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Correspondence: Maria J. Gutierrez, M.D., mgutie10@jhmi.edu.

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Consortium/Collective Authors

The USIDNET Consortium

(Listed alphabetically by last name)

Adams Juan⁶, Akhter Javeed¹³, Apter Andrea³¹, Ballas Zuhair⁸, Ballow Mark²², Bennion Jeffrey³⁵, Berger Melvin²⁹, Bonilla Francisco⁷, Buckley Rebecca⁴, Calabrese Leonard¹⁷, Calderon Jose²⁷, Caldwell Jason²³, Chen Karin²¹, Cheng Laurence¹², Costa Reis Patricia³, Cunningham-Rundles Charlotte¹, Dorsey Morna¹², Fernandez Jim¹⁷, Fuleihan Ramsay², George Christopher³⁶, Gonzalez Gabriel⁴⁰, Guillot Richard³³, Gundling Kathleen¹², Haddad Elie¹⁴, Hostoffer Robert²⁴, Hernandez-Trujillo Vivian³⁴, Joshi Avni¹¹, Kirkpatrick Charles³⁰, Kleiner Gary⁹, Knight Adina²⁶, Kobayashi Roger⁴¹, Lehman Heather²², Lowe David³², Lugar Patricia⁴, Muskat Mika¹², Notarangelo Luigi¹⁸, Ochs Hans¹⁵, Overby Terry³⁸, Patel Niraj¹⁶, Puck Jennifer¹², Rabinowitz Robert⁴², Routes John⁶, Secord Elizabeth¹⁰, Shapiro Ralph²⁵, Stein Mark²⁰, Strober Warren¹⁸, Suez Daniel⁵, Sullivan Kathleen³, Tanner Bobo²⁸, Uygungil Burcin¹⁹, White Martha³⁷, Wright Dowain³⁹, Yu Grace².

1. Mount Sinai School of Medicine, New York, NY
2. Ann & Robert H. Lurie Children's Hospital, Chicago, IL
3. The Children's Hospital of Philadelphia, Philadelphia, PA
4. Duke University Medical Center, Durham, NC
5. Daniel Suez MD, Allergy, Asthma and Immunology Clinic, Irving, TX
6. Medical College of Wisconsin, Milwaukee, WI
7. Boston Children's Hospital, Boston, MA
8. University of Iowa Hospitals and Clinics, Iowa City, IA
9. Memorial Healthcare System, Hollywood, FL
10. Children's Hospital of Michigan, Detroit, MI
11. Mayo Clinic, Rochester, MN
12. University of California San Francisco (UCSF), San Francisco, CA
13. Advocate Hope Children's Hospital, Oak Lawn, IL
14. Sainte-Justine University Hospital, Montreal, QC
15. Seattle Children's Hospital, Seattle, WA
16. Levine Children's Hospital, Charlotte, NC
17. Cleveland Clinic Foundation, Cleveland, OH
18. Clinical Research Center, The National Institutes of Health, Bethesda, MD
19. Children's National Medical Center, Washington, DC
20. Allergy Associates of the Palm Beaches, North Palm Beach, FL
21. University of Utah, Salt Lake City, UT
22. Women and Children's Hospital of Buffalo, Buffalo, NY
23. Wake Forest University, Winston-Salem, NC
24. University Suburban Health Center, South Euclid, OH
25. Midwest Immunology Clinic, Plymouth, MN
26. Alabama Allergy and Asthma Center, Birmingham, AL
27. Yale University, New Haven, CT
28. Vanderbilt University Medical Center, Nashville, TN
29. University Hospitals of Cleveland, Cleveland, OH
30. University of Colorado Health Science Center, Denver, CO
31. Presbyterian Medical Center, Philadelphia, PA
32. Olmsted Medical Group, Rochester, MN
33. Northshore Allergy & Immunology, Covington, LA
34. Miami Children's Hospital, Miami, FL
35. Logan Regional Hospital, Logan, UT
36. Littlestown Family Medicine, Littlestown, PA
37. Institute for Asthma & Allergy, Chevy Chase, MD
38. Harrisonburg Medical Associates, Harrisonburg, VA
39. Children's Hospital of Central California, Madera, CA
40. Allergy, Asthma & Sinus Center, Palm Beach Gardens, FL
41. Allergy, Asthma & Immunology Associates, Omaha, NE
42. Allergy Asthma & Clinical, Toms River, NJ

Phenotypic Characterization of Patients with Rheumatologic Manifestations of Common Variable Immunodeficiency

Maria J. Gutierrez¹, Kathleen E. Sullivan², Ramsay Fuleihan³, The USIDNET Consortium, and Clifton O. Bingham III⁴

¹Division of Pediatric Allergy and Immunology, Johns Hopkins University, Baltimore, PA, USA.

