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Review Article

Large Granular Lymphocyte Leukemia and Sjogren Syndrome: An Update of the Cases Reported in Literature and a New Clinical Perspective

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Abstract

Sjogren syndrome is a chronic autoimmune disease which disproportionately affects women, characterized by intense inflammation and destruction of the exocrine glands and multi-organ involvement. Furthermore, it is commonly associated with other autoimmune and hematological disorders and the latter of which are the focus of this brief review. More specifically, the association between Sjogren syndrome and large granular lymphocyte leukemia will be explored: this hematological malignancy, characterized by a clonal expansion of either T or NK cells, is usually extremely rare, but has been reported with a certain frequency in association with autoimmune disorders.

Until now, about thirty cases of an association between these two disorders have been reported: the review of their clinical and laboratory characteristics highlights frequent symptoms (cytopenia and autoimmune manifestations, especially involving the thyroid) and laboratory findings (such as an overwhelming involvement of T CD8 cells). These elements seem to underline commonalities in the pathogeneses of the two disorders, and on one side suggest that focusing on these common elements might help understand the diseases better (for example, by helping to

elucidate the role of T CD8 cells in Sjogren syndrome); on the other hand, they underline how important it is to conduct a thorough and timely screening for comorbidities in cases of Sjogren syndrome or large granular lymphocyte leukemia, in order to better treat the whole spectrum of the patients' problems.

Keywords: Sjogren Syndrome; Large Granular Lymphocyte

1. Introduction

Sjogren Syndrome (SS) is a chronic autoimmune systemic disease that mainly affects the exocrine glands (mostly salivary and lacrimal, but also oropharyngeal, nasal and vaginal in women), which are targeted by an intense inflammation, to the point of destruction [1]. Therefore, patients typically present ocular and oral symptoms with skin, nasal and vaginal dryness often associated. Systemic involvement such as musculoskeletal pain and fatigue is a common feature of this disorder: these symptoms, together with the dryness, represent the classic triad reported by a large number of patients. Specific organ involvement is frequent and up to 30-50% of SS patients present articular, pulmonary, neurological, or renal engagement [1].

Immunological and hematological alterations (such as hypergammaglobulinemia, cryoglobulinemia and various autoantibodies) are often described [2]. Indeed, SS is commonly associated with other autoimmune disorders, such as rheumatoid arthritis: these cases were once labelled as "secondary SS" in contrast to "primary SS" where there are no other autoimmune diseases; this distinction is now under debate, as the clinical management is the same for the two categories [1]. Leading causes of mortality in this disease include lymphoma, organ involvement (most commonly pulmonary, renal and vascular), infections and cardiovascular disease [3]. More specifically, Non-Hodgkin's lymphomas (NHL) occur in approximately 2.7-9.8% of SS patients and recent data reported that NHL risk increases 2.2% per year of age with a 4.3-fold increased risk in SS compared to the general population. 90% of these NHL are mucosa-associated lymphoid tissue lymphomas, diffuse large B-cell lymphomas and marginal zone lymphomas, but T cell-derived malignancies have been reported as well, such as angioimmunoblastic T cell lymphomas, T cell cutaneous involvement, pleomorphic T cell lymphomas, and T cell large granular lymphocyte (T-LGL) leukemia [4].

T-LGL is a clonal expansion of T cells and represents one of the two classes which LGL is divided into in the 2016 World Health Organization classification, together with natural killer cell LGL (NK-LGL) [5]. Up to one third of patients are asymptomatic at diagnosis indicating the usually indolent nature of this disorder, but when symptoms are present the most common ones are linked to the autoimmune condition and hematological impairment, as well as cytopenia. [6]. The diagnosis rests on the evidence of a chronic clonal lymphocyte expansion together with the appropriate clinical presentation: the first step of this process is usually represented by cytology, followed by flow cytometry and monoclonality assessments (in T-LGL cases, with T-cell receptor rearrangement analysis) [6]. Therapy, which is required in 60% of cases at diagnosis, is based on immunosuppressive agents, with methotrexate, cyclophosphamide and ciclosporin A usually preferred as first-line treatment [6].

The association between SS and T-LGL, although reported and recognized, has not been studied in depth as the one between other autoimmune diseases and this lymphoproliferative disorder (e.g. Felty syndrome, which is now hypothesized to be part of the same disease spectrum as LGL [7]): therefore, all cases of LGL and SS found through a literature search have been collected here, and in the following sections will be briefly described and discussed. The search has been limited to those cases where SS represented the main pathological condition, rather than those cases where it was secondary to other autoimmune disorders, which have been better discussed elsewhere (e.g. for rheumatoid arthritis, [8]).

