Severe, life-threatening phenotype of primary Sjögren's syndrome: clinical characterisation and outcomes in 1580 patients (the GEAS-SS Registry)

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ABSTRACT

Objective. *To analyse the clinical features and outcomes of patients presenting with life-threatening systemic disease in a large cohort of Spanish patients with primary Sjögren's syndrome (SS).*

Methods. *The GEAS-SS multicentre registry was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included more than 20 Spanish reference centres with substantial experience in the management of SS patients. By January 2018, the database included 1580 consecutive patients fulfilling the 2002 classification criteria for primary SS. Severe, life-threatening systemic disease was defined as an activity level scored as "high" in at least one ESSDAI domain.*

Results. *Among 1580 patients, 208 (13%) were classified as presenting a severe, potentially life-threatening systemic disease: 193 presented one ESSDAI domain classified as high, 14 presented two high scored domains and only one presented three high activity domains. The ESSDAI domains involved consisted of lymphadenopathy in 78 (37%) cases, CNS in 28 (13%), PNS in 25 (12%), pulmonary in 25 (12%), renal in 21 (10%), cutaneous in 19 (9%), articular in 18 (9%), haematological in 7 (3%) and muscular in 4 (2%). Patients with severe systemic disease were more frequently men (p=0.001) and had a higher frequency of anaemia (p<0.001), lymphopenia (p<0.001), rheumatoid factor (p=0.021), low C3 levels (p=0.015), low C4 levels (p<0.001) and cryoglobulins (p<0.001). From a therapeutic point of view, systemic patients received more frequently glucocorticoids (p<0.001), immunosuppressants (p<0.001), intravenous immunoglobulins (p=0.008) and rituximab (p<0.001). We found an overall mortality rate of 20% in severe systemic patients, a rate that reached 33% in patients presenting two or more high systemic involvements; these patients had a higher frequency of low C4 levels (p=0.012) and cryoglobulins (p=0.001) in comparison with those with a single severe organ involved.*

Conclusion. *13% of patients with primary SS develop a potentially life-threatening systemic disease (mainly lymphoma, but also severe internal organ involvements including nervous system, the lungs and the kidneys). This subset of patients requires intensive therapeutic management with a mortality rate of nearly 20% of cases.*

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that affects overwhelmingly women between the fourth and sixth decades of life (1). More than 95% of patients present with sicca symptomatology (mainly oral and ocular dryness) caused by dryness of the mucosal surfaces (2). The clinical spectrum of SS extends from sicca symptoms to systemic involvement and includes many organ-specific manifestations, including an enhanced risk of lymphoma, one of the most severe complications a SS patient may develop (3). Treatment of the disease is based principally on the management of sicca syndrome mainly with topical measures, and the use of

immunosuppressive / biological agents for systemic manifestations (4).

Systemic features may be the presenting manifestation or appear after the disease is diagnosed, and clearly mark the disease prognosis. Although various studies have identified several clinical and immunological prognostic factors related to poor outcomes (development of lymphoma, death) (5), very few studies have analysed the clinical phenotype of patients presenting with severe, potentially life-threatening systemic manifestations. We have recently reported that cryoglobulinaemic vasculitis present at diagnosis predicts mortality (6), while Baldini *et al*. (7) found severe systemic manifestations in 15% of patients, especially those with an immunological profile suggestive of B cell activation. A practical message is that patients with this clinical/immunological "high risk" pattern should receive a closer follow-up and, probably, earlier and more intense systemic therapy.

The development of the EULAR-SS disease activity index (ESSDAI) (8) by the EULAR task force on SS represented a step forward in the evaluation of systemic SS, and is currently the key standard tool used for measuring systemic activity of primary SS patients. The ESSDAI includes specific organ-by-organ definitions and allows homogeneous evaluation of systemic features in large series of patients classifying systemic activity in each organ as low, moderate or high. Therefore, those patients presenting the maximum degree of systemic activity (high) in a specific domain may be classified as having severe systemic Sjögren's syndrome.

The aims of this study were to identify those patients presenting with severe, potentially-life-threatening systemic manifestations defined according to high systemic activity scored by the ESSDAI, and to characterise their phenotype, therapeutic management and outcomes, in a large cohort of Spanish patients with primary SS.

Patients and methods

Patients

The GEAS-SS Study Group was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included 20 Spanish centres with substantial experience in the management of patients with systemic autoimmune diseases. By January 2018, the database included 1580 consecutive patients who fulfilled the 2002 classification criteria for primary SS (9). Exclusion criteria were chronic HCV/HIV infection, previous lymphoproliferative processes and associated systemic autoimmune diseases. Diagnostic tests for SS (ocular tests, parotid scintigraphy and salivary gland biopsy) were administered according to the European Community Study Group recommendations (9). Clinical and laboratory data were collected and computerised according to a standard protocol (5).

