Antitopoisomerase I antibody in patients with systemic lupus erythematosus/sicca syndrome without a concomitant scleroderma: two case reports

Abstract We describe two female patients with classic systemic lupus erythematosus (SLE) and secondary sicca syndrome associated with topoisomerase I (topo-I, Scl-70) antibody, a specific marker for scleroderma (SSc), which is rarely found in other collagen diseases. During the course of the disease, the sera of these two patients were repeatedly found to be positive for topo-I antibody following a positive screening by ANA-EIA. Neither patient had clinical evidence of scleroderma. One patient remains well nearly 4 years from the first positive serological test. The progression to sicca syndrome in that patient occurred 2 years after having tested positive for antitopo-I antibody. Her frozen serum also tested positive for anti-Scl-70 by the Western blot technique. The other patient, however, died after developing renal and cardiopulmonary complications of lupus, including Libman Sachs endocarditis and pulmonary hypertension. Contrary to the previous patient, the onset of sicca syndrome in this case had preceded the expression of positive antitopo-I antibody. The present cases and other similar previously reported ones are therefore unique in the sense of being a serological challenge to the high specificity of antitopo-I to scleroderma. In addition, they may also represent a new subset of SLE with or without sicca syndrome, which is characterised by the absence of features of scleroderma despite the presence of antitopo-I antibody.

Keywords Anti-Scl-70 · Antitopoisomerase I antibodies · Scleroderma · SLE

Introduction

It is widely acknowledged that some autoantibodies are highly specific to certain autoimmune diseases. Antitopoisomerase I (topo-I, Scl-70) antibody is known to be a specific marker for scleroderma (SSc). In early studies it was detected in 75% of patients, with the diffuse form being associated with a high frequency of internal organ involvement [1,2]. It was also found to be a marker for the development of scleroderma in patients with primary Raynaud’s phenomenon [3]. Furthermore, its combination with anti-RNA polymerase II (RNAPII) has been associated with a more severe form of SSc in Japanese patients (higher frequency of diffuse disease, pigmentation changes, flexion contractures and acro-osteolysis) than with antitopo-I alone [4]. Apart from the few reports indicating otherwise, patients with SLE and other connective tissue diseases are not known to have antitopo-I in their sera, unless they have or are progressing to SLE/SSc overlap syndrome [5–8].

During routine examination of the sera of 22 patients with SLE by anti-Scl-70 ELISA following a positive ANA-EIA, two were unexpectedly found to be positive for this antibody. These cases are described here.

Case reports

Case 1

A 53-year-old Arab woman presented in early 1997 with polyarthralgia and generalised myalgia of 1 year’s duration. She had a mild malar rash, generalised muscle tenderness, borderline hepatomegaly and moderate hypertension. She had no evidence of active synovitis. Mild leukopenia of 3.2–4 × 10⁹/L was repeatedly present. The diagnosis of SLE was made following a positive ELISA for ANA (kit supplied by Gull Laboratories, Germany) and anti-Sm antibodies (kit supplied by Cogent Diagnostics, Edinburgh). Other assays, including...
anticardiolipin, rheumatoid factor, LE cells, VDRL, and Coombs’ test were negative. Muscle enzymes were not raised and the electromyographic studies did not reveal any myopathic pattern. Serum complement was at the lower level of the normal range (550 mg/L, N = 550–1200). However, she responded well to oral prednisolone (30–7.5 mg/day) and nifedipine (10 mg three times daily). By June 1998 the serological profile by ELISA had become positive for anti-(ds) DNA, Ro/SS-A, La/SS-B, RNP and, unexpectedly, also for Scl-70 (41.6 U/ml, N = 0–15). No new symptoms arose at that point until March 1999, when sicca syndrome was diagnosed following a complaint of dry and irritated eyes and a positive Schirmer’s test. She declined minor salivary gland biopsy. A few months later her profile remained positive for anti-Sm, RNP and for Scl-70 antibodies (27 U/ml, N = 0–15) as well. Concomitantly, the ECG, echocardiography, pulmonary function test and oesophageal isotope scan were unremarkable. During the follow-up period over the last 3 years, the patient has remained well on oral prednisolone (7.5–10 mg/day) and nifedipine (10 mg three times daily). Features of systemic sclerosis, including sclerodactyly, digital ulcers, Raynaud’s phenomenon, calcinosis, hyper- or hypopigmentation, telangiectasias, dysphagia and pulmonary fibrosis, have not to date been observed in this patient. Her serum sample, however, which had tested positive for ELISA before in 1999 and was stored frozen at −70°C, was found to be positive by the Western blot technique for anti-Scl-70 antibodies (Innogenetics, Belgium), as the test became available.

