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SHORT COMMUNICATION

Systemic lupus erythematosus associated with ANCA-associated vasculitis: an overlapping syndrome?

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Abstract Systemic lupus erythematosus (SLE) and small-sized vessel vasculitis are usually two distinguishable autoimmune diseases. However, a vasculitis may be found in the course SLE but rarely corresponds to an ANCA-associated vasculitis (AAV). We report four cases of de novo SLE associated with AAV, our aim being to discuss the clinical significance of this association. We included four patients fulfilling the criteria for both SLE and AAV and followed in two different university hospitals between 1996 and 2009. In light of a 20-year literature review (25 described clinical cases), we discussed the etiopathogeny of such an association. All patients presented a severe renal involvement (creatininemia ranging from 120 to 370 μmol/l) and thrombopenia (ranging from 45,000 to 137,000 platelets/mm^3). The other main clinical symptoms were arthritis ($n = 3$), serositis ($n = 2$) and intra-alveolar hemorrhage ($n = 2$). An inflammatory syndrome was noticed at diagnosis in all cases. ANCAs were MPO-ANCAs in all cases. Two out of these four patients were also diagnosed with antiphospholipid syndrome. The frequency of this association seems not fortuitous. Although the etiopathogenic mechanisms of such an association remain to be more precisely described, several clinical, histological and immunological features support the hypothesis of the existence of a SLE-AAV overlapping syndrome. Moreover, clinicians must be aware of such an overlapping syndrome, notably because its initial presentation can be very severe.

Keywords ANCAs · ANCA-associated vasculitis · ANAs · Systemic lupus erythematosus

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by several immunological abnormalities [1, 2] leading to the development of autoantibodies directed against nuclear components: antinuclear antibodies (ANAs). ANCA-associated vasculitides (AAV) are histologically characterized by a small-sized vessel vasculitis associated with anti-neutrophil cytoplasmic antibodies (ANCAs) positivity [3]. These two diseases are only rarely associated: a vasculitis may occur in the course of SLE but rarely responds to AAV classification criteria. Indeed, when ANCAs are tested positive in the course of SLE [4], no vasculitis is usually found.

However, the serologic association of ANAs and ANCAs has been reported, but the prevalence of this association varies, depending on the study population. Indeed, the prevalence of this association also depends on the techniques used for ANAs and ANCAs screening [4]. The indirect immunofluorescence (IIF) pattern of perinuclear-staining (P)-type ANCA on neutrophils corresponds to an artifact of the ethanol fixation technique [5] and is easily confused with ANAs. When focusing on the specificity of ANCAs frequently associated with AAV (i.e., MPO-ANCAs and PR3-ANCAs), their association with ANA seems exceptional [6–13]. For these reason, the reports describing the clinical association of both associated pathologies [14–16] are particularly rare.

We report four patients with SLE who were ANCA positive and who also presented with clinical signs of AAV. We also review 55 other such cases in the English literature over the past 20 years and discuss the etiology of such an association.

Materials and methods

Between 1996 and 2009, in two different university hospitals, we collected information on adult patients either diagnosed with SLE and showing the diagnostic criteria of AAV or diagnosed with AAV and responding to the American College of Rheumatology (ACR) criteria for SLE [17]. ANAs were determined by IIF, using Hep-2 cells (Bio-Rad, Marnes-La-Coquette, France). All the patients were tested for MPO- and PR3-ANCA using LUMINEX/FIDIS techniques. Four patients were included (Table 1). None was positive for anti-glomerular basement membrane (GBM) antibodies.

We searched the English literature in Medline using the terms ANA and ANCA for papers published between January 1990 and January 1, 2010 [6–16, 18–22]. We also searched all the references from the manuscripts retrieved and consulted our local experts. We were able to identify 98 cases of SLE associated with MPO-ANCA positivity and eight cases of SLE associated with PR3-ANCA positivity. This excluded all patients treated with hydralazine [14, 23], thioridazine or propylthiouracil, known to induce SLE and/or AAV. Only 53 and 2 cases could be considered significant, respectively. In some cases, the detection levels of MPO-ANCA or PR3-ANCA were so low and were eventually associated with several other ANCA specificities that the authors considered these false-positive results