²Division of Allergy and Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

³Division of Allergy and Immunology, Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA

⁴Divisions of Rheumatology and Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Abstract

Patients with common variable immunodeficiency (CVID) have a higher incidence of rheumatologic disorders. To delineate this clinical association, we investigated the phenotypic features of patients with CVID affected by these conditions.

Methods: We conducted a retrospective analysis of 870 pediatric and adult patients with CVID included in the United States Immunodeficiency Network (USIDNET) registry. Outcomes included clinical characteristics (age, gender, ethnicity, rheumatologic diagnosis, comorbidities), infectious history and basic immunophenotype (serum immunoglobulin levels, CD19+ B cells and CD4/CD8 ratio) in patients with CVID and rheumatologic disorders compared to those with non-inflammatory CVID. Demographic and clinical data were compared using chi-square, Fisher's exact or Wilcoxon-Mann-Whitney tests. Non-parametric tests, single and multiple logistic regression models were used to evaluate the relationship between CVID-associated rheumatologic disorders and basic immunophenotypic parameters (IgA, IgM, CD19+ B-cell counts and CD4/CD8 ratios)

Results: Physician-reported rheumatic diseases were present in 5.9% of patients with CVID (n=51) included in the registry. Although CVID affects both sexes equally, and patients are of predominantly White-Caucasian ethnicity, there were more females (3.3:1 female to male ratio) and increased proportion of non-white patients in the rheumatologic disease group (p<0.05). Specific disorders included: inflammatory arthritis (n=18), Sjogren's syndrome (n=11), SLE (n=8), Raynaud's syndrome (n=8), vasculitis (n=9), MCTD (n=3), other (n=5). In about one-third of patients, a rheumatologic condition was associated with an additional inflammatory complication or malignancy. In regards to the immunophenotype parameters compared (CD19+ B-cell counts, CD4/CD8 ratio, IgA and IgM), no significant differences were demonstrated between the two groups.

Conclusion: Our findings highlight the coexistence of primary antibody immunodeficiencies and systemic rheumatologic disorders, describe the spectrum of rheumatologic manifestations, and contrast differences in relevant demographic, clinical and immunophenotype parameters in the largest registry of CVID patients in the U.S. In spite of its limitations, our study details the

intersection of systemic autoimmunity and CVID and provides valuable insights into these two groups of disorders. Further delineating the link between systemic autoimmunity and humoral immunodeficiencies can provide novel insights into the immune abnormalities underlying these related conditions.

I. INTRODUCTION

Common Variable Immunodeficiency (CVID), the most commonly diagnosed primary immunodeficiency (PID),(1) encompasses a heterogeneous group of disorders characterized by recurrent infections and poor antibody production.(2) Although specific molecular defects explain only few cases,(3) the phenotype of CVID often involves defective terminal B-cell differentiation.(4) CVID is estimated to affect 1:10,000 to 50,000 individuals and accounts for approximately 35% of all diagnosed primary immunodeficiency in the US.(1) Up to 50% of CVID patients have an inflammatory phenotype characterized by non-infectious complications which include manifestations such as granulomatous inflammation, inflammatory lung disease, malignancy, organ-specific and systemic autoimmunity.(4)

General features of patients with autoimmune manifestations of CVID include immunophenotypical differences such as decreased percentages of B-cells and switched memory B-cells and an increased proportion of CD21^{low} cells (CD19+ CD21- CD38-).(5, 6) Higher IgM levels and increased CD4/CD8 ratio have also been associated with the development of autoimmunity in CVID patients.(7–10) The most common autoimmune manifestation reported is autoimmune cytopenias, but a wide range of complications occur.(4, 11, 12)

Rheumatologic disorders, as a group, are one of the most common autoimmune manifestations of CVID.(7, 13) These two groups of disorders seem to be closely related, and in certain cases common genetic associations and shared inheritability have been described.(14, 15) The most common CVID-associated rheumatologic disorder is chronic inflammatory arthritis (adult and juvenile forms) reported in approximately 3 % of CVID patients.(4, 7, 11, 13) Less frequent disorders include Systemic Lupus Erythematosus (SLE) and vasculitis present in less than 1% of patients.(10, 16) Rarer conditions, such as inflammatory myositis, Behcet's disease, and Sjogren's syndrome have also been described.(16, 17) Some series report some features of this group such as slightly higher baseline IgG levels, autoantibody formation, and family history of autoimmunity.(4, 7, 9, 11, 13, 18) Nonetheless, few additional details are known about patients featuring rheumatologic complications of CVID.

