Shared pathogenetic features between Common Variable Immunodeficiency and Sjögren's syndrome: clues for a personalized medicine

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Keywords: common variable immunodeficiency disorders, Sjögren's syndrome, autoimmunity, immunodeficit, lymphoproliferation, BAFF, B cells, Interferon

Abstract:

Common variable immunodeficiency disorders (CVID) are a group of rare diseases of the immune system and the most common symptomatic primary antibody deficiency in adults with an estimated rate of diagnosis of 80% in subjects more than 16 years old. The "variable" aspect of CVID refers to the approximately half of the patients who develop non-infective complications, mainly autoimmune features, in particular organ specific autoimmune diseases including thyroiditis, and cytopenias. Among these associated conditions, the incidence of lymphoma, including mucosal associated lymphoid tissue (MALT) type, is increased.

Although these associated autoimmune disorders in CVID are generally attributed to Systemic Lupus Erythematosus (SLE), we we propose that Sjogren's syndrome (SS) is perhaps a better candidate for the associated disease. SS is an autoimmune disorder characterized by the lymphocytic infiltrates of lacrimal and salivary glands, leading to dryness of the eyes and mouth. Thus, it is a lymphocyte aggressive disorder, in contrast to SLE where pathology is generally attributed to auto-antibody and complement activation. Although systemic lupus erythematosus (SLE) shares these features with SS, a high frequency of MALT lymphoma distinguishes SS from SLE. Also, the higher frequency of germ line encoded paraproteins such as the monoclonal rheumatoid factor (RF) found in SS patients would

be more consistent with the failure of B-cell VDJ switching found in CVID; and in contrast to the hypermutation that characterizes SLE autoantibodies.

Thus, we suggest that SS may fit as a better "autoimmune" association with CVID. In fact, examining the underlying biologic mechanisms that promote lymphoid infiltration by dysregulated lymphocytes and lymphoma in CVID may provide new avenues for treatment in both CVID and SS. Since the diagnosis of SLE or rheumatoid arthritis is usually based on specific autoantibodies, the associated autoimmune features of CVID patients may not be recognized in the absence of autoantibodies.

Introduction

Common variable immunodeficiency disorders (CVID) are a group of rare diseases of the immune system and the most common symptomatic primary antibody deficiency in adults. They comprise a group of disorders with similar antibody deficiency but myriad of different aetiologies, most of which remain poorly understood. CVID are sometimes complicated with autoimmune features. Several biological mechanisms have been recently implicated in the development of these complications, including the decrease in the number of circulating switched memory B cells, CD21low B cell expansion, interferon signature and B-Cell Activating Factor (BAFF) hyper-expression. All of them these mechanisms prevent the emergence of somatic mutation among the autoantibodies in CVID patients. Thus, CVID provides an opportunity to understand processes such as neutropenia, thrombocytopenia, and lymphoproliferation in the absence of the affinity selected autoantibodies that we normally invoke as pathogenetic mechanisms.

It is worth recalling the original studies by Kunkel et al () pointed out that germ line genes (encoding both heavy and light chains) that were found as autoantibodies in patients with Waldenstrom's macroglobulinemia that had not undergone significant affinity selected maturation and recombination. For example, the germ line encoded antibodies with mixed cryoglobulin or cold agglutinin activity were sequenced and found to have a limited repertoire that was defined as conserved "idiotypes" and later found to have sequence due to germ line encoded heavy and light chains. Of interest, similar limited expression of light chains was found in the RF of SS patients (ie. the 17-109 idiotype) but not in the highly variable light chains of RF in SLE patients. Further, the B-cell lymphomas of SS show a marked limitation of their surface immunoglobulin heavy and light chains. In contrast, autoantibodies with extensive somatic diversifaction mechanisms are the hallmark of SLE and these patients do not have the elevated frequency of B-cell MALT lymphomas..

In this review we look at the potential link between CVID and SS based on the high frequency of lymphoma in both groups. This contrasts with the most reviews that suggest SLE is the main "associated" systemic autoimmune disorder. This change of view is more than semantic and emphasizes that SS is a disorder of "aggressive" hyperactivated lymphocytes that infiltrate tissues in comparison to SLE that is characterized by its pathogenic antibodies that play a role through immune complexes and complement activation.

1 Clinical features, autoimmune aspects and heterogeneity of CVID

Common variable immunodeficiency (CVID) represents the most frequent clinically expressed primary immunodeficiency (PID) in adults, accounting for more than 50% of cases of PIDs, with an estimated incidence of 1:25,000-1:50,000.(1,2) Discrepancies in the availability of appropriate

diagnostic methods, disease awareness and data registration cause important geographic differences in prevalence, with the highest value observed in the USA, and the lowest rates documented in Middle East and Africa.(3)

The term CVID was firstly coined in 1971 by the World Health Organization to express a diagnosis of exclusion from other antibody deficiency syndromes with more specific clinical and inheritance patterns.(4) Since then, CVID diagnostic criteria have been revised many times, (1,5–7) matching the evolution in the clinical, immunological and genetic knowledge on the disease. They include clinical manifestations attributable to immune system failure, serum hypogammaglobulinemia with reduction in serum immunoglobulin G, A and/or M levels by at least 2 standard deviations below age-appropriate reference levels, significantly reduced isotype switched memory B cells, impaired or absent antibody response to pathogens and polysaccharide vaccinations, in the absence of secondary causes of hypogammaglobulinemia or profound T-cell deficiency. (7,8)