2. Epidemiology

SS incidence varies between 3 and 11 cases per 100 000 individuals, while its prevalence is between 0.01 and 0.72%; it affects mainly women, with a female to male ratio close to 10:1, and it is usually diagnosed between 30 and 50 years of age [1]. Hematological diseases, more specifically lymphomas, represent one of the main causes of death [3]: one-third of cancers developed by patients are B-cell lymphomas [9], putting them at a sixteen-fold increased risk compared to the general population, which increases over time (the cumulative risk at five years from diagnosis being reported to be 3.4%, and that at fifteen years 9.8%) [10].

Comparatively less information is available regarding other hematological malignancies, with no data on T-LGL prevalence among SS patients currently available. On the other hand, LGL represents 2-5% of chronic lymphoproliferative diseases in Europe and North America, with 85% of the cases being of T origin [11], but it is more widespread among patients with autoimmune diseases [12].

Overall, 15 to 44% of LGL patients present an autoimmune disease [6], with rheumatoid arthritis being the most common, but vasculitis, systemic sclerosis, autoimmune thyroid disease, and other autoimmune diseases also being reported [11]; SS has been reported to have a prevalence of over 25% in LGL patients in one case series [13]. With the exception of aggressive NK-LGL, the disease is considered to be indolent, with an overall survival of around 70% at ten years [11]; less than 10% of patients develop severe infections, which represent the main cause of disease-related mortality [14].

3. Description of the Cases

Until now, about thirty cases of an association between SS and LGL have been reported, through both descriptive studies and case reports [13, 14, 15-19]. The characteristics of the patients from most case series [13-19] are reported in table 1 (it was not possible to obtain data from the four SS patients reported in the [15]). As expected, most patients are female, with only one man reported; the median age at diagnosis is 66 (range: 30 to 82 years old). It is somewhat difficult to ascribe the clinical manifestations to either SS or LGL, but it is possible to notice that cytopenias are by far the most common (found in seventeen patients), with leukopenia being the most widespread among them; other symptoms reported include sicca symptoms, arthralgia, and lung and kidney involvement.

In addition, about half of the patients also developed other autoimmune or hematological disorders, with autoimmune disorders of the thyroid being by far the most common (five cases of Hashimoto thyroiditis and three

cases of positive anti-thyroid antibodies without overt symptoms); other reported conditions include anemia of chronic disease and diabetes. Finally, treatment for these patients mainly consisted in immunosuppressive agents, together with supportive therapy for the cytopenias where needed (i.e. transfusions and granulocyte colony-stimulating factor): rituximab was commonly used for SS and lymphoma treatment in one series [14], while another popular choice is methotrexate, followed by cyclosporin A and hydroxychloroquine.

With regards to laboratory findings, the mean and median lymphocyte counts at diagnosis were respectively $3.9*10^9$/L and $3.1*10^9$/L (range: 0.8 to $9.6*10^9$/L). All but one case presented T-LGL, with CD8+ T cells being the ones overwhelmingly involved; when the immunophenotype was studied more in depth, these cells were found to express CD45RA (or, in one case, CD45R, no further analyses having been carried out) and CD57 (albeit the latter at varying levels), while CD16 and CD56 could either be expressed or not, in accordance to previous reports on T-LGL [6, 11]. When clonality was assessed, in most cases a clonal rearrangement of the T cell receptor (TCR) gene was found, although in a few cases the profile was oligoclonal rather than monoclonal; interestingly, in one case reported by [14], CD4+ T cells also showed an oligoclonal profile. Other laboratory findings included the presence of rheumatoid factor, anti-SSA and anti-SSB antibodies, and less commonly anti-nuclear antibodies and extractable nuclear antigen antibodies, which are common findings both in SS and LGL [1, 6, 11]. Finally, the polyclonal hypergammaglobulinemia and monoclonal components reported in two cases are other common findings in LGL, and monoclonal components have also been reported in SS [1, 6, 11].

