Anti-PM/Scl antibodies in connective tissue disease: Clinical and biological assessment of 14 patients

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Abstract

Introduction

Anti-PM/Scl antibodies (Anti-PM/Scl) represent a rarely encountered type of antinuclear antibodies. They have mainly been reported in association with idiopathic inflammatory myositis – systemic sclerosis overlap syndromes (also called scleromyositis or sclerodermatomyositis) but also with polymyositis, dermatomyositis and systemic sclerosis without features of overlap syndromes. Studies concerning characteristics of patients with anti-PM/SCl are rare and include small numbers of patients.

Patients and methods

Retrospective review of clinical and biological characteristics of 14 patients with anti-PM/Scl in two University Hospitals: one in Belgium (Erasme Hospital, Bruxelles) and one in France (Hautepierre Hospital, Strasbourg).

Results

Seven patients were identified in Erasme and 7 in Strasbourg: 5 with systemic sclerosis – (dermato)myositis overlap syndromes, 4 with dermatomyositis, 1 with polymyositis, 3 with systemic sclerosis, 1 with primary Sjögren's syndrome. The most frequently observed clinical characteristics (85% of patients) were: pulmonary interstitial disease and arthralgia or arthritis. No patient of our series died or developed cancer (mean follow-up: 6.1 years).

Conclusions

Our study failed to identify an homogeneous clinical pattern in patients with anti-PM/Scl, except for 2 characteristics shared by 85% of the patients. This lack of homogeneity is in agreement with preceding literature. We confirm the favourable prognosis associated with the presence of anti-PM/Scl, despite the high incidence of interstitial pulmonary disease. The absence of cancer associated with presence of anti-PM/Scl represents a partial explanation. Finally, we report herein the second case of primary Sjögren's syndrome associated with anti-PM/Scl.

Key words

Anti-PM/Scl antibodies, polymyositis, dermatomyositis, systemic sclerosis, overlap syndromes, primary Sjögren's syndrome.

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Introduction

In 1977, Wolfe *et al.* (1) described a novel auto-antibody called anti-PM1. In a series of 18 patients with myositis and/or systemic sclerosis, 12 presented an overlap syndrome between the two diseases sometimes called scleromyositis. A few years later, in 1984, Reichlin *et al.* described a new specific autoantibody closely related to anti-PM1, anti-PM/Scl antibody (2). Among the 22 patients of this study, 21 presented with myositis and 10 with systemic sclerosis, 9 of the 22 having an overlap syndrome. Several other studies have confirmed the association between anti-PM/Scl and idiopathic inflammatory myopathy and/or systemic sclerosis (2-5). Nevertheless, a homogeneous clinical pattern associated with anti-PM/Scl has never been identified, except in Marguerie's study (4). Among 32 patients, 6 common clinical characteristics were found in more than 50% of patients: Raynaud's phenomenon (100 %), scleroderma (97%), arthritis (97%), myositis (88%), restrictive syndrome or lung fibrosis (78%) and dysphagia (78%).

Anti-PM/Scl are directed against a nucleolar macromolecular complex of peptides of 75 (PM/Scl-75 protein) and 100 kDa (PM/Scl-100 protein), with PM/Scl-75 being considered the main autoantigen (6). This autoantigenic complex is the human homologue of the yeast exosome, which is an RNA-processing complex (7).

These autoantibodies are observed in 6% of isolated idiopathic inflammatory myositis (dermatomyositis/polymyositis), 2% of isolated systemic sclerosis and 24% of overlap type scleromyositis (4, 5). Among all patients with PM/Scl, 43 to 88% have scleromyositis or sclerodermatomyositis.

The aim of our study was to analyse clinical and biological characteristics of Caucasian patients with anti-PM/Scl detected in two University Hospitals: Erasme University Hospital in Brussels and Strasbourg University Hospitals.

Patients and methods

Patients

The medical records of every patient with anti-PM/Scl in the two centers were retrospectively analysed without prior selection.