Definition of variables

The date of disease diagnosis was defined as the date when the attending physician confirmed fulfillment of the 2002 criteria (9). Systemic involvement was defined according to the ESSDAI (8), which evaluates 12 domains or organ systems. Each domain is divided into 3–4 levels according to the degree of activity and scored as 0 (no activity), 1 (low activity), 2 (moderate activity) or 3 (high activity). The ESSDAI score at diagnosis was retrospectively calculated by examination of medical records in order to collect disease activity at SS diagnosis. Severe systemic disease was defined as the presence of the maximum degree of systemic activity (high) in at least one of the following ESSDAI domains: lymphadenopathy/lymphoma, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, central nervous system and haematological. Death and cause of death were collected through the medical record: causes of death were categorised as systemic disease (death directly related to underlying systemic organ involvement or haematological neoplasia) and systemic-unrelated (infection, cardiovascular disease and other causes) as previously reported (5).

Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. The Chi-square test was used to study the association between high activity level with gender, ethnicity, diagnostic tests for SS, immunological markers, treatment and mortality. One-way ANOVA tests were used to compare the mean age at diagnosis. All significance tests were two-tailed and values of $p<0.05$ were considered significant. *p*-values were adjusted for multiple comparisons using the false discovery rate (FDR) correction. All analyses were conducted using the R v. 3.2.3 for Windows statistical software package (https://www.R-project.org/).

Results

a) Baseline characterisation

Baseline characteristics are summarised in Table I. The cohort consisted of 1580 patients, including 1468 (93%) females with a mean age at diagnosis of 55.3 (range, 14–88). At diagnosis, 1539 (97.4%) patients presented dry mouth, 1518 (96.1%) dry eye, 1235/1398 (88.3%) had altered ocular diagnostic tests (Schirmer's test and/or corneal staining), 1065/1238 (86%) altered parotid scintigraphy and 635/790 (80.4%) a salivary gland biopsy showing focal lymphocytic infiltration (Chisholm-Mason grade 3–4). The main immunologic features at diagnosis were ANA ≥1/80 in 1373/1570 (87.5%) patients, anti-Ro/SS-A in 1185/1574 (75.3%), RF in 697/1510 (46.2%), anti-La/SS-B in 716/1568 (45.7%), low C4 levels in 176/1482 (11.9%), low C3 levels in 166/1496 (11.1%), monoclonal gammopathy in 129/1243 (10.4%) and cryoglobulinaemia in 106/1167 (9.1%) patients.

b) Characterisation of high systemic activity

After a mean follow-up of 10.2 years, 208 (13%) patients developed systemic disease scored as high ESSDAI activity in the following domains: lymphoma (n=78), central nervous system (n=28), peripheral nervous system (n=25), pulmonary (n=25), renal (n=21), cutaneous (n=19), articular (n=18), haematological (n=7, including 4 patients with autoimmune thrombocytopenia, 2 with haemolytic anaemia, and one with both severe cytopenias) and muscular (n=4).

Table II summarises the main epidemiological/clinical features, therapeutic management and outcomes for each domain. There were 180 (86%) women with a mean age of 59.1 years (range 15–88) at the time of diagnosis of high systemic activity, although there was a significant different distribution of the age at presentation according to the involved organ (Fig. 1).

There was a wide variety of clinical presentations, although the most frequent in each domain were localised lymphoma (n=41), symmetric polyarthritis (n=17), vasculitic ulcers in the legs (n=10), severe ILD (n=24), renal failure (n=11), severe myopathy (n=4), ganglionopathy (n=11), myelitis (n=9) and severe thrombocytopenia (n=5). The affected organs with the widest heterogeneous clinical and histopathological scenarios are the lungs, the kidneys and the nervous system (Fig. 2).

Therapeutic management overwhelmingly included glucocorticoids, immunosuppressive agents and/or biologics. Patients with lymphoma were mainly treated with RTX-based chemotherapic regimens; the remaining patients were treated with glucocorticosteroids (85%), immunosuppressive agents (44%), rituximab (11%), intravenous immunoglobulins (8%) and plasma exchanges (2%). Organ by organ, the immunosuppressive agent more frequently used was azathioprine for pulmonary and neurological features, and methotrexate for articular; rituximab and intravenous immunoglobulins were mainly used in patients with neurological involvement. Rates of complete response varied widely, from the 20–30% observed for involvement of internal organs (neurological, pulmonary and renal) to the 70–100% reported for articular, cutaneous and haematological involvements.

At the end of the follow-up, 15 (7%) patients initially classified as primary SS met the criteria for an additional disease, including rheumatoid arthritis (n=9), vasculitis (n=3), myopathies (n=2) and SLE (n=1) (Table III). Forty-two (20%) patients died, including patients for each domain except for the articular domain, of whom all but 4 died due to causes their systemic involvement.