Source	Sex	Age at diagnosis	Clinical manifestations	Lymphocyte count at diagnosis (*10^9/L)	Clonality	Immunophenotypic markers	Laboratory findings	Associated autoimmune or hematological disease	Treatment undergone for SS and LGL
Molad et al. 2001	F	65	Arthralgia, keratoconjunctivitis sicca, fatigue, weight loss	2.9 (maximum value reached: 4.5)	Not determined	CD8+, CD57+, CD16+	RF +, ANA +, anti-Ro antibodies +	None reported	Cyclosporin A
Molad et al. 2001	F	70	Neutropenia, xeropthlamia, xerostomia, fatigue, arthritis	6.3	Not determined	CD8+, CD57+/-	RF +, ANA +	Hashimoto thyroiditis	Not reported
Ergas et al. 2002	F	30	Pure red cell aplasia, amegak-aryocytic throm-bo-cytopenic pu-rpura, xeropthalmia, xerostomia	2.5	Clonal rearrangement of the TCR gene	CD8+, CD45R+	None reported	Hashimoto tyroiditis, premature ovarian failure	Azathioprine, blood and platelet transfusions, high dose intravenous immuneoglobulin, cyclosporin A, methotrexate, cyclophosphamide
Friedman et al. 2006	F	44	Pure red cell aplasia, agranulocytosis, immmune thrombocytopenia	7.8	Clonal rearrangement of the TCR gene in all but one patient	CD8+	None reported	None reported	Not reported
Friedman et al. 2006	F	68	None reported	4.2		CD4+, CD57+	Antithyroid antibodies +	Polycystic ovarian syndrome, anemia of chronic disease	Not reported
Friedman et al. 2006	F	64	None reported	4.1		CD4+	Antithyroid antibodies +	Angioneurotic edema	Not reported
Friedman	F	72	None reported	2.8		CD8+,	None reported	Diabetes, anemia	Not reported

et al. 2006						CD57+		of chronic disease	
Friedman et al. 2006	F	73	None reported	3.8		CD8+, CD56+	None reported	CREST syndrome	Not reported
Friedman et al. 2006	F	75	None reported	3.1		CD4+	None reported	Hashimoto thyroiditis	Not reported
Friedman et al. 2006	F	66	Agranulocytosis, immune thrombocy-topenia	4.3		CD8+	None reported	Hyperparathyroidism	Not reported
Friedman et al. 2006	F	64	Leukopenia	1		CD8+	None reported	Hashimoto thyroiditis, vitiligo	Not reported
Friedman et al. 2006	F	61	Agranulocytosis	1.2		CD8+	None reported	Diabetes	Not reported
Friedman et al. 2006	F	43	Agranulocytosis, Raynaud's phenomenon	0.8		CD8+	Monoclonal IgG k component	None reported	Not reported
Friedman et al. 2006	F	66	None reported	2.3		CD4+	Antithyroid antibodies +	None reported	Not reported
Friedman et al. 2006	F	63	None reported	9.6		CD8+, CD57+	None reported	Hashimoto thyroiditis	Not reported
Friedman et al. 2006	F	71	None reported	7.3		CD8+, CD56+	None reported	None reported	Not reported
Franco et al. 2010	F	73	Neutropenia, fever, splenomegaly, cervical lymphadenopathy, xerofthalmia, xerostomia	1.7	Clonal rearangement of the TCR gene	CD8+, CD57+, CD56-	Polyclonal hypergammaglobulinemia, monoclonal IgA lambda component,	Chronic disease related anemia	Methotrexate

							RF +, ANA +		
Baber et al. 2019	F	55	Arthralgia, interstitial nephritis, neutropenia	8.5	Oligoclonal TCR beta chain rearrangement	CD8+	Anti-SSA antibodies and RF +	Lymphoma	Hydroxy-chloroquine, R-bendamustine, methotrexate, G-CSF
Baber et al. 2019	M	62	Neutropenia	3.1	Oligoclonal TCR beta chain rearrangement	CD8+	Anti-SSA and anti-SSB antibodies and RF +	None reported	None
Baber et al. 2019	F	82	Autoimmune thrombo-cytopenia, neutropenia	2.4	Not determined	CD8+	None reported	None reported	None
Baber et al. 2019	F	80	Arthralgia, neutropenia	7.3	Not determined	NK cells	Anti-SSA antibodies +	None reported	None
Baber et al. 2019	F	80	Polyartritis, peripheral neuropathy, myositis, neutropenia	0.9	Oligoclonal TCR beta chain rearrangement	CD8+	RF +	None reported	Prednisone, methotrexate, rituximab
Baber et al. 2019	F	52	Arthralgia, interstitial lung disease, glomerulo-nephritis, cryo-globulinemia, neutropenia	0.9	TCR beta chain rearrangement monoclonal in CD8+ T cells and oligoclonal in CD4+ T cells	CD8+	RF +	None reported	Prednisone, rituximab