The 14 patients of the present study have been followed from 1985 to 2004 in Erasme Hospital in Brussels (n = 7) and in Hautepierre Hospital in Strasbourg (n = 7) in the Departments of Internal Medicine, Rheumatology and Neurology. These two university hospitals are referral centers for systemic inflammatory rheumatic diseases, but also practise highly diversified medical activity allowing a very large recruitment of patients.

Methods

In Erasme Hospital, the search for antinuclear antibodies (ANA) was performed by immunofluorescence (IF) on HEP 2 cells (classical method, on human larynx carcinoma cells) for the oldest sera, then on HEP 2000 cells, transfected to over-express SSA antigen, which improves the sensitivity for detection of anti-SSA antibodies. The search for anti-PM/Scl is performed in every patient with an ANA associated with nucleolar fluorescence on one hand and either an homogeneous or a speckled fluorescence pattern on the other hand. The search for anti-PMScl was performed by immunodiffusion until 2001 and then by immunodot (kit ANA-Porfil 3 EUROLINE / BIOGNOST), which allowed improving the sensitivity for anti-PMScl detection.

In Hautepierre Hospital, the search for ANA is performed by IF on HEP 2 cells. Search for anti-PM/Scl is performed by immunodiffusion (kit Ingene 102) in every patient with an ANA and speckled / nucleolar pattern in IF. Positivity of anti-PM/Scl is confirmed by immunodot in the department of autoimmunity in Centre Hospitalier de Luxembourg (Professor Humbel).

Diagnostic criteria for polymyositis (PM) and dermatomyositis (DM) are the classical criteria of Peter and Bohan (8). Diagnostic criteria for systemic sclerosis are the classical criteria of the American Rheumatism Association (9).

Every patient has been evaluated by two senior physicians who established the diagnosis in the setting of multidisciplinar discussions.

Table I. Clinical and biological data of the patients.

		Erasme Hospital (Bruxelles) (n = 7)							Hautepierre Hospital (Strasbourg) (n = 7)						
Patients Data	Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14
	Sex	F	F	F	F	F	F	F	F	F	F	M	F	F	F
	Age	46	34	70	60	56	33	33	43	36	34	71	25	75	57
	Duration of follow-up (yrs)	4.5	1	20	2.5	11	7.5	2	12	3.5	3	8	3	14	3
	Diagnosis	Primary Sjogren	Dermato-myositis (DM)	Overlap (DM/Scl)	DM	Systemic sclerosis	DM	Overlap (PM/Scl)	Systemic sclerosis	Overlap (PM/Scl)	Overlap (DM/Scl)	PM	DM	Overlap (PM/Scl)	Systemic sclerosis
Clinical Data	Raynaud	+	–	+	+	+	–	+	+	+	–	–	+	+	+
	Pulmonary involvement	+	+	+	+	+	+	+	–	+	+	+	–	+	+
	Articular involvement	+	+	+	+	+	+	+	+	–	+	+	+	–	+
	Sicca syndrome	+	+	–	–	–	–	+	–	–	+	+	–	+	–
	Renal involvement	–	–	–	–	+	–	–	–	+	–	–	–	+	–
	Dysphagia and/or deglutition abnormalities	+	–	–	–	–	+	–	–	–	–	–	–	+	–
	Cancer	–	–	–	–	–	–	–	–	–	–	–	–	–	–
	Others	–	Hyperkeratosis of the hands	–	–	Myositis < penicillamine	–	–	Myasthenia < penicillamine	–	Hyperkeratosis of the hands	Initial diagnosis seronegative rheumatoid arthritis	–	Sclerodermic renal crisis	–
Biological Data	ANA: fluorescence	S/N	S/N	H/N	S/N	S/N	S/N	H/N	S/N	S/N	S/N	S/N	S/N	S/N	S/N
	Antigenic specificity other than PM Scl	–	–	–	–	–	–	–	–	–	–	RO/SS-A	–	–	–
	FR IgM (>20U/ml)	–	+	–	+	NP	+	–	–	–	+	–	–	–	–
	Anti-phospholipid Ab and/or lupic anticoagulant cryoglobulinemia	–	–	–	NP	NP	–	–	NP	+	–	–	–	–	–
	Cryoglobulin	–	–	+	NP	NP	–	NP	–	+	+	–	–	NP	–

Overlap (DM/Scl): Overlap syndrome between dermatomyositis and systemic sclerosis; Overlap (PM/Scl): Overlap syndrome between polymyositis and systemic sclerosis; S/N: Speckled/nucleolar; H/N: Homogeneous/nucleolar; NP: Not performed; N: normal.

