

Patients with overlap autoimmune disease differ from those with 'pure' disease

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ABSTRACT

Objective: To determine frequency, demographic and treatment characteristics of patients with an overlapping second autoimmune illness (2nd AI).

Methods: We analysed two cohorts containing 897 patients with 'pure' systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome or antiphospholipid syndrome (APS) and 424 patients with one of these diagnoses plus at least one 2nd AI.

Results: A 2nd AI occurred in 38% of all patients diagnosed as having SLE (with or without a 2nd AI), 30% with RA, 52% with Sjögren's syndrome and 43% with APS. Compared to those without 2nd AI, patients with 2nd AI differ in age, sex, race and treatment at last visit.

Interpretation: These differences may have important implications for understanding treatments, outcomes and mechanisms of SLE and related diseases.

INTRODUCTION

Treatment standards and physicians' understanding of disease mechanisms and of outcomes for patients with systemic lupus erythematosus (SLE) and other rheumatic autoimmune diseases derive from studies of patients with well-defined diagnoses, based on classification or diagnostic criteria.^{1–5} However, many patients who fulfil criteria for one diagnosis have overlapping findings of a second autoimmune illness (2nd AI).⁶ For instance, patients with SLE together with rheumatoid arthritis (RA) are said to have 'rhupus',⁷ those with features of several diagnoses are said to have 'mixed connective tissue disease',⁸ and other patients who incompletely fulfil criteria are said to have 'undifferentiated connective tissue disease'.⁹ Other combinations of overlap, for instances of SLE and scleroderma or RA and multiple sclerosis (MS), do not have names. Most disease-specific studies that form the basis of clinical descriptions, analysis of mechanisms, outcome measurements or treatment guidelines do not specifically state if patients with a 2nd AI are or are not included. Thus, it is difficult to determine whether conclusions apply to those with overlap disease or if the results attributed to 'pure' disease are altered because they are included.

KEY MESSAGES

- ▶ Overlapping autoimmune disease is common in patients with SLE.
- ▶ Patients with overlap differ in age, sex, race and treatment from those without overlap.
- ▶ These differences may be important for interpretation of clinical and basic science studies.

The Barbara Volcker Center for Women and Rheumatic Disease (BVC) is a specialty referral centre in the Rheumatology Division of Hospital for Special Surgery. BVC physicians preferentially, but not exclusively, see patients with complex AIs, such as SLE, RA, Sjögren's syndrome and antiphospholipid syndrome (APS). The BVC patient population is racially, ethnically and economically diverse and is weighted towards women. In this study, we used the BVC database to examine whether patients with overlap differ in demography and treatment from those with 'pure' disease.

METHODS

Our hypothesis was that patients with and without 2nd AI differ in demography and in treatment. We defined 2nd AI as the occurrence of a diagnosable second rheumatic and/or non-rheumatic autoimmune disease in patients with criteria-defined SLE, RA, Sjögren's syndrome and/or APS (see Appendix).

This study retrospectively reviews all patients recorded in electronic databases of two cohorts seen at BVC. Cohort 1 contains demographic, clinical and treatment data on all patients seen by one physician between 1 May 2002 and 15 November 2014. Cohort 2 contains diagnosis (but not detailed demography and treatment) information for two other BVC physicians since July 2008. We calculated overlap frequency using both cohorts; we used only cohort 1 to calculate demography and treatment statistics. Because some patients had been seen by more than one BVC physician, cohorts were purged of duplicate entries, the most recent visit being chosen for analysis.

We assessed the occurrence of overlap in four groups of patients: (a) patients with SLE,



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defined by American College of Rheumatology (ACR) criteria;¹ (b) those with RA, defined by ACR 1987 criteria;² (c) those with Sjögren's syndrome, defined by ophthalmologist-prescribed artificial tears or punctal plugs, salivary gland hypertrophy and/or cryoglobulinaemia (we did not use the 2012 criteria for patients with Sjögren's syndrome⁴ because most did not have the biopsies that are required); and (d) those with APS (Sydney revision of the Sapporo criteria).⁵ Under APS, we also included patients with high-titre antiphospholipid antibody and the following non-criteria manifestations: echocardiographically or MRI-documented cardiac valve disease, typical MRI-documented brain disease not otherwise explained, histopathologically documented APS nephropathy or leg ulcers not otherwise explained.¹⁰ In the tables, patients with two or more of SLE, RA, Sjögren's syndrome or APS diagnoses are included in each relevant diagnosis.