In 2008, Chapel et al. firstly categorized CVID complications, identifying five distinct phenotypes: no complications, autoimmunity, polyclonal lymphocytic infiltration, enteropathy and lymphoid malignancy. (9) Subsequently, other studies attested the classification of CVID based on the presence of complications, and the concomitance of certain features, as autoimmunity, lymphocytic interstitial lung disease and lymphoid hyperplasia, was noted. (10,11)

More recently, the 2016 International Consensus document on CVID supported further analysis on the associations between genetics, clinical presentation, disease severity and immunotype, allowing the distinction into "infection-predominant", "inflammatory predominant" and "autoimmunity predominant" entities. (1)

The latest European society of Immune Deficiency (ESID) (2019) diagnostic criteria include autoimmune and inflammatory conditions as primary clinical presentations, in addition to laboratory abnormalities. (8)

If the increased risk of recurrent infections (e.g. upper and lower respiratory tract infections by encapsulated bacteria) is well established, it has also emerged that at least 30% of patients show additional non-infectious conditions, as autoimmune, autoinflammatory, granulomatous, lymphoproliferative and/or malignant complications, especially in patients with low fraction of isotype switched memory B cells. (1,6,11,12)

Autoimmune diseases occur in nearly 30% of patients with CVID, representing the most common non-infectious manifestations, (11,12) and can be observed before CVID diagnosis in up to 17.4% of patients and as the only clinical manifestation at the time of diagnosis of CVID in 2.3% of patients. (13) A distinction is made between autoimmune cytopenias (e.g. immune thrombocytopenia, autoimmune hemolytic anemia), organ specific autoimmune diseases (e.g. Graves thyroiditis, insulin dependent diabetes mellitus), and systemic autoimmune diseases (e.g. Rheumatoid Arthritis, primary SS, Systemic Lupus Erythematosus). (9)

Autoimmune cytopenias are the most common autoimmune features, as they were found to be 700 times more prevalent in a European cohort of 2700 CVID patients (ESID registry) than in the general population, (12,14) and are often associated with other non-infectious complications, as interstitial lung disease, (11,15) granulomatous and lymphoproliferative disease, splenomegaly, organ specific disease, but not to systemic autoimmunity. (16,17) CVID patients affected by autoimmune cytopenia frequently show significantly reduced numbers of isotype switched memory B cells and an increased proportion of CD21low B cells in peripheral blood. (17,18) Hypothyroidism accounted for 3.5% of organ specific autoimmune manifestations, followed by alopecia areata and vitiligo (2.7%), and type 1 diabetes (1.6%) in the aforementioned ESID cohort. (12)

Systemic autoimmune diseases, properly rheumatic disease, were found in 5,9% of all cases in a cohort of 870 CVID patients analyzed from the USIDNET registry, accounting for almost 40% of the detected global autoimmune manifestations. One third of patients with CVID-associated rheumatologic disorders had an additional inflammatory complication or malignancy.(19) Among CVID patients

affected by rheumatologic conditions, a female predominance has been noted, while inflammatory arthritis has been reported as the most frequent rheumatological manifestation (3%), followed by SS (11/870 in USIDNET registry), Systemic Lupus Erythematosus (SLE), vasculitis and Behçet's disease and others. (19–21)
Of note, in CVID patients, the overall risk of lymphoid malignancies (e.g. extra-nodal non-Hodgkin B cell lymphoma) ranges between 2 and 10%,(11,21) while the risk of gastric cancer was reported as 10-fold increased (22).
All these data support the need of stratification of CVID patients in subgroups distinct by phenotypic and, possibly, endotypic characteristics, in order to identify target treatments, best practices for monitoring subjects with specific features, and consequently improve outcomes.

In 35 patients with CVID followed at our Centre, the Rheumatology Clinic of Udine, Italy, 28/35 (80%) showed at least one autoimmune manifestation; among them, we collected 18 patients with autoimmune thyroiditis, 8 with seronegative SS, 4 with undifferentiated connective tissue diseases with SS-like features, 3 with LES/discoid lupus, 2 with systemic vasculitis, 4 with seronegative spondyloarthritis, 3 with coeliac disease, 1 with autoimmune hepatitis and 2 with immune thrombocytopenia. All 28 patients showed autoantibodies, mainly anti-tireoperoxidase (18/28); however, only one patient showed anti-SS-A antibodies. In patients without anti-SS-A antibody, the SS diagnosis was supported by ultrasonography in…and lip biopsy in…

2 CVID and autoimmunity

The pathogenesis of autoimmune complications is poorly understood, as well, and is counterintuitive because these patients are defined by their inability to make antibodies yet still mount autoimmune reactions. Some general assumption may support this paradox:

a) the co-existence of hypo- and hyper-immune states in the same individual at the same point in time is not implausible given the complexity of the immune system.;
b) both T and B cells abnormalities may contribute to the development of autoimmunity in CVID patients;
c) increased autoreactive B cells and reduced T regulatory cells may be involved in the pathogenesis of autoimmunity in CVID.