Clinical abnomalities

Diagnosis of lung involvement is made on the basis of interstitial infiltrates demonstrated by tomodensitometry and/or abnormality of diffusion capacity for carbon monoxide (DLCO). Joint involvement is diagnosed on the basis of arhralgias or arthritis. Renal involvement is diagnosed when proteinuria (> 0.15 g per day), elevation of serum creatinin (> 1.2 mg/dl) or decrease in creatinin clearance are observed repeatedly and are not related to drug toxicity (e.g. D-penicillamine) or an associated disease (e.g. diabetes mellitus or hypertension). Diagnosis of esophageal involvement is made on the basis of an abnormal barium swallow or manometry or a history of dysphagia, laryngeal aspiration or aspiration pneumonia.

Results

Mean duration of follow-up of the 14 patients with anti-PM/Scl was 6.1 years after the diagnosis (1-20 years). Clinical and biological characteristics of these patients are detailed in Table I.

Corticosteroids were administered to all patients, among whom 4 underwent methylprednisolone pulses.

Immunosuppressive drugs were given to the majority of patients: hydroxychloroquine (1/14), azathioprine (2/14), methotrexate (3/14), cyclophosphamide (1/14), intravenous immunoglobulins (2/14), γ interferon (1/14), D-penicillamine (3/14) and infliximab (1/14), the latter of which was used in the setting of a clinical trial for the patient with primary Sjögren's syndrome (10). In our retrospective study - given the diversity of disease course and clinical manifestations - we were unable to evaluate the efficacy of these treatment options. Of the 4 patients treated with D-penicillamine for systemic sclerosis, 2 had to interrupt the treatment because of new-onset autoimmune manifestations (1 case of myasthenia, 1 case of myositis) which regressed after cessation of D-penicillamine.

Discussion

This retrospective analysis of 14 patients with anti-PM/Scl largely confirms previous published data. We further underline several points as follows:

Table II. Characteristics of patients with anti-PM/Scl antibodies.

	Reichlin n = 20	Genth n = 12	Marguerie n = 32	Oddis n = 23	Present series n = 14
Clinical features					
Raynaud	55%	92%	100%	65%	71%
Interstitial pulmonary disease	35%	42%	78%	30%	85%
Arthralgia/arthritis	50%	58%	97%	83%	85%
Dysphagia/Deglutition abnormalities	?	36%	78%	?	21%
Renal involvement	?	0%	3%	0%	21%
Sicca syndrome	?	25%	34%	?	43%
Diagnosis					
Idiopathic inflammatory myopathy	55%	8%	3%	26%	38%
Systemic sclerosis	4%	50%	12%	30%	15%
Scleromyositis or sclerodermatomyositis	41%	42%	85%	43%	38%
Primary Sjögren's syndrome	-	-	-	-	1 patient out of 14

Previous series of patients with anti-PM/Scl have shown that this autoantibody is associated with myositis and/or systemic sclerosis, which is confirmed by our study. Nevertheless, we identified one patient with primary Sjögrens's syndrome associated - at time of diagnosis - with interstitial lung disease and lacking any feature of systemic sclerosis or myositis. Only one other case of isolated primary Sjögren's syndrome associated with presence of anti-PM/Scl has been reported in the literature (11). In the largest series of patients with anti-PMScl, Schnitz found only 5 patients among 55 without clearly identified systemic sclerosis and/or myositis. Nevertheless, except for the case of primary SS, the 4 other patients had clinical features typically observed in these disorders. These 4 patients had signs and symptoms not sufficiently evolved to fulfill classification criteria for a well-defined connective tissue disease. Hence they could be considered as having undifferentiated connective tissue disease (UCTD) (12). To the best of our knowledge, the prevalence of anti-PM/Scl in UCTD has not been defined.

