg.

Follow-up for all SSc patients began at the date of SSc diagnosis. Survival status was determined as of 31 January, 2009. We contacted all patients and/or their general practitioners by telephone.

2.2. Electrophoretic techniques

All serum samples were collected in the patient's home center and analyzed at the Immunochemistry Department at Pitié-Salpêtrière (Paris, France). Capillary electrophoresis (Capillarys, Sebia, Evry-Lisse, France) and immunofixation (Hydragel 9 IF, Sebia, Evry-Lisse, France) were performed on all serum samples.

Capillary electrophoresis results were classified as (i) normal, (ii) an abnormal band, corresponding to a discrete homogenous protein band that suggested a monoclonal component and (iii) other abnormalities in the γ-globulin region, which include hypo γ-globulinemia, hyper γ-globulinemia and restriction of heterogeneity.

Immunofixation results were classified as (i) normal, (ii) monoclonal immunoglobulin (MIg) and (iii) restriction of heterogeneity.

2.3. Statistical analyses

Statistical analyses used Fisher's exact test to compare frequencies, the Mann–Whitney-*U*-test to compare mean values, linear logistic regression to perform multivariate analysis, the log-rank test for a univariate analysis to predict factors influencing survival, and Cox models to perform multivariate survival analyses.

3. Results

3.1. Patients

The study included 244 patients with SSc (216 women and 28 men, mean ± SD age at diagnosis 49 ± 14 years), 10 of them lost to follow up. In all, 118 had diffuse systemic sclerosis (dSSc), 82 of them with positive anti-Scl70 antibodies, and 126 had limited systemic sclerosis (lSSc), 94 of them with positive anti-centromere antibodies. Table 1 summarizes the major clinical features, including other associated autoantibodies and treatments. Mean age at serum sample analysis was 55 ± 14 years. The median follow-up after SSc diagnosis was 94 months (range: 1–398) and median follow-up after serum sample analysis 37 months (range: 1–100). The median modified Rodnan score was 6 [0–37], and digital ulcers were reported in 106 patients (43%). ILD was diagnosed in 41% of patients, PAH in 13%, and rheumatoid factor found in 5%. Sjögren syndrome was also seen in 31 patients (13%), who had anti-SSA or SSB antibodies or both. Anti-cardiolipin (aCL) or anti-ribonucleoprotein (RNP) or anti-thyroperoxydase (TPO) antibodies were present in 21 patients (7%). Anti-mitochondrial antibodies were found in six patients (2.5%), four of whom had symptomatic primary biliary cirrhosis (PBC). Isolated IgM anti-beta2-glycoprotein I (anti-β2GP1) antibodies were found in five patients (2%), three with anti-phospholipid syndrome. Ten percent of these SSc patients (n = 25) also had cancer (Table 1).

In all, 90 (37%) of the patients had undergone steroid therapy (prednisolone ≤ 10 mg/day), either at serum sample analysis or earlier, and 43 (18%) had been treated with an immunosuppressive regimen. These treatments were significantly more frequent among patients