Table IV summarises the comparison of the main epidemiological, clinical, laboratory and immunological features at diagnosis between patients presenting with and without high systemic disease. Patients with severe systemic disease were more frequently men (13.5% *vs*. 6.1%, p=0.001) and had a higher frequency of anaemia (20.9% *vs*. 10.7%, p<0.001), lymphopenia (20.9% *vs*. 10.7%, p<0.001), rheumatoid factor (55% *vs*. 44.8%, p=0.021), low C3 levels (17.2% *vs*. 10.2%, p=0.015), low C4 levels (21.2% *vs*. 10.5%, p<0.001) and cryoglobulins (22.9% *vs*. 6.7%, p<0.001). From a therapeutic point of view, systemic patients received more frequently glucocorticoids (62.5% *vs*. 32.4%, p<0.001) especially at a dosage equal or higher than 10 mg/d (56.7% *vs*. 18.6%, p<0.001), immunosuppressants (41.3% *vs*. 12%, p<0.001), intravenous immunoglobulins (6.2% *vs*. 2.3%, p=0.008) and rituximab (20.2% *vs*. 1.2%, p<0.001). A comparison between the 15 patients who presented with a multisystemic severe involvement (with high activity in at least two different domains) and the 193 who presented with a single severe organ involvement showed that multisystemic patients had a higher frequency of low C4 levels (50% *vs*. 18.9%, p=0.012) and cryoglobulins (58.3% *vs*. 20.3%, p=0.001) in the unadjusted analysis (Table V).

Table I. Baseline characteristics of 1580 patients with primary SS.

Variables at the time of SS diagnosis	n=1580
Gender (Female)	1468 (92.9)
Ethnia (White)	1511 (95.6)
Age at diagnosis	55.3 ± 15.4
Dry eye	1518 (96.1)
Dry mouth	1539 (97.4)
Abnormal ocular tests	1235/1398 (88.3)
Positive minor salivary gland biopsy	635/790 (80.4)
Parotid sialography	1065/1238 (86)
Anti-Ro antibodies	1185/1574 (75.3)
Anti-La antibodies	716/1568 (45.7)
Anaemia (Hb<11g/L)	258/1541 (16.7)
Leukopenia (<4000/mm^3)	274/1541 (17.8)
Thrombocytopenia (<150000/mm^3)	101/1541 (6.6)
Neutropenia (<1500/mm^3)	154/1540 (10)
Lymphopenia (<1000/mm^3)	186/1539 (12.1)
Monoclonal band	129/1243 (10.4)
ANA+	1373/1570 (87.5)
RF+	697/1510 (46.2)
Low C3 levels	166/1496 (11.1)
Low C4 levels	176/1482 (11.9)
Cryoglobulins	106/1167 (9.1)

HB: haemoglobin; ANA: antinuclear antibodies; RF: rheumatoid factor.

Discussion

Primary SS is often considered a chronic, non-life-threatening disease, overwhelmingly dominated by dryness, fatigue and pain. However, systemic involvement is increasingly recognised as part of the disease spectrum, since it is present at diagnosis in 70-80% of patients (7, 10), and plays a key role in the prognosis of primary SS, with the joints, lungs, skin and peripheral nerves being the organs most frequently involved. Three recent multicentre studies including more than 2,500 European patients from France, Spain and Italy have confirmed that primary SS is, undeniably, a systemic autoimmune disease (7, 10, 11). In one of these studies, Baldini *et al*. (7) found severe systemic manifestations in 15% of patients, defined on the basis of the requirement of immunosuppressive drugs, including active synovitis (11%), axonal sensory-motor neuropathy (2%), severe neutropenia or lymphopenia (14%), diffuse purpura or ulcers related to cutaneous vasculitis (6%), renal involvement (2%), myositis (0.5%) or CNS involvement (1%) and lymphoma (5%).

Severe, life-threatening involvement has been rarely investigated in primary SS, and few data about their impact on disease survival is available. A review of 2241 patients with primary SS in which

Table II. Main epidemiological and clinical features, therapeutic management and outcomes of patients with high ESSAI in each domain.