The prevalence of sicca syndrome in other series of anti-PM/Scl patients varies from 0 to 45% depending on the diagnostic tools that are used . In our 6 patients presenting with sicca syndrome, 5 underwent a minor salivary gland biopsy. A lymphoid infiltrate suggestive of SS (grade 3 or 4 according to Chisholm's classification) was identified in 2 of them.

The large majority of patients with anti-PM/Scl are diagnosed as myositis and/or systemic sclerosis, but the prevalence of the different clinical manifestations is highly variable from one series to another (Table II). This can be explained by the variability of criteria used to identify these complications. In our series, prevalence of renal involvement (defined as renal failure or proteinuria of more than 0.15 g per day) is of 23% (n = 3), whereas Genth - defining renal involvement as rapidly progressive renal failure or malignant arterial hypertension - found a prevalence of 0%. With such a definition, only one of our patients would have been considered as having renal involvement . In the 3 patients in our series with renal involvement, we considered it was related to systemic sclerosis, and therefore did not perform biopsy. The frequency and the severity of pulmonary involvement differ between series reaching 85% in our series.

Diagnostic value of anti-PM/Scl is interesting because, in the literature, 43 to 88% of anti-PMScl positive patients have overlap syndromes (scleromyositis or sclerodermatomyositis).

Nevertheless, other autoimmune markers for these overlap syndromes have been described depending on genetic factors. Among Japanese patients with scleromyositis, 50% have anti-Ku antibodies, whereas anti-PMScl are very

rare. Inversely, only 10% of North American patients with scleromyositis have anti-Ku (13).

None of the patients in our series died, in accordance with the favourable prognosis observed in the literature: only one death related to connective tissue disease is reported, due to pulmonary hypertension (4). Among all auto-antibodies encountered in systemic sclerosis, anti-PMScl is associated with the best prognosis, despite the frequency of interstitial lung disease and the frequent overlap with myositis. This observation could be due to several factors:

- Patients in our series with interstitial lung involvement responded well to corticosteroids - as described in the literature - and none of them developed severe respiratory failure. Such patients, therefore, generally do not require cyclophosphamide for pulmonary involvement.
- No muscular or myocardial complication occurred in patients with myositis .
- To the best of our knowledge, among all patients with anti-PM/Scl described in the literature, an occurrence of cancer has been reported only once : a heavy smoker (more than 50 packets per year) died from lung cancer, 15 years after the onset of connective tissue disease (5). The delay between the onset of the two diseases makes a causal relationship very unlikely.

Every patient with anti-PM/Scl in our study had high ANA levels , with either a speckled / nucleolar pattern (13/14), or a homogeneous / nucleolar pattern (1/14) in immunofluorescence. The only antigenic specificity observed other than anti-PM/Scl was an anti-Ro/SS-A identified in one patient (patient N° 11 - Table I). In the literature, detection of other auto-antibodies is rarely observed in patients with anti-PM/Scl: one patient with anti-dsDNA (4) without lupus feature and one patient with anti-JO1 (5). On the other hand, rheumatoid factor positivity seems to be higher reaching 28% (n=4) in our study, 66% in Marguerie's series and 50% in Genth's series (3).

Conclusion

Anti-PMScl antibodies are specific markers of systemic sclerosis and myositis and particularly of the overlap syndromes, scleromyositis or sclerodermatomyositis. Presence of this antibody is a good prognostic factor as there appears to be no association with malignancy. Furthermore, the associated lung involvement is generally not aggressive and responds well to corticosteroids.

Anti-PMScl - detected by immunofluorescence - must be identified by specific methods (immunodiffusion, immunoblot), justifying close collaboration with a specialised laboratory.

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