Studies on B and T cell immune dysregulation found many possible responsible factors for autoimmunity appearance, such as the expansion of CD21low B cells and related reduction of T regulatory cells; (23) the reduction of switched memory B cells; (17,24) the low levels of naïve CD8+ (25) and CD4+ (23,25,26) T cells and the elevated TH1 and interferon gamma signature, (27) related to the increase in T helper type 1 and follicular T CD4+ cells. (28,29) Conflicting evidence emerged on the role of BAFF and IL-7. (10,15,30,31)
The role of the gut microbiome in CVID has been also explored. Impaired immunity may result in a diminished barrier function, causing an increased microbial translocation across intestinal barrier which may in turn stimulate persistent systemic immune activation and consequent disruption of immune homeostasis. (32–35) Markers of this condition are lipopolysaccharides (LPS) and soluble CD14 and IL-2, which are increased in the serum of CVID patients, and with higher levels found in patients with autoimmune complications. (35)

2.1 Challenge of Identifying SS in CVID

Even if autoimmune clinical manifestations reported in CVID mostly resemble SLE, we suggest that SS may fit as a better "autoimmune" association. One recent study from academic institutions with expertise in SS has shown that almost 50% of patients diagnosed as SLE with dry eye symptoms actually had SS when the patients were re-examined for the presence of anti-SSA antibody and other clinical features of SS. (36)
After the patient is initially labelled as SLE, it is rare that the underlying diagnosis is re-examined.
As a result, SS patients with extraglandular manifestations, that might benefit from new trials of therapy, are never considered.
Moreover, patients affected by CVID might show SS typical manifestations even in the absence of SS related autoantibodies, determining a condition resembling seronegative SS. This clinical manifestations include both glandular (e.g. sicca symptoms) and extraglandular manifestations (e.g. constitutional manifestations, interstitial lung disease, tubular nephritis, haemolytic anemia, thrombocytopenia). (37) Thus, patients with SS-related manifestations in CVID should be investigated more thoroughly, with functional, instrumental and histopathological tests (e.g. minor salivary gland biopsy) in addiction to laboratory parameters.

2.2 SS like features in CVID patients who lack autoantibody to SS-A

The characteristic pathologic picture in both glandular and extraglandular manifestations of SS is the "aggressive" lymphocyte that infiltrates tissues. This may be reflected in the "focus score" that counts clusters of lymphocytes in a minor salivary gland biopsy, the analogous infiltrates of the lacrimal glands, the lymphocytic clusters in the lung in lymphocytic interstitial pneumonitis (LIP) or the markedly increased frequency of lymphoma.
Although elegant models have shown that SS-A is a chaperone molecule to both single and double stranded viral nucleotides, it is the resistance of SS-A to breakdown in the apoptotic bleb that makes it an attractive candidate for perpetuating the autoimmune cycle. The binding to antibody to SS-A (whose production is closely linked to HLA-DR3) provides a mechanism for Fc internalization of the SS-A/hYRNA complex with subsequent internalization and translocation to the toll-like receptor (TLR). (38) Yet, the finding of lymphoid infiltrates and lymphoma and CVID indicate that there is more to the story.
In fact, since CVID patients lack detectable circulating autoantibodies including anti-SS-A estimation of the role of SS pathogenetic factors in CVID is likely to be grossly underestimated. For example, it has been shown that activation of TLR receptors by viral and bacterial nucleic acids play a role in CVID by promoting interferon alpha pathway rather than TNF alpha upon stimulation. (39) Also, non-coding small RNAs are also important. (40) Other common factors such as T-follicular type and T-helper type phenotype and B-cells expressing low levels of CD as well as reciprocal decrease in regulatory T-cells and isotype switched memory B cells will be reviewed below.
Thus the lesson for rheumatologists from CVID is that we have considered the cardinal feature of SS as SS-A antigen and antibody that targets. However, also in the absence of antibody to SS-A we see the lymphocyte aggressive features that characterize its dysautonomic features (dry eyes, dry mouth, dry skin, interstitial pneumonitis, interstitial nephritis, and increased frequency of lymphoma).

3 Relevant clues from the genetics of CVID

While CVID is mainly a polygenic and multifactorial disease, recent technical advances in next generation sequencing (NSG) allowed to discover a monogenic cause in up to 15-30% of cases. (41,42)

Thirteen monogenic mutations associated with CVID are listed on the Online Mendelian Inheritance in Man (OMIM) database. Between them, some are specifically associated with autoimmunity: the loss-of-function variants in TACI, a BAFF and APRIL receptor encoded by TNFRSF13B gene, in which autoimmunity prevalence reaches 23%; (43) ICOS deficiency and the heterozygous loss-of-function (LOF) variants in NFKB1 and NFKB2, (44) the last two associated with autoimmunity in more than half of cases in large European cohorts; (45,46) STAT3 gain-of-function (GOF), which presents with early onset and quite severe manifestations of autoimmune disease; (47) LRBA and CTLA-4 deficiencies, which cause excessive T cell activation and loss of immune tolerance, supporting the role of T cell disfunction as a key pathway in CVID; (48,49) GOF mutation in the gene PIK3CD (phosphoinositide 3-kinases) encoding for PI3Kδ and determining "activated PI3Kδ syndrome," a syndrome characterized by impaired T- and B-cell development and function, autoimmunity and lymphoproliferation, in particular MALT lymphoproliferation.

3.1 TACI

Defect of TACI, is one of the first mutations to be linked to CVID (80). It is also among the most common genetic variants found, detected in up to 10% of CVID patients who can be either heterozygous or homozygous for the mutation (81). Notably, CVID patients heterozygous for the TNFRSF13B variant have a higher risk of developing autoantibody-mediated autoimmunity than those with homozygous mutations (82). By regulating the function of several other receptors, TACI may be involved in central B cell tolerance and that reduced function results in loss of tolerance and resultant autoimmunity. By contrast, in homozygous individuals, the complete loss of TACI function results in the inability to maintain continuous autoantibody production that would otherwise result in autoimmunity (82).