Case 2

A 50-year-old Arab woman was diagnosed with SLE in 1992 following a history of several years of arthralgias and myalgias associated with scarring discoid lupus of the scalp and positive assays for ANA and (ds) DNA antibodies. Assays for extractable nuclear antigens (ENA), anticardiolipin antibodies, rheumatoid factor, LE cells, VDRL, serum complement, and Coombs’ test were either negative or normal. Initial assays for the autoantibodies had been performed in another laboratory. She was maintained on hydroxychloroquine (400–200 mg/day) and her condition remained quiescent. In early 1996 she developed a dry mouth and eyes and a positive Schirmer’s test, typical of sicca syndrome, for which artificial tears were prescribed. She too refused to have a biopsy of the minor salivary gland. By the end of the year the disease suddenly became somewhat aggressive, with the development of a malar rash, photosensitivity, puffiness of the face and polyarthritis. Chest radiographs showed bilateral basal plate-like atelectasis of the lungs. On subsequent investigations in our laboratories, the anti La/SS-B (ELISA, Cogent Diagnostics) and IgG isotype anticardiolipin (ELISA, Gull Laboratories) antibodies became positive, along with ANA and (ds) DNA antibodies, and prednisolone (45 mg/day) was commenced.

In early 1998 the pulmonary function test showed a restrictive ventilatory defect. There was no evidence of renal or cardiac involvement at that time. Two successive assays carried out over a 3-month period revealed markedly elevated (ds) DNA Abs (> 50 U/mL on both occasions, N = 0–4), constantly elevated anti-La/SS-B (26.6 and 36.5 U/mL, respectively, N = 0–10), and a rising level of anti-Scl-70 antibodies (18.5 and 49.1 U/mL, respectively, N = 0–15). CT of the lungs showed no evidence of pulmonary fibrosis. A few months later, further deterioration occurred as she began to experience repeated attacks of pulmonary oedema associated with progressive renal impairment. Cardiac evaluation revealed severe non-thromboembolic pulmonary hypertension (right ventricular systolic pressure (RVSP) was 50 ± 15 mmHg), tricuspid regurgitation and Libman Sachs verrucous endocarditis of the mitral valve. She was managed in the intensive care unit till her death from multiple organ failure in March 1999. The last serological profile was positive for ANA and anti-(ds) DNA antibodies, which was markedly raised, but negative for anti-La, anticardiolipin, anti-Scl-70 and anticentromere antibodies. As in the first case, clinical manifestations of scleroderma had been absent throughout the course of her illness.

Discussion

Both patients fulfilled the ARA criteria for SLE [9] and satisfied the criteria of Vitali et al. for Sjögren’s syndrome [10]. They had been evaluated regularly for number of years without overlapping features of scleroderma, yet unexpectedly their sera contained antitopo-I antibody. These positive results were, however, incidental findings following a positive screening of the sera by ANA-EIA. This test qualitatively detects total autoantibodies of the IgG and IgM class to the extractable nuclear antigens and to (ds) DNA, histone and centromere. ANA-EIA has been shown to be substantially equivalent in sensitivity and of higher specificity than the widely used indirect immunofluorescence assay ANA-IFA in relation to patient diagnosis [11,12]. Furthermore, the specific anti-Scl-70 ELISA is also found to be a reliable test, and as good as the immunoblot method in detecting anti-Scl-70 antibody [13,14]. Recent work by Henry et al. on antitopo-I autoantibody response in SSc has shown that titres and immunodominant domains recognised by both primary and secondary antitopo-I antibodies are highly variable over time. This suggests continual antigen presentation and regulation of the antibody response in SSc during the disease course [15]. The fluctuations of the antibody in the present cases may therefore suggest that a similar mechanism should also act in SLE patients positive for Scl-70 antibody. There are only a few reports in the literature describing patients similar to ours who had tested positive for antitopo-I in a classic SLE setting. Mukai et al. described three patients with this antibody