Table 1 Clinical cases

	Patient 1 74 yo F	Patient 2 35 yo F	Patient 3 21 yo F	Patient 4 76 yo F
Clinical signs in accordance with SLE diagnosis		Discoïd lupus		Discoïd lupus
	Arthritis	Arthralgia	Arthritis	Arthritis
			Serositis	Pericarditis
	Thrombopenia, hemolytic anemia	Thrombopenia	Thrombopenia*	Thrombopenia*
			Anemia*	
Clinical signs possibly in accordance with ANCA vasculitis	Bloody sinusitis, cerebral ischemia*, intra-alveolar hemorrhage	Epistaxis, myocardial ischemia*	Rhinitis, excavated pulmonary nodules	Intra-alveolar hemorrhage
Nephritis: histology and fluorescence deposits	Proliferative and crescentic	Extracapillary and crescentic	Endo and extracapillary proliferative and necrotizing	nd
	Endomembranous and mesangial IgG, IgM, C3	IgG, vascular	IgG, IgM, C3, C1q, GBM, not vascular	nd
Biological tests				
Serum creatinin (μmol/l)	370	310	350, Hemodialysis	410, Hemodialysis
Protéinuria (g/day)	0.6	>6	2.5	0.5
Hématuria/leucocyturia ($\times 10^4$/ml)	+/3	++/100	+/27	+/200
C-RP (mg/l)	70	72	72	56
Hemoglobin (g/dl)	7.9	10.2	7.8	6.3
ANAs	1/5,120, Homogenous	1/640, Speckled	1/2,560, Homogenous	1/160
Anti-DNA Antibodies by Farr test (>nr)	10	6	8	nd
Complement (C3)	87%	70%	36%	90%
MPO-ANCAs (>nr)	7	22	12	4
Lupus anticoagulant/anti-cardiolipine/anti-β-2-GP1 antibodies	+/−/−	−/−/−	+/+/−	−/−/−

Nr normal range, *yo* year old, *F* female, * shared symptoms, *GBM* glomerular basal membrane, *nd* not determined

Table 2 Literature review: clinical, histological and immunological characteristics of 25 patients with available description

References Patient Type of ANCA associated with AAN	NASR [10] 37 yo F MPO-ANCA	NASR [10] 50 yo F MPO-ANCA	ARAHATA [6] 39 yo F MPO-ANCA	HIRAI [8] 19 yo F MPO-ANCA	KOBAYAHI [9] 42 yo F MPO-ANCA	CAVAGNA [7] 76 yo F MPO-ANCA	CAVAGNA [7] 47 yo F PR3-ANCA	YU [13] 7 Patients MPO-ANCA	SPRONK [12] 6 Patients MPO-ANCA	NISHIYA [11] 5 Patients MPO-ANCA
Clinical signs in accordance with SLE diagnosis	Arthritis Thrombopenia	Malar rash Pericarditis	Arthritis Pancytopenia	Rash Arthritis Serositis AIHA		Malar rash Arthritis Serositis AIHA	Arthritis Serositis Leucopenia		Rash: 1p Arthritis: 5p Serositis: 2p Cytopoenia: 3p	Rash: 3p Arthritis: 3p Serositis: 2p Cytopoenia: 1p
Nephritis: histology and fluorescence deposits	Necrotizing and crescentic IgG, vascular	Necrotizing and crescentic IgG, vascular	Necrotizing and crescentic IgG, IgM, C3, C1q, GBM, not vascular	Necrotizing and crescentic IgA, IgG, C3, C1q, along glomerular capillary wall		Necrotizing and crescentic IgG, C3, C1q, mesangial		Necrotizing and crescentic	nd, 2p	Extramembranous (1p)
Clinical signs possibly in accordance with ANCA vasculitis					Intra-alveolar hemorrhage	CNS, Mastoïditis	CNS, Mastoïditis		CNS (2p), vasculitis (1p)	CNS (1p)

P patient(s), *nd* not determined, *AIHA* autoimmune hemolytic anemia, *GBM* glomerular basal membrane

for ANCAs. Only a few patients were described clinically in these studies. However, we could get significant but not exhaustive details for 25 patients (Table 2).

Case reports (Table 1)

Case 1

A 74-year-old Caucasian female was hospitalized for a partially reversible left leg deficit. She had a history of bronchial dilatation and relapsing idiopathic thrombocytopenic purpura in the context of lupus anticoagulant positivity. She had also a history of seronegative nondestructive polyarthritis. She had suffered polyarthralgia and bloody sinusitis for 6 months. Neurological investigations showed evidence of an ischemic stroke in the right anterior cerebral artery and cerebellar postero-inferior arteries, of unknown origin. The patient later developed rapidly progressive renal failure. This was associated with an inflammatory syndrome and profound nonhemolytic and a regenerative anemia. Serologic testing showed a mild decrease in C3, positive ANAs and anti-DNA antibodies by Farr test. MPO-ANCAs were also positive. Lupus anticoagulant, anticardiolipin antibodies and other auto-antibodies were negative. Renal biopsy showed a diffuse and global proliferative and crescentic glomerulonephritis. No microthrombi were observed. Endomembranous and mesangial IgG, IgM and C3 deposits were observed. A few days after admission, the patient complained of dyspnea and a bronchoalveolar lavage (BAL) confirmed intra-alveolar hemorrhage. Despite antibiotic and immunosuppressive treatments, the patient developed severe thrombopenia, related to a hemophagocytic syndrome. Three months later, she was diagnosed with secondary hepatic lesions of an adenocarcinoma. She died at the 7th month of follow-up.