3.2 LRBA and CTLA-4

LRBA (lipopolysaccharide-responsive beige-like anchor) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) deficiencies are two closely related protein deficiencies that were detected in patients with CVID and autoimmunity (83). CTLA-4 is an inhibitory T cell receptor that negatively regulates immunity by inhibiting excessive T cell activation and maintaining immune tolerance via its effect on TR cells (83). LRBA, on the other hand, is thought to play a role in CTLA-4 cell surface expression (84). Deficiencies in both these proteins thus cause excessive T cell activation and breakdown of immune tolerance, resulting in autoimmunity.

3.3 STAT3

Gain-of-function (GOF) mutations in STAT3 have been identified in CVID as well as those with less profound antibody defects (75, 78). One mechanism through which STAT3 is thought to lead to autoimmunity is by promoting the activation and expansion of autoimmunity-associated TH17 cells (47, 48). While a heightened TH1 response has been linked to CVID complications, features of these STAT3 GOF patients indicate that other forms of hyperactivated T cell responses, namely TH17, may also promote an autoimmune CVID phenotype. Additionally, increased STAT3 activation may impair B cell differentiation (87) leading to hypogammaglobulinemia and heightened autoreactivity found in association with CVID or more mild forms of hypogammaglobulinemia.

3.4 PI3Kdelta

Class IA phosphoinositide 3-kinases (PI3Ks) are heterodimeric lipid kinases that are involved in regulating cell growth, survival, and activity. Recently, a GOF mutation in the gene PIK3CD encoding PI3Kδ has been found in patients with CVID-like disease and autoimmunity. Patients heterozygous for this mutation developed the so-called "activated PI3Kδ syndrome," or APDS, of which ~200 patients have been described to date (88). Activated PI3Kδ syndrome is characterized by impaired T- and B-cell development and function, autoimmunity, and lymphoproliferation. While effector cells proliferate, naïve, and central memory T-cell subsets remain metabolically quiescent, likely contributing to autoimmunity, lymphoproliferation, and immunodeficiency seen in this syndrome (91)

3.5 NF-kB

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a family of transcription factors that are crucial for B-cell maturation, survival, differentiation, class switching, as well as self-tolerance (92). It is also a fundamental transcription factor for cytokine production by innate immune cells as well as other vital cell signalling pathways that expand beyond the immune system (93). NF-κB1 and NF-κB2 deficiencies were first described in patients of CVID affected families who were found to carry autosomal dominant mutations in NFKB1 and NFKB2 genes, respectively (94, 95). Mutations affecting the inducible T-cell co-stimulator (ICOS) are closely related to NF-κB deficiencies since NF-κB are activated by ICOS receptors. Because ICOS activation is essential for terminal B cell differentiation and immune tolerance (96) both ICOS and NF-κB deficiencies result in CVID-like immunodeficiency syndromes and autoimmunity (77). NFKB2 mutations, in particular, lead to autoimmunity affecting the skin, hair and nails, such as alopecia and trachyonychia, and less frequently autoimmune cytopenias, and are characterized by pituitary hormone deficiencies (99). Interestingly, dysregulation of NFkB in glandular epithelial cells results in SS-like features (Wang X, Shaalan A, Liefers S, Coudenys J, Elewaut D, Proctor GB, Bootsma H, Kroese FGM, Pringle S. Dysregulation of NF-kB in glandular epithelial cells results in Sjögren's-like features. PLoS One. 2018 Aug 1;13(8):e0200212. doi: 10.1371/journal.pone.0200212), as well as expression of NF-κB at both the mRNA and protein level was up-regulated in SS-lymphoma-BAFF-RHis159Tyr-derived B cells, linking the innate to the adaptive immunity upregulation and lymphoma in SS (Papageorgiou A, Mavragani CP, Nezos A, Zintzaras E, Quartuccio L, De Vita S, Koutsilieris M, Tzioufas AG, Moutsopoulos HM, Voulgarelis M. A BAFF receptor His159Tyr mutation in Sjögren's syndrome-related lymphoproliferation. Arthritis Rheumatol. 2015 Oct;67(10):2732-41. doi: 10.1002/art.39231. PMID: 26097183).

4 Common features between CVID and Sjögren's syndrome

4.1 Lymphoproliferation

Both CVID and primary SS are strongly related to lymphoproliferation and lymphoma, in particular NHL B cell and MALT-type lymphoma.

4.1.1 CVID and lymphoproliferation

A multicenter registry of CVID by Yakaboski et al., which collected data from 1091 CVID patients, shown that CVID patients with a lymphoproliferative pattern had a 2.5-fold increased risk of

developing lymphoma. The most common forms of benign lymphoid hyperplasia in CVID are splenomegaly and lymphadenopathy, but lymphoid hyperplasia and polyclonal lymphoproliferative infiltrations frequently affect other organs tissues such as lungs and gastrointestinal. The lung represents the prevalent extranodal site for lymphoproliferative disorders, which include follicular bronchiolitis, lymphoid interstitial pneumonia, and pulmonary nodular lymphoid hyperplasia. (51) Interstitial lung disease (ILD) represents the radiological picture of pulmonary lymphoproliferation, as demonstrated by histopathological studies on ILD. (10) Chapel et al. confirmed polyclonal lymphoid infiltrate as a predictor of lymphoma in CVID, which increased by 5 times the risk of developing lymphoma. (9) The main histotypes of lymphoma in CVID are represented by mature B-cell malignancies followed by Hodgkin's lymphoma and rarely by MALT-type lymphomas. (52–54)
The presence of a 2-step transformation mechanism is hypothesized, as in non-Hodgkin's lymphoma.(9) A benign lymphoproliferation is deeply linked to the immune dysregulation intrinsic to CVID patients, as observed in other primitive immunodeficiencies such as CTLA-4 haploinsufficiency and STAT 3 gain of function mutations and as do autoimmune diseases such as primary SS. (47,48,55) In CVID, mutation of TACI, reduction of isotype-switched memory B cells, expansion of CD21 low B cells, expression of an interferon signature, expansion of inflammatory innate lymphoid cells and retained B cell function are all linked with development of autoimmunity and lymphoproliferation.(20)