ESSDAI domain	Lymphoma	Articular	Cutaneous	Pulmonary	Renal	Muscular	PNS	CNS	Haematological
Patients									
n (%)	78 (37%)	18 (9%)	19 (9%)	25 (12%)	21 (10%)	4 (2%)	25 (12%)	28 (13%)	7 (3%)
Multiple involvement (%)	4/78 (5%)	0/18 (0%)	7/19 (37%)	6/25 (24%)	5/21 (23%)	0/4 (0%)	6/25 (29%)	3/28 (11%)	2/7 (29%)
Women (%)	66 (85%)	17 (94%)	16 (84%)	22 (88%)	18 (86%)	3 (75%)	21 (84%)	25 (89%)	7 (100%)
Mean age (range)	62 (31-87)	53 (31-75)	60.3 (32-88)	67.12 (43-87)	60.61 (25-83)	47.5 (34-57)	56.64 (34-82)	52.14 (15-84)	55.4 (19-87)
Clinical diagnosis (n)	Local lymphoma (n=41) Systemic (n=37)	Oligoarthritis (n=1) PA (n=17) PA (n=17)	Urticaria (n=2) Diff. Purpura (n=7) Ulcers legs (n=10)	COPD no smoke (n=1) ILD NS (n=1) LIP (n=4) NSIP (n=6) UIP (n=9) ON (n=3) Shrinking lung (n=1)	Haematuria (n=1) Nephritic (n=2) Nephrotic (n=2) Proteinuria (n=5) Renal failure (n=11)	Severe weakness (n=4)	PN (n=7) CIPD (n=1) Ganglionopathy (n=11) MM (n=7)	Cerebral vasc (n=1) CVA (n=5) Meningitis (n=7) MS-like (n=4) Seizures (n=2) Myelitis (n=9)	HA (n=3) ITP (n=5)
Histopathological diagnosis (n)	MALT (n=33) DLBC (n=11) Others (n=34)	Not applicable	Leukocytoclastic (n=10) Necrotising (n=2) Other diagnosis (n=3)	NIL (n=1) NINE (n=3)	IN (n=4) MPGN (n=4) PGN (n=3) MGN (n=2) MCGN (n=1) SFGN (n=1) Sclerosis (n=1) Unconclusive (n=1)	DM (n=1) No conclussive (n=1) IBM (n=1) NS (n=1)	SV vasculitis (n=1) MV vasculitis (n=1) NS (n=1) Unconclussive (n=3)	Not applicable	Not applicable
Treatment (n)	RTX-based Cht (n=39), non-RTX Cht (n=13), radiotherapy/ surgery (n=6), nothing (n=6), others (n=5), no data (n=9)	GC (n=18), MTX (n=11), LFM (n=5), Aza (n=2), RTX (n=1), ETA (n=1) HCQ (n=8)	GC (n=18), Aza (n=4), MTX (n=3), CYC (n=2), MF (n=2), NS (n=1)	GC (n=23), Aza (n=7), MF (n=4), CYC (n=1), RTX (n=2), HCQ (n=3)	GC (n=17), CYC (n=4), TAC (n=2), MF (n=2), CyA (n=1), RTX (n=2), HCQ (n=3)	GC (n=3), Aza (n=2)	GC (n=20), Aza (n=3), MF (n=2), RTX (n=5), IVIG (n=8), HCQ (n=2), Pex (n=1)	GC (n=15), Aza (n=6), CYC (n=5), MF (n=2), RTX (n=3) HCQ (n=1), IVIG (n=2), IFNb (n=1)	GC (n=7), HCQ (n=1)
Therapeutic response									
Complete response	41/64 (64%)	13 (72%)	15 (79%)	6 (24%)	4/20 (20%)	2 (50%)	7/24 (29%)	8 (29%)	7 (100%)
Partial response/stabilisation	12/64 (19%)	5 (28%)	0 (0%)	15 (60%)	8/20 (40%)	1 (25%)	12/24 (50%)	16 (57%)	0 (0%)
No response	10/64 (16%)	0 (0%)	4 (21%)	4 (16%)	8/20 (40%)	1 (25%)	5/24 (21%)	4 (14%)	0 (0%)
Outcomes									
Other diseases	0 (0%)	RA (n=9) (50%)	PAN (n=1), PAM (n=1) (10%)	0 (0%)	SLE (n=1), PAM (n=2)	DM (n=1), IBM (n=1)	0 (0%)	0 (0%)	0 (0%)
Death	15 (19%)	0 (0%)	3 (16%)	5 (20%)	4 (20%)	1 (25%)	2 (8%)	3 (11%)	2 (28%)

MALT: mucosa-associated lymphoid tissue; DLBC: diffuse large B-cell lymphoma; RTX: rituximab; Cht: chemotherapy; PA: polyarthritis; GC: glucocorticosteroids; MTX: methotrexate; LFM: leflunomide; Aza: azathioprine; ETA: etanercept; HCQ: hydroxychloroquine; RA: rheumatoid arthritis; Diff. : diffuse; CYC: cyclophosphamide; MF: mycophenolate; NS: not specified; PAN: polyarteritis nodosa; PAM: microscopic polyangiitis; COPD: Chronic obstructive pulmonary disease; ILD; interstitial lung disease; LIP: lymphocytic interstitial pneumonia; NSIP: non-specific interstitial pneumonia; UIP: usual interstitial pneumonia; ON: organising pneumonia; IN: interstitial nephritis; MPGN: membranoprolifetive glomerulonephritis; PGN: proliferative glomerulonephritis; MGN: membranous glomerulonephritis; MCGN: mesangiocapillary glomerulonephritis; SFGN: segmental and focal glomerulonephritis; TAC: tacrolimus; SLE: systemic lupus erythematosus; DM: dermatomyositis; IBM: inclusion body myositis; PN: polyneuropathy; CIPD: chronic idiopathic demyelinating polyradiculopathy; MM: multiplex multineuritis; SV: small-vessel; MV: medium-vesssel; IVIG: intravenous immunoglobulins; Pex: plasma exchanges; CVA: cerebrovascular accident; MS: multiple sclerosis; IFNb: interferon beta; HA: haemolytic anaemia; ITP: immunothrombocytopenia.