Case 2

A 35-year-old African woman was admitted for polyarthralgia, repeated epistaxis and rapidly progressive glomerulonephritis. Renal histology showed extra- and endocapillary proliferative glomerulonephritis with glomerular necrosis. MPO-ANCAs were positive. Surprisingly, she was also ANA positive and showed serum hypocomplementemia. Treatment consisted of steroids plus cyclophosphamide. Oral cotrimoxazole was also started. The patient remained in remission for 6 years but then relapsed with polyarthralgia, episcleritis, discoid lupus lesions and glomerulonephritis. A second renal biopsy showed tubulointerstitial fibrosis but no recent glomerular lesions. MPO-ANCAs were still positive and were associated with anti-Sm antibodies and serum hypocomplementemia. The use of immunosuppressive permitted a 4-year remission. However, the patient finally relapsed with sever glomerulonephritis. The third renal biopsy diagnosis was in accordance with extracapillary and crescentic glomerulonephritis, without mesangial proliferation or immunoglobulin deposits. Myocardial ischemia and severe thrombopenia developed. The MPO-ANCA levels were low, whereas anti-DNA antibodies were positive by Farr test. Antiphospholipid antibodies were negative. Finally, combined therapy with steroids and cyclophosphamide was restarted, and the patient is still in remission at a follow-up of 15 months.

Case 3

A 21-year-old Caucasian woman was admitted for Wegener's granulomatosis. The diagnosis was made on the association of weight loss, rhinitis, cutaneous eruption, excavated pulmonary nodules and glomerulonephritis. A renal biopsy disclosed endo- and extracapillary proliferative and necrotic glomerulonephritis, with IgG and IgA deposits, whereas a cutaneous biopsy revealed leukocytoclastic vasculitis. MPO-ANCAs were positive. Surprisingly, the patient's ANA levels were slightly positive without any specificity. Even though an inflammatory syndrome was noticed, the complement level was normal. Treatment with oral steroids and cyclophosphamide was given for 1 year, and this gave remission for 7 years. MPO-ANCAs became negative. However, she relapsed with chorea. ANAs were still positive as were lupus anticoagulant, anticardiolipin (IgG) and MPO-ANCAs. Because these neurological events were regressive, no treatment was started. One year later, she was admitted to our intensive care unit (ICU) for global cardiac failure caused by aortic and mitral valve insufficiency with thickening of both valves. She also displayed digital necrosis, consciousness difficulties with recent ischemic lesions on cerebral imaging (bilateral frontal and parietal lobes and right semi-ovale center). She showed renal failure with severe hypertension necessitating hemodialysis. Thrombopenia and anemia occurred; the haptoglobin level was normal, and schizocytes were absent. Lupus anticoagulant was still positive, anticardiolipin antibodies were also slightly positive, whereas anti-β2-GPI-antibodies were negative. The patient was diagnosed with a catastrophic antiphospholipid syndrome. At the same time, she presented with signs of SLE: bilateral exudative pleuresis and pericarditis. ANAs were still positive with anti-DNA specificity by Farr test. Complement was low, and MPO-ANCAs were still positive. Anticoagulation therapy, i.v. steroids and cyclophosphamide, were administered, and plasma exchange was done. The patient's evolution was

slowly favorable, and she was still in remission at the 12-month evaluation.

Case 4

A Caucasian woman was followed for 40 years for discoid lupus erythematosus, treated successively with hydroxychloroquine and thalidomide. She presented at the age of 66 years with polyarthritis requiring low doses of steroids. Three years later, she relapsed, with diffuse alopecia and polyarthritis. ANAs were positive, without anti-DNA specificity. At the age of 76, she was hospitalized in an ICU for acute respiratory failure, related to an intra-alveolar hemorrhage (hemoptysis, bilateral alveolar pulmonary syndrome and BAL disclosing 98% of siderophages). Renal failure developed rapidly. This was at least in part due to severe hypotension, but signs of glomerulonephritis were also present. A mild pericarditis and a transitional thrombopenia occurred. ANAs, anti-DNA and antiphospholipid antibodies were negative, whereas MPO-ANCAs were positive. Despite an inflammatory syndrome, hypocomplementemia was noticed. Pulmonary and renal biopsies could not be performed. After mechanical ventilation, hemodialysis and plasma exchange, i.v. injections of steroids and pulses of cyclophosphamide, the patient's evolution was good and the respiratory and renal functions normalized. At the 8th month of evaluation, the patient was still in remission.