4.1.2 SS and lymphoproliferation

B-cell clonal expansion is a key feature of SS and progression to B-cell lymphoma occurs in about 5% of patients (relative risk of 44). The progression from polyclonal, to benign clonal lymphoproliferation, to overt lymphoma in SS is one of the few human models in which one can study B-cell lymphomagenesis and its link to immune dysregulation. (*De Vita, S., Boiocchi, M., Sorrentino, D., Carbone, A., Avellini, C., Dolceti, R., Marzotto, A., Gloghini, A., Bartoli, E., Beltrami, C. A., and Ferraccioli, G. F. (1997) Characterization of prelymphomatous stages of B cell lymphoproliferation in Sjo¨gren's syndrome. Arthritis Rheum. 40, 318–331.)*
The pathological hallmark of SS is MALT arising in chronically inflamed tissues, mainly in salivary glands, where inflammation, autoimmunity and lymphoproliferation coexist, creating a complex biological and immunological substratum that fuels autoreactive B lymphocytes persistence and promotes their proliferation, towards a clonal selection and a possible lymphoma development (*DE VITA S, DE MARCHI G, SACCO S, GREM-ESE E, FABRIS M, FERRACCIOLI G: Preliminary classification of nonmalignant B cell proliferation in Sjögren's syndrome: perspectives on pathobiology and treatment based on an integrated clinico-pathologic and molecular study approach. Blood Cells Mol Dis 2001; 27: 757-66.; ANDERSON LG, TALAL N: The spectrum of benign to malignant lymphoproliferation in Sjögren's syndrome. Clin Exp Immunol 1972; 10: 199-221.*
In SS the prevalent histological type of lymphoma is marginal zone and particularly mucosa associated lymphoproliferative tissue (MALT) lymphoma of the salivary glands but other histotypes are described and lung is one of the prevalent organ targets of lymphoproliferation besides exocrine glands. (50)
In primary SS, splenomegaly and lymphadenopathy also represent well established lymphoma risk factors, in addition to salivary gland swelling.(56,57) Moreover, in primary SS patients the typical histopathological feature of ILD is lymphocytic interstitial pneumonia (LIP).(58,59) Both lung and stomach are other sites of lymphoma development in primary SS, other than salivary and lacrimal glands.(56,57)

All these immunopathogenic aspects are partly shared by both primary SS and CVID and define these two entities as unique conditions in which we can observe the multistep process of lymphomagenesis, proceeding from fully benign lymphoproliferation to nonmalignant disorders to lymphoma.(20,55) The exact mechanisms which drive the early stage of lymphomagenesis of both diseases remain to be determined. A chronic antigen stimulation (auto-antigens or potential infectious triggers) are evoked, but also genetic aspects and epigenetic theories are emerging. (Salzer, Wheat, Jorgensen). Recent evidence of acquired somatic mutations in genes of expanded rheumatoid factor

B cell clones in SS have been published, demonstrating a shared mechanism with lymphoid malignancy and getting light to new potential drivers of lymphoproliferation in autoimmune diseases (Singh M, Jackson KJL, Wang JJ, Schofield P, Field MA, Koppstein D, Peters TJ, Burnett DL, Rizzetto S, Nevoltris D, Masle-Farquhar E, Faulks ML, Russell A, Gokal D, Hanioka A, Horikawa K, Colella AD, Chataway TK, Blackburn J, Mercer TR, Langley DB, Goodall DM, Jefferis R, Gangadharan Komala M, Kelleher AD, Suan D, Rischmueller M, Christ D, Brink R, Luciani F, Gordon TP, Goodnow CC, Reed JH. Lymphoma Driver Mutations in the Pathogenic Evolution of an Iconic Human Autoantibody. Cell. 2020 Mar 5;180(5):878-894.e19. doi: 10.1016/j.cell.2020.01.029. Epub 2020 Feb 13. PMID: 32059783).

4.2 BAFF hyperexpression

4.2.1 CVID and BAFF hyperexpression

Patients with CVID present immune dysregulation and have an increased risk to develop non-Hodgkin's lymphoma. Theincreased levels of BAFF might facilitate this risk, however contrasting studies have been published on this issue up to now. Knight at al. demonstrated high serum levels of BAFF, APRIL and TACI in CVID patients, however, they didn't found a correlation to immunological or clinical phenotype. (30)
Similarly, Kreuzaler et al. showed increased BAFF serum concentration in CVID patients, without a clear correlation to clinical parameters, immunodeficiency-related inflammatory disease and to B cells subsets.(76)
On the contrary, Maglione et al. showed that ILD progression in CVID correlates with increased levels of IgM, particularly with the production of IgM within B cell follicles in lung parenchyma; the main stimulator of pulmonary B cell hyperplasia seems to be BAFF, which was increased both in the blood and in the lung of CVID-ILD patients.(77)