mortality rates and causes of death were detailed in 9 studies found that 17 (8%) out of 221 reported deaths were due to SS-related systemic involvement but excluding lymphoma (12). Reported overall mortality rates in primary SS cohorts have decreased progressively during the last four decades, from a rate of 40% in the seminal study by Kassan *et al.* (13) in 1978, from the 5–15% in studies published in the 2000s (14-18). Although mortality is mainly attributed to systemic disease and lymphoma, studies often include any mortality cause. Recently, we reported in our cohort that more than 50% of deaths were classified as unrelated to primary SS, with an overall SMR of 4.66 in comparison with general Spanish population that lowered to 2.51 when causes of death unrelated to SS were excluded (cardiovascular disease, non-haematological neoplasia) (5). In the present study, we found an overall mortality rate of 20% in severe systemic patients, a rate that reached 33% in patients presenting two or more high systemic involvements. Among the

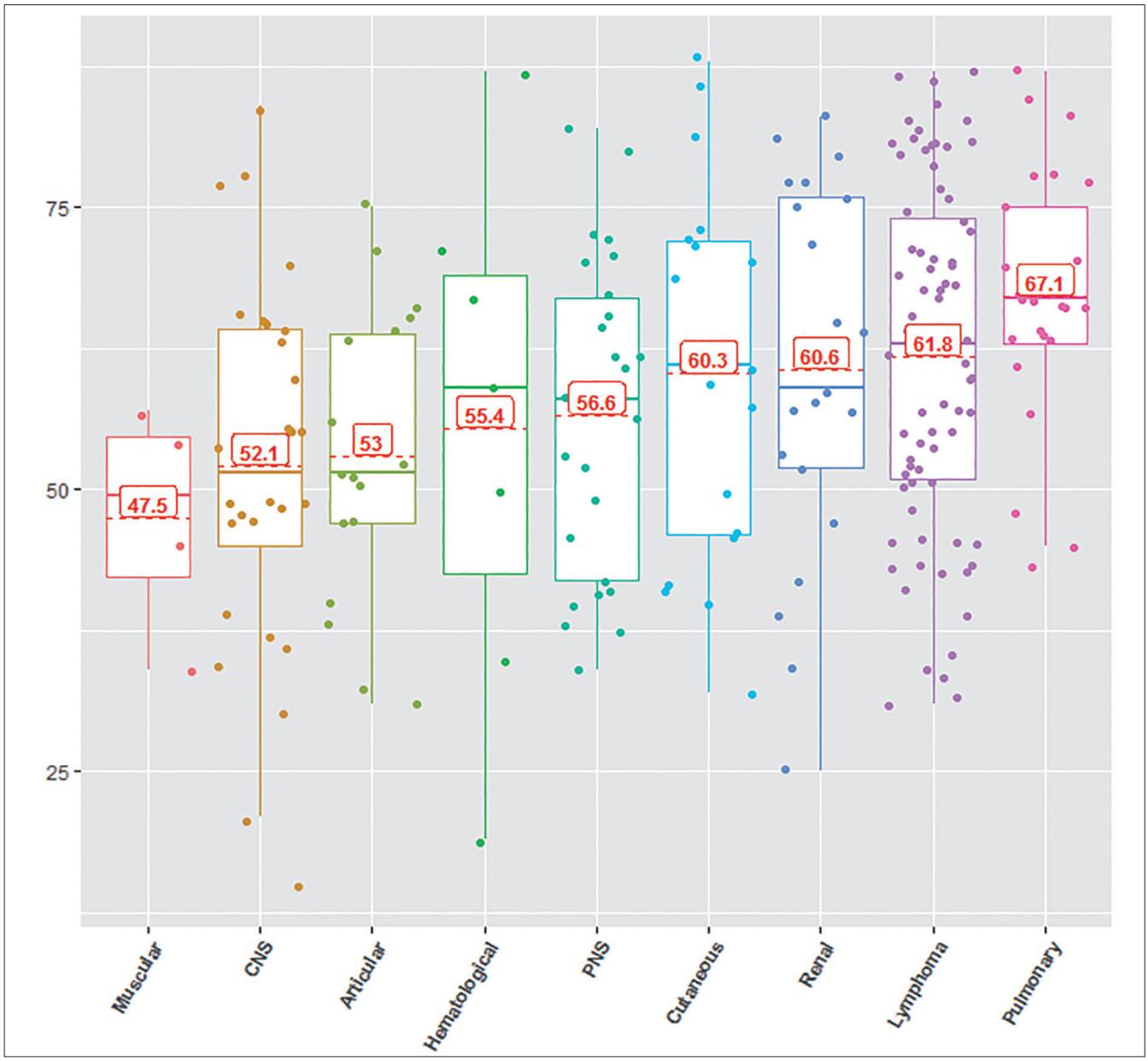

Fig. 1. Mean age at diagnosis of patients with high systemic activity in each organ ESSDAI domain.

42 deaths reported, 38 (90%) were directly related to high systemic activity.