BVC physicians confirmed all diagnoses of SLE, RA, Sjögren's syndrome, APS and other rheumatic 2nd AI. Non-rheumatic 2nd AIs were usually confirmed by us, according to conventional clinical criteria. However, in many cases, the diagnosis of non-rheumatic 2nd AI had been made by outside physicians. We considered autoimmune thyroid disease separately from other non-rheumatic 2nd AI because of prior suggestions of its high prevalence in patients with rheumatic disease.

Many patients were first seen on referral after many years of illness, some 2nd AI diagnoses were remote and relied on patient recall and/or incomplete outside records. For this reason, concatenation and remote treatment were not considered accurate enough to merit detailed analysis. Instead, we analysed treatment at the patient's most recent visit.

People with serological abnormalities only or with non-autoimmune rheumatic illness, such as osteoarthritis, gout, fibromyalgia and osteoporosis, were not included in this study. This study was approved by the Hospital for Special Surgery Institutional Review Board.

STATISTICS

Within group, incidence comparisons are made by χ^2 analysis using 2x2 contingency tables and a Bonferroni correction when indicated. Mean ages are compared by Student's two-tailed t test using two degrees of freedom.

RESULTS

Frequency of overlap

The BVC databases contained 3887 individual patients (2542 in cohort 1 and 1345 in cohort 2), of whom 1321 had diagnoses of SLE, RA, Sjögren's syndrome and/or APS. Eight hundred and ninety-seven (68%) had diagnoses of 'pure' disease and 424 (32%) had one of these four diagnoses combined with one or more 2nd AI.

The two cohorts demonstrated similar frequencies of 2nd AI. A 2nd AI occurred in 38% of patients with SLE, 30% of patients with RA, 52% of patients with

Sjögren's syndrome and 43% of patients with APS (tables 1–4). No obvious pattern of overlap of a specific 2nd AI occurred among patients, nor was there predilection for a specific 2nd AI to occur among patients who had more than one overlapping illnesses. Coexistence of SLE with APS was common. Depending on the original rheumatic disease diagnosis, autoimmune thyroid disease occurred in 11%–26% of patients.

Demography

Demographic and last-visit treatment data for patients in cohort 1 are shown in table 5. Patients with 'pure' SLE were younger than patients with SLE and 2nd AI. Patients with 'pure' RA were less often female than those with 2nd AI, and 'pure' Sjögren's syndrome were more often seen in white patients.

Effect of overlap on treatment at last visit

At last visit, patients with SLE and a 2nd AI were less likely to receive corticosteroid and/or hydroxychloroquine (HCQ) than those with 'pure' SLE (table 5). Patients with RA and a 2nd AI were more likely to receive HCQ, and patients with APS and a 2nd AI were more likely to receive corticosteroid, HCQ and immunosuppressive therapy than those with 'pure' disease. Patients with Sjögren's syndrome with and without overlap did not differ in treatment.

Concatenation of overlap

Three clinical patterns of overlap occurred. In the most common pattern, patients had two or more well-defined autoimmune rheumatic diagnoses simultaneously present, such as 'rhus'. In the second pattern, a rheumatic AI coexisted with a non-rheumatic AI, such as Hashimoto thyroiditis, MS or Crohn's disease. In the third pattern, onsets of 2nd AIs were asynchronous, but in no fixed sequence: rheumatic and non-rheumatic 2nd AI could precede or follow diagnosis of the index illness. The intervals between occurrences of the two or more diagnoses, when known, were highly variable. A few patients evolved from one rheumatic diagnosis (eg, SLE) to another (eg, RA) over many years. In these patients, conversion was both clinical and serological and included the development of erosive disease and typical biopsy-proven subcutaneous nodules. Two patients redeveloped clinical and serological SLE after years of clinical and serological RA.