4.2.2 SS and BAFF hyperexpression

A substantial literature demonstrated that both BAFF and APRIL are present in excess amount in the sera of patients with systemic autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, primary SS, SLE, HCV-related cryoglobulinemic vasculitis and that dysregulation of BAFF has a role in outbreak of autoimmunity.(62–67) In mice model, the overexpression of BAFF in mice leads to hyperplasia, autoimmunity, hyperglobulinemia and splenomegaly, while the normal expression of BAFF allows B cells survival and maturation.(68)
Groom et al. provided an interesting parallel between a SS-like pathology that emerges in BAFF transgenic (Tg) mice and high levels of BAFF found in a large proportion of patients with primary SS.(69) In BAFF Tg mice there's an excessive survival signal to autoreactive B lymphocytes, probably linked to a dysregulation of tolerance at the splenic level, where they observed an enlargement of marginal zone B-cell subset. B cells with an MZ-like phenotype infiltrate the salivary glands of BAFF Tg mice. Parallelly, unbalanced BAFF production in the lymphoid infiltrates of the salivary glands of primary SS patients promote recruitment of a specific and potentially pathogenic subpopulation of B cells.(69) The finding that epithelial cells also produce BAFF supported the hypothesis of the crucial role of BAFF in the pathogenesis of primary SS, leading to immune dysregulation through an autocrine pattern of self-stimulation.(70) High levels of BAFF were correlated with the specific autoantibodies of SS, anti-SSA / SSB, and BAFF was also found mainly in local lymphoid and inflammatory microenvironments.(71) In addition, BAFF upregulation correlates both with primary SS activity disease (higher ESSDAI score) and B cell prelymphomatous and malignant lymphoproliferative disorders.(72) Genetic mutations in BAFF-mediated pathway may significantly contribute to this risk

of malignant evolution.(73) The efficacy of belimumab, an human monoclonal antibody targeting soluble BAFF, and approved for the treatment of SLE, in a phase II clinical trial of primary SS strongly supported the pathogenic role of BAFF in this autoimmune disease,(74,75) and led to phase III trials of belimumab in co-administration with rituximab in primary SS (NCT02631538).

Thus, BAFF-related pathologic findings might occur in a similar manner in the salivary glands of primary SS as well as in the lung of CVID, possibly reflecting the main target site of inflammation and lymphoproliferation in primary SS and CVID, respectively.

4.3 B cell abnormalities

It is well known that B cell compartment is pivotal in both primary SS and CVID pathogenesis. Two B cell subpopulations have been shown to play a central role in both these entities: switched memory B cells and CD21low/-B cells. The formers are CD19+CD27+IgM-IgD- memory B cells which have undergone the isotypic switch; the latter are a peculiar B cell subset that under expresses CD21, a coreceptor of BCR, and at the same time expresses higher levels of IgM, CD11c, CD19 and CD95. CD21low/-B cells belong to a unique anergic B cell population which is polyclonal, pre-activated, enriched in autoreactive clones and can express highly autoreactive antibodies, including ANA and rheumatoid factor.(78,79) The nature of this cell population was extensively studied also in the context of HCV related cryoglobulinemia; in both HCV related cryoglobulinemia and CVID, anergic subset of CD21low/- B cells appears expanded and characterized by high constitutive expression of extracellular signal regulated kinase (pERK).(80–82) Moreover a BAFF hyperexpression and aberrant type I and II IFN response are thought to support CD21-/low B cell population, suggesting a profound interconnection between dysregulated innate and adaptative immunity.(78,83)

4.3.1 CVID and B-cell abnormalities

Since the early 2000s the role of switched memory B cells and CD21low/- B cells in CVID has been investigated. Warnatz et al. observed a significant decrease in class-switched B memory cells in CVID patients compared to healthy controls and identified a CVID subgroup, clinically characterized by splenomegaly and autoimmune disorders, with a high proportion of CD21low/- B cells. These findings suggested a correlation between low switched memory B cells, increased CD21low/- B cells and autoimmune and lymphoproliferative disorders in CVID.(24,84) In 2008 the EUROclass trial confirmed B cell homeostasis as a pathogenic and clinically meaningful item in this disease.(6) In particular, the reduction of IgM-, IgD- CD27+ switched memory B cells represents the most common aberration in CVID, and it correlates with decrease in serum IgA and IgG levels. While in EUROclass trial a reduced number of switched memory B cells (2% or less) was related with granulomatous disease and splenomegaly but not with autoimmune conditions,(6) Sanchez Ramon et al. found that levels of switched memory B cells <0,55% had 3.3 fold higher risk to correlate with autoimmune disease ($p=0.001$).(85) Many other studies confirmed these results.(20,78,79,86) Also in the large cohort of USIDNET register lower levels of switched B memory cells were observed in CVID-Rheum group.(19)

4.3.2 SS and B-cell abnormalities

On the other hand, there is strong evidence of unbalance of B cell subpopulations also in SS. Many authors found that memory and switched memory B cells are reduced in primary SS compared to

controls,(87–89) and this unbalance appears to be related to disease duration and activity.(89) Saadoun et al. found an increase of CD21low/- B cells in primary SS and in particular in primary SS with lymphoproliferative disorders (LPD), suggesting a key role of this B cell population in SS related lymphomagenesis.(90,91) As in CVID, they found that CD21low/- B cells are enriched in autoreactive clones and express highly autoreactive antibodies, such as rheumatoid factor, as a consequence of a chronic antigenic stimulation; this mechanism was preliminary linked to lymphoproliferation in primary SS and in HCV infection.(92) The persistence of these cells can represent the initial reservoir for monoclonal expansion of a transformed clone and drive to B cell lymphoproliferation.(93) Other papers support the correlation between the presence of B cell NHL in primary SS patients and the proportion of circulating CD21low/- B cells.(94,95)

In conclusion, there are some similarities between B cell subpopulation profile in primary SS and in CVID. From the therapeutic perspective, the pivotal role of B cell explains the interest in anti-B cell drugs, such as rituximab, in CVID patients with autoimmune or nonmalignant lymphoproliferative manifestations.(96) Moreover, rituximab as well as other B cell targeted drugs have already been investigated in primary SS with some encouraging results.(80)
Another strategy may be that of specifically targeting CD21low/- B cells through an anti FcRL5 recombinant immunotoxin. This approach was preliminary studied by Cacoub et al. for the treatment of HCV related vasculitis since this cell population was seen to highly express FcRL5.(97)
As this marker was found to be overexpressed also by CD21low/- B cells both in CVID (78,79) and primary SS (90) the same possibility could be considered for the latter two diseases.