The identification of baseline factors that confer a poor prognosis may be very useful in identifying, at diagnosis, patients who require a closer follow-up and treatment as early as possible. Vasculitis, hypocomplementaemia, cryoglobulins and monoclonal gammopathy have been identified as predictive factors in prospective European studies (15-23), and in a recent study, we added to these factors cytopenias and a higher mean ESSDAI score at diagnosis (5); those patients with high activity level in at least one domain had a higher mortality rate, as did those who had a high overall score (ESSDAI >13) according to the categories proposed by the EULAR Task Force (24). In the present study, we found that those patients who present with the highest ESSDAI score in the different domains were more frequently men, had a higher frequency of cytopenias (anaemia and lymphopenia) and immunological parameters directly related to mixed cryoglobulinaemia (RF, hypocomplementaemia and serum cryoglobulins). In addition, cryoglobulins were detected in nearly 60% of our patients with multiple high systemic involvement, with a mortality rate in these patients three-fold higher than that found in the non-severe SS population. Once again, we found that cryoglobulins play a central role in the severe systemic Sjögren's phenotype (6). Patients with cryoglobulinaemia, especially when there is vasculitic involvement, should be closely followed and treated early due to the high risk of adverse outcomes. However, a potential limitation of the study is the retrospective design, a fact that explains why cryoglobulins are not tested in all patients.

There are no controlled studies evaluating the therapeutic management of SS patients with a potential life-threat-

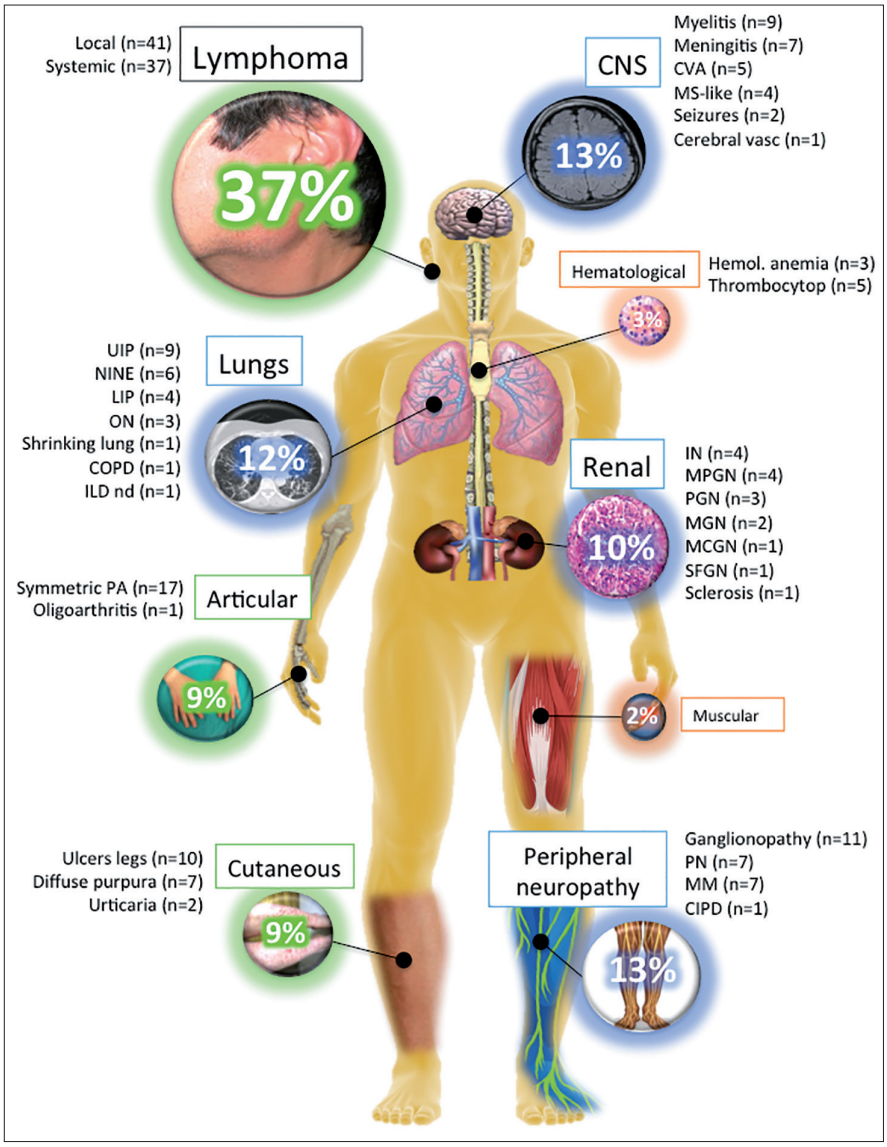

Fig. 2. The mosaic of clinicopathological presentations of severe systemic Sjögren's syndrome: organ-by-organ summary.

Table III. Main features of 15 patients diagnosed with an additional disease during the follow-up.