Discussion

SLE and AAV are both rare diseases. Even though the number of cases of SLE associated with AAV reported in the literature is low, this association occurs more frequently than the coincidental occurrence of two unrelated diseases. Focusing on the diagnosis of SLE associated with MPO-ANCAs or PR3-ANCAs, we were able to distinguish some clinical and biological arguments supporting the hypothesis of an overlapping syndrome between SLE and AAV. All the 4 patients reported herein presented with clinical and biological signs of both diseases. Even though the time between the first manifestations of one autoimmune disease to the second ones could be more than 10 years, there were signs according to both diagnoses already at the beginning of the first disease (including ANA positivity in case of the first occurrence of AAV in Patients 2 and 3). Given the clinical descriptions of the cases in the literature and our four cases, the overall clinical presentation appears heterogeneous. Indeed, from the literature, it is difficult to show that a particular SLE phenotype emerges clearly in patients with MPO-ANCAs. However, some have suggested the possibility of a higher prevalence of pericarditis, arthritis and above all necrotizing and crescentic glomerulonephritis in case of SLE associated with ANCAs [4]. Among the current patients and in the literature (Table 2), serositis occurred moderately (nine cases), whereas arthritis (15 cases) occurred more frequently. Surprisingly, all our patients plus nine in the literature displayed cytopenia.

The initial presentation of this overlapping syndrome is often severe with both vital and functional prognoses being poor (Patients 1, 3 and 4), especially in case of pneumo-renal syndrome. Indeed, all our four patients presented with severe renal involvement (2 patients required hemodialysis). This was in agreement with the literature reporting 19 patients with renal involvement. This prevalence of 68% of glomerulonephritis occurring in SLE associated with MPO-ANCA is higher than that usually reported for SLE without ANCA. Interestingly, in the 29 patients analyzed here, necrotizing and crescenting glomerulonephritis was the major pattern observed on renal biopsy (14 patients, 50% of the MPO-ANCA positive SLE patients). Even though this could display a certain bias, it is difficult to set aside this high prevalence. Moreover, these epidemiologic considerations are strengthened by the histological features. Indeed, although necrotizing and crescentic glomerulonephritis has been reported in patients with SLE but lacking ANCAs [13, 24], it is of note that this "pauci-immune glomerulonephritis" is common in patients with AAV. Moreover, in some cases, the immune deposits are confined to the glomerular vessels.

These epidemiological, clinical and histological considerations support our hypothesis of an overlapping syndrome between SLE and AAV, as first suggested by Nasr et al. [10]. Moreover, in our experience, none of the two autoimmune diseases predominates and the severity of this overlapping syndrome is carried by both diseases. Interestingly, this overlapping syndrome could also be associated with an antiphospholipid syndrome (Patients 1, 3 and one similar case described in the literature [6]). However, as there was no evidence for microthrombotic nephropathy by renal histology in these cases, further observations are needed to confirm this hypothesis.

Importantly, all these 4 patients were MPO-ANCA positive at high levels. This finding is in agreement with the literature, as more than 96% of the cases of SLE associated with ANCA also had MPO-ANCAs. MPO-ANCAs are frequent in case of microscopic polyangeitis, whereas PR3-ANCAs are more closely associated with WG. AAV with renal involvement and/or intra-alveolar hemorrhage has been shown to correspond to a TH1 immune mechanism [25, 26]. Indeed, it has been shown that this pathway was also activated during SLE-associated glomerulonephritis [27], suggesting a pathogenic link between these two diseases. Moreover, the occurrence of both drug-induced SLE and AAV after hydralazine therapy

also supports the hypothesis of a shared mechanism between these two autoimmune diseases [4, 28].

In summary, the association of SLE and AAV is rare but not fortuitous. Moreover, the four cases reported herein and the literature review argues for the existence of an overlapping syndrome, frequently characterized clinically by arthritis, cytopenia and renal involvement with a renal histology of necrotizing and crescentic glomerulonephritis. Because of a severe initial presentation, and especially in case of atypical symptoms occurring in the course of SLE (including intra-alveolar hemorrhage) or in the course of AAV (including pancytopenia or hypocomplementemia), the clinician must be aware of this association and search for both ANAs and ANCAs in such cases.

Conflict of interest All authors declare no conflict of interest.

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