4.4 Interferon signature

Type I and II interferons (IFN) are cytokines which play a central role in regulation of immunity and inflammation. They are expressed in response to physiological and pathological conditions such as stress, infections and also in autoinflammatory and autoimmune diseases. A paradigmatic example is the role of type I IFN in SLE, which are markedly overexpressed. (98) Since their contribution in loss of immunotolerance, they were considered as potential therapeutic targets of drugs such as anifrolumab, an anti-type I IFN receptor monoclonal antibody [NCT 02446899]. Type II IFN (IFN gamma), instead, appears more significant in diseases characterized by a prominent lymphoproliferative component, such as primary SS.(99)
Anyhow, IFNs are capable of driving activation of JAK-STAT signaling pathway that induce expression of canonical IFN-stimulated genes (ISG) encoding molecules critical for antiviral response, antigen presentation, autoimmunity and inflammation.(100) This increased ISG expression pattern in tissues and in circulating blood cells is defined IFN signature, which is one of the possible key items shared among primary SS and CVID with autoimmunity. In particular, an upregulated IFN signature expression distinguishes CVID patients with inflammatory complication, including autoimmunity and, at the same time, it is an hallmark of various systemic autoimmune diseases such as SLE, systemic sclerosis, myositis and primary SS.(20,101)

4.4.1 CVID and interferon signature

Regarding CVID, few papers have been published on the role of IFN signature.(27,102) Park et al. applied blood transcriptional profiling to characterize the immunologic networks in subjects with CVID who have inflammatory and autoimmune complications.(27) One of the main finding was the

presence of a strong IFN signature in this subset of patients; more specifically, subjects with CVID and inflammatory/autoimmune conditions displayed significantly over-expressed interferon-related transcriptional modules and pronounced downregulation of transcript related to the B cell, plasma cell and T cell modules as compared to CVID without these conditions or controls. Cols et al. clearly demonstrated a key role for type II IFN in CVID inflammatory disease; in particular they found a significant expansion of circulating IFN gamma producing innate lymphoid cells (typically ILC3) in CVID patients with noninfectious complications compared to those without and identified these cells in the affected mucosal tissues of lung and gastrointestinal tract.(102) Notably, these cells, that also correlate with inflammation and produce IL17, were detected in salivary glands of primary SS patients, although their role in this autoimmune disease in not known.(103) However, ILC3 are not the only cells responsible for the production of IFN gamma in CVID with autoimmunity and lymphoproliferation; indeed, Unger et al. demonstrated a Th1 skewed CD4 T-cell population that highly express IFN-gamma both in peripheral blood and in lymph-nodes. Moreover, in the same study, IFN gamma immune environment is thought to participate in expansion of circulating CD21low/- B cells.(29)

4.4.2 SS and interferon signature

On the other hand, many studies highlight the pivotal role of innate immunity and IFN in primary SS.(104,105) The presence of IFN-induced gene expression was been demonstrated in salivary glands, peripheral blood mononuclear cells, isolated monocytes and B cells of primary SS patients and type I IFN signature was associated with higher disease activity and higher levels of autoantibodies.(106–111) Type II IFN signature was also detected in salivary glands of primary SS patients.(112) Two studies by Bodewes et al. confirmed the central role of overactivated innate immunity and IFN system in primary SS.(113,114) In two large European primary SS cohorts they shown the presence of systemic upregulation of both type I and type II IFN. Type I IFN signature, induced mainly by IFN alpha, was the most prevalent in both cohorts, while type II IFN signature, mainly induced by IFN gamma, was found only in patients who already expressed an upregulation in IFN type I. Furthermore, salivary glands analysis of primary SS patients revealed a predominant type II activation pattern.(113,114)

Accordingly to these results, they suggested that an aberrant activation of type I IFN response could drive autoantibody production, partly by direct activation of autoreactive B cells and partly by cytotoxic effect, accumulation of cellular debris and expression of autoantigen Ro52.(115,116) Additionally, type I IFNs induce the expression of BAFF, whose levels correlate with higher autoantibodies production and maybe the development of lymphoproliferative complications.(114)

Nezos et al., to clarifying the contributory role of both type I and II IFN signatures in the induction of different SS clinical phenotypes and lymphoma development, remarked the predominance of type I IFN signature in peripheral blood of primary SS patients in contrast to prominent type II IFN signature in SS minor salivary gland (MSG) biopsies. They also demonstrated a strong association between high IFN gamma in MSG tissue and lymphomagenesis.(99)

Interestingly, a prominent type I IFN signature was also associated with markers of B cell overactivity, such as anti-SSA antibodies, that can be attributed to type I IFN induced BAFF overproduction.(111,117) In the setting of lymphomagenesis both type I and II IFN transcript levels were considerably increased in MSG tissues derived from primary SS derived lymphoma, implying a direct role of these cytokines, and in particular IFN gamma, in this process.(99)