High activity ESSDAI	Additional disease	Follow-up (years)	Criteria for additional disease
Symmetric polyarthritis	RA	9	Erosive arthritis, rheumatoid nodules, RF+
Symmetric polyarthritis	RA	10	Erosive arthritis, CCP+
Symmetric polyarthritis	RA	6	Erosive arthritis, CCP+
Symmetric polyarthritis	RA	3	Erosive arthritis, CCP+
Symmetric polyarthritis	RA	11	Erosive arthritis, CCP+
Symmetric polyarthritis	RA	9	Erosive arthritis, CCP+
Symmetric polyarthritis	RA	2	Erosive arthritis, CCP+
Symmetric polyarthritis	RA	2	Erosive arthritis, axial involvement, RF+
Symmetric polyarthritis	RA	1	Erosive arthritis, CCP+
Diffuse purpura	PAN	6	Cutaneous biopsy
Diffuse purpura, glomerulonephritis	PAM	2	Renal biopsy, MPO+
Diffuse purpura, glomerulonephritis	PAM	8	Renal and cutaneous biopsies
Glomerulonephritis	SLE	14	Renal biopsy, lymphopenia, ANA+, DNA+
Severe weakness	DM	1	Muscular biopsy, Mi2+
Severe weakness	IBM	1	Muscular biopsy

ening phenotype, and only some retrospective studies (with <10 patients) and isolated case reports have been reported (25). Methylprednisolone and cyclophosphamide pulses are the most frequent therapeutic approach used in patients with severe systemic vasculitis or CNS involvement, with plasma exchange being added in the most severe situations (26), while rituximab is increasingly reported as a promising therapy, not only in patients with life-threatening situations but also in those with associated B-cell lymphoma (27-29). Our study shows that in real life practice, more than 20% of patients scored as having high ESSDAI activity in at least one domain were treated with rituximab, underlining its role in the management of severe, life-threatening Sjögren's syndrome.

With respect to the organ-by-organ ESSDAI analysis, there are three key messages for clinical practice that can be derived from the results of our study. The first is that the development of high activity in some specific organs is closely associated with the development of an additional systemic disease. This was especially reported in the articular and muscular domains, in which 50% of cases that were scored as high developed finally other diseases (rheumatoid arthritis and specific myopathies (30), respectively). In patients presenting with severe cutaneous and renal involvements, the frequency was of only 10%, including 4 cases of non-cryoglobulinaemic vasculitis and one case of SLE, while no additional systemic diseases appeared in patients with high activity at the pulmonary, neurological and haematological domains. The practical message is that some severe involvements in primary SS such as severe symmetric polyarthritis (≥6 synovitis) or severe muscular disease (severe weakness) are not only among the less frequent severe features, but also are mainly associated with the development of additional diseases, and therefore, to evolve from a primary form to an associated SS. The second practical message is that some severe systemic involvements are diagnosed earlier (below 55 years in patients with muscular, CNS and articular involvements) while oth-

Table IV. Comparison of the main epidemiological, clinical, laboratory and immunological features at diagnosis between patients presenting with and without high systemic disease.

Variables at the time of SjS diagnosis	High ESSDAI (n=208)	No high ESSDAI (n=1372)	*p*-value	Adjusted *p*-value
Gender (Female)	180 (86.5)	1288 (93.9)	**<0.001**	**0.001**
Ethnia (White)	200 (96.2)	1311 (95.6)	0.832	0.896
Age at diagnosis	55.6 ± 14.9	55.2 ± 15.5	0.769	0.896
Dry eye	201 (96.6)	1317 (96)	0.800	0.896
Dry mouth	202 (97.1)	1337 (97.4)	0.962	0.997
Abnormal ocular tests	170/184 (92.4)	1065/1214 (87.7)	0.087	0.151
Positive minor salivary gland biopsy	103/118 (87.3)	532/672 (79.2)	0.054	0.102
Parotid sialography	131/146 (89.7)	934/109 (85.5)	0.213	0.314
Anti-Ro antibodies	150/206 (72.8)	1035/1368 (75.7)	0.427	0.597
Anti-La antibodies	97/205 (47.3)	619/1363 (45.4)	0.664	0.845
Anaemia (Hb<11g/L)	49/206 (23.8)	209/1335 (15.7)	**0.005**	**0.014**
Leukopenia (<4000/mm^3)	40/206 (19.4)	234/1335 (17.5)	0.574	0.765
Thrombocytopenia (<150000/mm^3)	21/206 (10.2)	80/1335 (6.0)	**0.034**	0.069
Neutropenia (<1500/mm^3)	21/206 (10.2)	133/1334 (10.0)	1.000	1.000
Lymphopenia (<1000/mm^3)	43/206 (20.9)	143/1333 (10.7)	**<0.001**	**<0.001**
Monoclonal band	23/172 (13.4)	106/1071 (9.9)	0.210	0.314
ANA+	188/208 (90.4)	1185/1362 (87.0)	0.208	0.314
RF+	110/200 (55.0)	587/1310 (44.8)	**0.009**	**0.021**
Low C3 levels	33/192 (17.2)	133/1304 (10.2)	**0.006**	**0.015**
Low C4 levels	40/189 (21.2)	136/1293 (10.5)	**<0.001**	**<0.001**
Cryoglobulins	39/170 (22.9)	67/997 (6.7)	**<0.001**	**<0.001**
Hydroxychloroquine	61 (29.3)	381 (27.8)	0.701	0.854
Gucocorticoids	130 (62.5)	445 (32.4)	**<0.001**	**<0.001**
Immunosuppressive agents	86 (41.3)	164 (12.0)	**<0.001**	**<0.001**
Intravenous immunoglobulins	13 (6.2)	31 (2.3)	**0.002**	**0.008**
Rituximab	44 (21.2)	16 (1.2)	**<0.001**	**<0.001**
Death	42 (20.2)	192 (14)	**0.025**	0.054

HB: haemoglobin; ANA: antinuclear antibodies; RF: rheumatoid factor.