Baber et al. 2019	F	67	Arthralgia, cryo-globulinemia, neutropenia	3.3	Monoclonal TCR beta chain rearra-ngement	CD8+	RF +	Pulmonary AL amyloidosis	Rituximab
Baber et al. 2019	F	67	Peripheral neuropathy, cryglobulinemia, neutropenia	1	Oligoclonal TCR beta chain rear-angement	CD8+, CD57+/-, CD45RA+	Anti-SSA and anti-SSB antibodies and RF +	None reported	Rituximab
Tavarozzi et al. 2020	F	39	Xerophtalmia, xerostomia, anemia, thrombo-cytopenia	8.2	Monoclonal TCR beta chain rear-angement	CD8+, CD57+/-, CD45RA+	ANA, ENA, and anti-SSA antibodies +	None reported	Hydroxy-chloroquine

Table 1: Table with the main characteristics of Sjogren Syndrome (SS) and Large Granular Lymphocyte (LGL) leukemia patients. Abbreviations: ANA: anti-nuclear antibodies; CREST: calcinosis, Raynaud's phenomenon, esophageal dysmobility, sclerodactyly and teleangectasia; F: female; G-CSF: granulocyte colony stimulating-factor; M: male; NSAIDs: non-steroidal antinflammatory drugs; RF: rheumatoid factor; TCR: T cell receptor.

4. Discussion

From this brief overview, it is possible to observe some peculiar characteristics of the association between SS and LGL. For example, it appears that cytopenias, reported both in LGL and SS separately [1, 6, 11], become more common when the two are present together, although the reasons for this are not clear. More specifically, one report [14] focused on neutropenia and hypothesized a link between it, LGL expansions and rituximab treatment: according to the authors, it is possible that LGL expansions are linked to this treatment rather than to SS, and that neutropenia is therefore induced by rituximab either directly (neutropenia, especially late-onset, being a known adverse effect of the treatment) or through LGLs (which could be responsible for an immune-mediated depletion of these cells). This hypothesis cannot explain all occurrences of neutropenia, since it was also found in untreated patients, but it is certainly intriguing and worth investigating. On the other hand, other reports have hypothesized common pathogenetic mechanisms for SS and LGL, rather than the latter being caused by treatment: in 2001, a first hypothesis was made that an undefined retrovirus could trigger both SS and SS associated LGL lymphocytosis, drawing on the similarities between this condition and HIV associated diffuse infiltrative lymphocytosis syndrome [18]. However, this hypothesis was abandoned when it was observed that LGL expansions also occur in autoimmune disorders other than SS [13], in favor of concentrating more on the involvement of LGLs in SS pathogenesis: in one case LGLs were found to infiltrate the salivary glands [18], and it was observed that the cytokine released by LGLs of patients with and without SS had a similar profile, suggesting that they may contribute to the autoimmune disorder [13].

Indeed, it is widely recognized that T cells play an important role in development of SS, by secreting cytokines and contributing to the hyperactivation of B cells; however, most studies have focused on CD4+ cells, and less on CD8+, populations, from which LGL leukemias originate. It is known that they are found in glandular infiltrates and that a certain proportion of them shows an activated, HLA-DR+ phenotype, but not whether they contribute to organ or systemic damage [20]. However, a disease signature study [21] has started to shed light on the matter, by linking the specific SS gene signature to CD8+ cells, more specifically T_{EMRA} and HLA-DR+ cells. This would support the hypothesis that an expansion of the CD8+ T_{EMRA} population, such as the one which constitutes the T-LGL leukemias found in the case reports, can contribute to the development of SS – and of other autoimmune conditions as well, as seems to be indicated by the association of different disorders in the case series. From what little is known, LGL leukemia pathogenesis combines lymphoproliferation, chronic inflammation and autoimmunity: the current hypothesis envisions an initial, unknown antigen giving rise to an oligoclonal and then, thanks to chronic stimulation, monoclonal lymphocyte population, which in turn produces inflammatory cytokines, acts as killer cells and resists apoptosis [11]. Such a dysregulated and pro-inflammatory environment can be more easily found in the context of other systemic autoimmune disorders, and in turn be ideal for the development of other similar conditions.

5. Conclusions

In conclusion, still too little is known about LGL and SS to confidently outline their pathogeneses and the relationships between them, but it appears clear that there are connections between the two, as well as with a variety of other autoimmune disorders: therefore, particular attention must be paid during the diagnosis and follow up of

autoimmune diseases to detect at an early stage the occurrence of LGL and vice versa – indeed, one report highlighted the high prevalence of SS in LGL leukemia patients and the importance of actively screening for SS symptoms, even if patients do not always report them unless prompted [13]. An early detection can enable appropriate treatment to be put in place, with effective options being available to control both SS and LGL at the same time and improve outcomes and quality of life.

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