Both CVID and primary SS are strongly related to lymphoproliferation and lymphoma, in particular NHL B cell and MALT-type lymphoma. One of main sites of B cell hyperplasia and lymphoma

development in CVID is the lung but also salivary glands can be involved in some cases.(51–54,118) Data suggest that IFN gamma could upregulate BAFF both in peripheral blood and in lung tissue , and locally BAFF could promote B cell survival and proliferation.(77,119) However, a clear role of BAFF in driving lymphoproliferative complications in CVID patients with autoimmunity is not demonstrated, yet.(30)
In any case, the evidences highlight the central role played by type II IFN in lymphoproliferation both in lung, as regards CVID, and in the salivary gland, as regards primary SS. This suggests a deep correlation between B cell proliferation and IFN gamma.

5 Use of "Anti-rheumatic therapies" in CVID and SS

Whereas immunoglobulin replacement therapy and improved anti-microbial drugs have significantly ameliorated CVID patients survival by reducing infectious complications, (12), patients with CVID affected by at least one non-infectious complication still have significant higher risk of mortality compared to the other CVID patients, since these clinical manifestations do not respond to the antibiotic and immunoglobulin replacement therapy alone. (11,21) Thus, it appears that noninfectious complications, especially gastrointestinal and pulmonary involvement, constitute the most difficult aspects of the CVID patient management. (1,21,120–122).
Over the last 5-10 years rituximab has been used in various non-infectious CVID complications, such as autoimmune cytopenias, granulomatous lymphocytic interstitial lung disease (GLILD) and non-malignant lymphoproliferative syndromes. (96) Also, Abatacept, a CTLA-4 immunoglobulin fusion protein, showed good results as a replacement therapy in patients affected by CTLA-4 and LRBA deficiency. (49,123) In addition, Tocilizumab and inhibitors of Janus Kinases (JAKs) were successfully trialed in patients with STAT3 gain of function mutations, as its activation occurs downstream of both IL-6 and JAKs targets. (47,124).
Of note, rituximab and, more recently, belimumab, as B-cell targeted therapies, have been applied in primary SS, and they resulted effective in particular in patients with systemic features. (74,75,125) Combination strategies with both drugs are currently under evaluation in primary SS and also in other autoimmune diseases. (67)
Yet, both tocilizumab and abatacept were employed as possible new treatments of primary SS, and even JAKs inhibitors are under evaluation in primary SS (NCT04496960).
The multicenter double-blind randomized placebo-controlled trial with tocilizumab in primary SS did not improve systemic features over 24 weeks of treatment compared with placebo; (126) however, tocilizumab might be effective in contrasting SS-related articular and pulmonary involvement, such as refractory organizing pneumonia; (127) moreover, tocilizumab has been recently approved by FDA for pulmonary fibrosis in systemic sclerosis. (128)
Two open studies have assessed abatacept in primary SS; the first demonstrated the reduction in glandular inflammation and an increase in saliva production, (129) while the second one showed the decrease of ESSDAI, ESSPRI, rheumatoid factor, and IgG levels but salivary and glandular functions did not improved. (130) Finally, the phase III trial failed to demonstrate any clinical benefit of abatacept in primary SS. (131)
On the other hand, leniolisib (CDZ173), a potent and selective oral inhibitor of PI3Kdelta(132) has been successfully used in a series of patients with Activated PIKdelta Syndrome (APDS), in which PI3Kdelta gain-of-function mutation results in lymphoproliferation of the MALT, T-cell senescence and immunodeficiency. Leniolisib normalized B cells in APDS, and improved lymphoproliferation(133).
Optimally, the cost of full genome sequence and machine learning algorithms will allow us to tailor therapy for each SS patient without risk of "knocking out" some critical lymphoid interaction or

creating a destructive "gain of function" autoimmune reaction against a previously "silent target organ.".

6 Conclusions

It is paradoxical that patients with CVID have a high frequency of associated autoimmune features. Increasing pathogenetic insights allowed to reconcile the lack of B-cell maturation and autoimmunity in the wider concept of dysregulated immune system, both diseases being influenced by genetic and epigenetic factors which can lead to different clinical phenotypes (Fig.1).
The association of hypogammaglobulinemia and autoreactive B cells in CVID patients has been commonly listed as "SLE-like." However, we prepose that the autoimmunity and lymphoproliferation associated with CVID is more closely associated with a SS like picture of immune dysregulation. In this context, CVID and Sjogren's syndrome, two conditions which can occur simultaneously and share several pathogenetic aspects, as well as targeted therapy (i.e., rituximab, abatacept), could represent a model of this immunological view. Therefore, better understanding of the underlying immunological mechanisms and specific genetic mutations that result in the immune dysregulation may lead to the development of new therapeutic targets for both the diseases.

7 Figures

Fig. 1: an integrated view of the immune system in primary immunodeficiency and autoimmune disorders.

8 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

9 Author Contributions

Luca Quartuccio, Salvatore De Vita, and Ginevra De Marchi conceived the study. All authors contributed to the literature review and interpretation of the data. The first draft of the manuscript was written by Luca Quartuccio, Ginevra De Marchi, Valeria Manfrè, Simone Longhino and Maria Teresa Rizzo, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

10 Funding

This research received no external funding.

11 Acknowledgments

We thank dr. Giulia Del Frate, MD, and dr. Donatella Colatutto, MD, for their contribution to the literature review and for making the figure, respectively.

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