DISCUSSION

Our data demonstrate that 2nd AIs, rheumatic and non-rheumatic, occur in 30%–52% of patients who have a diagnosis of SLE, RA, Sjögren's syndrome or APS. Patients with SLE with overlap differ in age and treatment from those with 'pure' disease, patients with RA differ in sex and treatment, patients with Sjögren's syndrome differ in race and patients with APS differ in treatment. Neither the high frequencies of 2nd AI nor

Table 1 Distribution of 2nd AI in 600 individual patients who had SLE

Diagnosis	APS	RA	Sjögren's	Other rheum	Thyroid	Non-rheum	No.	Total	Per cent
SLE only								371	62
	+						75		
		+					16		
SLE +1 other dx			+				18	201	34
				+			19		
					+		40		
						+	33		
	+	+					1		
	+		+				1		
	+		+	+			1		
	+		+	+			3		
SLE + ≥ 2 other dx	+				+		4	28	5
	+				+	+	1		
	+					+	8		
		+		+			2		
		+			+		2		
		+				+	1		
		+	+	+			2		
		+			+	+	1		
		+		+	+		1		
ALL SLE	94	25	28	28	49	44	229	600	100

APS accounted for most overlaps, but other illnesses were frequent.
2nd AI, second autoimmune illness; APS, antiphospholipid syndrome; dx, diagnosis; RA, rheumatoid arthritis; rheum, rheumatic 2nd AI; SLE, systemic lupus erythematosus.

the demographic and treatment differences between patients with 'pure' disease and those with 2nd AI are acknowledged in most contemporary clinical descriptive, treatment, outcome and mechanistic discussions of these illnesses.

Chambers *et al*⁶ reviewed ethnicity, time course and cumulative damage occurring in a 26-year experience of patients with SLE. In that series, 61 (15%) of 401 patients had overlap syndromes. Compared to matched patients

without overlap, patients with 2nd AIs had more disease-associated damage; there were no ethnic differences. The authors did not report the roles of age, sex or treatment. In comparison, our study found a higher prevalence (38%) of overlap among patients with SLE, important differences in age and treatment patterns between those with and without 2nd AI and parallel differences among patients with RA, Sjögren's syndrome and APS. We did not find ethnic differences in the

Table 2 Distribution of 2nd AI in 309 patients who had RA

Diagnosis	SLE	APS	Sjögren's	Other rheum	Thyroid	Non-rheum	No.	Total	Per cent
RA only								217	70
	+						16		
		+					3		
RA +1 other dx			+				13	81	26
				+			7		
					+		25		
						+	17		
	+	+					1		
	+			+			2		
	+				+		2		
RA + ≥ 2 other dx	+		+	+			2	11	4
	+					+	1		
	+				+	+	1		
			+			+	1		
					+	+	1		
ALL RA	25	4	16	11	29	21	92	309	100

There was no dominant illness accounting for overlap.

2nd AI, second autoimmune illness; APS, antiphospholipid syndrome; dx, diagnosis; RA, rheumatoid arthritis; rheum, rheumatic 2nd AI; SLE, systemic lupus erythematosus.

Table 3 Distribution of 2nd AI in 157 patients who had Sjögren's syndrome

Diagnosis	SLE	APS	RA	Other rheum	Thyroid	Non-rheum	No.	Total	Per cent
Sjögren's only								76	48
Sjögren's +1 other dx	+						18		
		+					3		
			+				13	65	41
				+			8		
					+		13		
						+	10		
Sjögren's + ≥ 2 other dx	+	+					1		
	+	+		+			1		
	+		+	+			2		
	+			+			1		
	+				+		4	16	10
	+					+	1		
			+	+			2		
			+			+	1		
				+	+		1		
					+	+	2		
ALL SJÖGREN'S	28	5	18	15	20	14	81	157	100

There was no dominant illness accounting for overlap.

2nd AI, second autoimmune illness; APS, antiphospholipid syndrome; dx, diagnosis; RA, rheumatoid arthritis; rheum, rheumatic 2nd AI; SLE, systemic lupus erythematosus.

occurrence of 2nd AI. The histories of a few of our patients indicate that overlap is not always static or cumulative; indeed, diagnoses can change repeatedly over time.

The high frequency of overlap suggests a need to consider its possible effect on conclusions drawn from prior studies. The differences we find between patients with and without a 2nd AI, together with the report of Chambers *et al* suggest that the effect of 2nd AI may be large. The retrospective design of both studies precludes a conclusive

answer to the question whether the quantitative or qualitative effect of overlap is or is not important for formulating treatment policies. To answer it definitively will require a prospective study that separately analyses 'pure' and overlap patients. Pending such a study, we advise that conclusions regarding mechanisms, treatment effects, outcomes and best practices not assume that the same rules apply to patients without and with overlap.