Table V. A comparison between patients presenting with a multisystemic severe involvement and those presenting with a single severe organ involvement.

Variables at the time of SjS diagnosis	Multiple organ high activity (n=15)	Single-organ high activity (n=193)	*p*-value	Adjusted *p*-value
Gender (Female)	13 (86.7)	167 (86.5)	1	1
Ethnia (White)	15 (100)	185 (95.9)	1	1
Age at diagnosis	52.3 ± 15.5	55.8 ± 14.8	0.379	0.816
Dry eye	15 (100)	186 (96.4)	1	1
Dry mouth	15 (100)	187 (96.9)	1	1
Abnormal ocular tests	13/15 (86.7)	157/169 (92.9)	0.319	0.816
Positive minor salivary gland biopsy	7/10 (70)	96/108 (88.9)	0.115	0.808
Parotid sialography	7/9 (77.8)	124/137 (90.5)	0.232	0.813
Anti-Ro antibodies	13/15 (86.7)	137/191 (71.7)	0.365	0.816
Anti-La antibodies	8/15 (53.3)	89/190 (46.8)	0.789	1
Anaemia (Hb<11g/L)	5/15 (33.3)	44/191 (23)	0.357	0.816
Leukopenia (<4000/mm^3)	2/15 (13.3)	38/191 (19.9)	0.740	1
Thrombocytopenia (<150000/mm^3)	2/15 (13.3)	19/191 (9.9)	0.655	1
Neutropenia (<1500/mm^3)	1/15 (6.7)	20/191 (10.5)	1	1
Lymphopenia (<1000/mm^3)	2/15 (13.3)	41/191 (21.5)	0.742	1
Monoclonal band	3/11 (27.3)	20/161 (12.4)	0.168	0.808
ANA+	14/15 (93.3)	174/193 (90.2)	1	1
RF+	11/15 (73.3)	99/185 (53.5)	0.180	0.808
Low C3 levels	3/14 (21.4)	30/178 (16.9)	0.712	1
Low C4 levels	7/14 (50)	33/175 (18.9)	**0.012**	0.174
Cryoglobulins	7/12 (58.3)	32/158 (20.3)	**0.007**	0.174
Hydroxychloroquine	4 (26.7)	57 (29.5)	1	1
Gucocorticoids	10 (66.7)	120 (62.2)	0.79	1
Immunosuppressive agents	6 (40)	80 (41.5)	1	1
Intravenous immunoglobulins	1 (6.7)	12 (6.2)	1	1
Rituximab	1 (6.7)	43 (22.3)	0.202	0.808
Death	5 (33.3)	37 (19.2)	0.191	0.808

HB: haemoglobin; ANA: antinuclear antibodies; RF: rheumatoid factor.

ers at older ages (over 65 years in those with pulmonary involvement). And the third practical message is the wide clinical and/or histopathological scenario found in some systemic organ-specific involvements, especially with respect to pulmonary (with predominance of UIP and NINE patterns), renal (predominance of membranoproliferative and proliferative glomerulonephritis) and neurological (predominance of myelitis and meningitis) involvements (Fig. 2). This mosaic of clinicopathological presentations still more enhances the need for a close multidisciplinary collaboration with the corresponding specialists, and underline the role of ESSDAI not only as a tool for measuring systemic activity, but also as a key determinant of prognosis in patients with primary SS, confirming the results of previous studies that linked high ESSDAI scores with poor outcomes (high risk of development of B-cell lymphoma and increased mortality) (5, 31-34).

In conclusion, 13% of patients with primary SS develop a potentially life-threatening phenotype that is defined as the development of high systemic ESSDAI activity in at least one organ domain, with an overall mortality rate of 20% (33% in patients with multiple severe involvements). The main severe clinical presentations included B-cell lymphoma and pulmonary and neurological involvements. Mean age at diagnosis, use of immunosuppressive/biological agents, therapeutic response and mortality rates varied widely among the different organ-specific ESSDAI domains. Measurement of systemic activity using the ESSDAI tool is very helpful in identifying a specific subset of patients with a poor survival and who are overwhelmingly treated with intense immunosuppressive regimens.

Appendix 1

The members of the SS Study Group, Autoimmune Diseases Study Group (GEAS), Spanish Society of Internal Medicine (SEMI) involved in this project have been:

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