Strengths of our study are that it is a large experience of rheumatologists at a university referral centre; it

Table 4 Distribution of 2nd AI in 406 patients who had APS

Diagnosis	SLE	RA	Sjögren's	Other rheum	Thyroid	Non-rheum	No.	Total	Per cent
APS only								233	57
	+						75		
		+					3		
APS +1 other dx			+				3	147	36
				+			28		
					+		16		
						+	22		
	+	+					1		
	+		+				1		
	+		+	+			1		
	+			+			3		
	+				+		4		
APS + ≥ 2 other dx	+					+	8	26	6
	+				+	+	1		
				+	+		3		
				+		+	3		
					+	+	1		
ALL APS	93	4	5	38	25	35	173	406	100

SLE accounted for most overlaps, but other illnesses were frequent.

2nd AI, second autoimmune illness; APS, antiphospholipid syndrome; dx, diagnosis; RA, rheumatoid arthritis; rheum, rheumatic 2nd AI; SLE, systemic lupus erythematosus.

Table 5 Demographic and last-visit treatment characteristics of patients with SLE, RA and APS with and without 2nd rheumatic and/or non-rheumatic illness AI in cohort 1 <colcnt=9>

Diagnosis (N)	Overlap	No.	Mean age years	Female %	White %	Steroid %	HCQ %	Immun %
SLE (399)	No overlap	265	42.1	94	66	59	55	29
	Overlap	134	47.1****	90	71	47*	42*	25
RA (198)	No overlap	147	54.7	86	74	47	16	61
	Overlap	51	54.3	100***	76	51	37***	57
Sjögren's (130)	No overlap	59	51.6	95	88	29	30	11
	Overlap	71	48.4	95	75*	28	30	20
APS (208)	No overlap	145	46.9	70	94	23	23	8
	Overlap	63	46.4	75	86	41**	37*	19*

Patients with two or more diagnoses are counted in each relevant diagnosis group. Statistically significant differences are shown in bold. Differs from those with no overlap, *p<0.05, **p<0.01, ***p<0.005, ****p<0.0005.

AI, autoimmune illness; APS, antiphospholipid syndrome; HCQ, hydroxychloroquine; Immun, immunosuppressive agent; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

should be easy for others to verify or refute our findings. A weakness is its retrospective design. Because our study emanates from a specialty clinic, the overlap rates we report may not be generalisable to clinics with different populations. However, that our two cohorts had similar rates of overlap suggests that the findings are real. Furthermore, when we have discussed these conclusions in public forums, physicians from other institutions have found them to have face validity. Presuming that others confirm our conclusions, re-evaluation of clinical trial design, treatment guidelines and administrative codes to account for such patients will be required.

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Competing interests None declared.

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APPENDIX

Autoimmune rheumatic diseases include: carotidynia, cryoglobulinaemia, dermatomyositis and polymyositis, discoid lupus erythematosus (LE), juvenile arthritis, nephrogenic fibrosing dermopathy, palindromic rheumatism, arthritis due to parvovirus B19, idiopathic pericarditis, polymyalgia rheumatica, psoriatic arthritis, isolated Raynaud's phenomenon, reactive arthritis (including sacroiliitis and spondyloarthropathy), relapsing polychondritis, retroperitoneal fibrosis, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, sarcoidosis, scleroderma (including CREST syndrome, morphea and linear scleroderma). Vasculitis was separately diagnosed when it merited separate analysis and treatment and was not associated with SLE, RA, Sjögren's syndrome or APS; it includes granulomatosis with polyangiitis, Behçet disease, Kawasaki disease, giant cell arteritis, Takayasu, polyarteritis nodosa and leucocytoclastic vasculitis. Non-rheumatic autoimmune diseases include: autoimmune haemolytic anaemia, autoimmune hearing loss, autoimmune hepatitis, uveitis and gastroparesis, alopecia (areata and totalis), coeliac,

Crohn's disease, cutaneous amyloid, type 1 diabetes, diabetes insipidus, erythema nodosum, eczema, erythema multiforme, granuloma annulare, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura not associated with SLE, MS, myasthenia gravis, neuromyelitis optica, primary biliary cirrhosis, pityriasis, psoriasis without arthritis,

retinitis pigmentosa, transverse myelitis, ulcerative colitis, generalised urticaria not associated with SLE or known allergen and vitiligo. Autoimmune thyroid disease includes: Graves, Hashimoto and high-titre antithyroid peroxidase or thyroglobulin antibody while euthyroid.