Accordingly, our study aimed to characterize the phenotypes of patients with CVID-associated rheumatologic complications included in the United States Immunodeficiency Network (USIDNET) registry, the largest U.S. registry of patients with PID.(19) First, we aimed to examine basic demographic differences between patients with CVID-associated rheumatologic disorders (CVID-Rheum) and those with non-inflammatory CVID (ni-CVID). Second, we characterized the specific rheumatologic diagnoses described in CVID patients included in the registry and described the additional inflammatory comorbidities associated to CVID patients with rheumatologic conditions. Finally, we sought to determine

whether differences exist in basic immunophenotype parameters (CD19+ B-cells and CD4/CD8 ratio, IgA and IgM levels) between the two groups as they reveal differences in CVID patients with autoimmunity(7, 8, 17) as well as in patients with other immune dysregulation disorders.(20)

II. METHODS

Subjects

We conducted a retrospective evaluation of data from a previously described registry.(19) Initially, there were 879 patients registered in our dataset with a clinical diagnosis of CVID. Nine patients with a different PID were excluded (7 had Transient Hypogammaglobulinemia of Infancy, 1 had Autoimmune Lymphoproliferative Syndrome and 1 had X-linked Lymphoproliferative Disorders type 2) (Figure 1).

Our study population included 870 patients with diagnosis of CVID enrolled in the USIDNET registry. We chose to use the USIDNET database since it is the largest cohort of patients with CVID available in the U.S.(19) The primary data source is the patient's clinical record. The inclusion in the USIDNET registry requires patients' consents and institutional IRB approvals. The designation of the diagnosis is made by the enrolling center, and the data is entered individually by the referring centers using an established data collection form.(21) Most enrolling centers are large academic institutions located across 23 states in the U.S. There were variable amounts of missing observations. Demographic variables with >25% missed observations (age of onset, age of diagnosis) are described (Table 1) but were not included in the statistical analysis.

Demographic Information

Basic demographic characteristics (sex, date of birth, age of onset, age of diagnosis and alive/deceased status) were extracted from the registry's database. Data on sex and date of birth were available for all patients. Current age was calculated subtracting the year of birth from year 2016 (last year ended at the time of this analysis). Age of onset and age of diagnosis were available in 50% and 72% of patients respectively. Survival status was available in 820 (94%) patients. Patients with no available survival data were assumed to be alive.

Clinical Phenotype

Phenotypic information was obtained from the USIDNET registry database. Our primary outcome, CVID-associated rheumatologic disease (CVID-Rheum) was a binary variable defined as the presence of any major physician-reported systemic autoimmune disorder associated with the diagnosis of CVID (Table 2). The non-inflammatory CVID group (ni-CVID) was defined as patients with no systemic autoimmunity or any other CVID-associated inflammatory manifestation listed on the database.

Additional CVID-associated inflammatory manifestations included: malignancy, autoimmune cytopenias, organ-specific autoimmune disease (skin, endocrine, neurologic, ocular, gastrointestinal, renal, or cardiac autoimmune disease), inflammatory lung disease

(bronchiolitis obliterans organizing pneumonia (BOOP)), interstitial lung disease, pneumonitis, ground glass opacities and/or bronchiolitis obliterans listed) and pulmonary or extrapulmonary granulomatous disease. Of note, patients with a listed diagnosis of sarcoidosis were grouped under the granulomatous manifestations and not in the systemic autoimmune group. Patients with inflammatory conditions were identified from the database's records of non-infectious complications, immunomodulatory therapy and malignancies. There were 158 patients who were not found on any lists recording non-infectious complications. Upon review of the data collection form and after consulting with the USIDNET registry staff, we made the assumption that these patients had none of the non-infectious complications recorded by the registry and therefore, they were assigned to the non-inflammatory CVID group.

Immunophenotype

Lymphocyte counts were extracted from flow cytometry data available on the registry's database. Cell counts are displayed in number of cells/microliter (cells/uL). CD4/CD8 ratios were calculated. Serum immunoglobulin concentrations were also available. Only IgA and IgM data were used in the current analysis as most patients were receiving IgG replacement, and it was not possible to determine whether the listed measurements reflected the patient's baseline or were obtained while on IgG therapy.

There were variable amounts of missing data for lymphocyte counts and immunoglobulins levels. Absolute lymphocyte counts (ALC) were available in 307 patients, CD4+ counts in 402, CD8+ counts in 380, CD19+ counts in 376. To decrease the amount of missing observations, cell counts were imputed, when possible. If missing, ALC counts were extrapolated from lymphocytes subpopulations percentages and counts (CD3+, CD4+, CD8+ or CD19+ cells) if available. In turn, when lymphocyte subpopulations counts were missing, we imputed values using the absolute lymphocyte count (ALC) and the specific cell type percentage (%). Using this method, we accrued ALC data on 454 patients, CD4+ cell counts on 452, CD8+ counts on 427 and CD19 counts on 425 individuals. Serum IgM levels were available in 694 patients and IgA levels in 693. Immunoglobulin values below the lower limit of detection were replaced by the result of the lower limit of detection listed, divided by the square root of 2.(22) Missing IgA and IgM values were not imputed. Memory B-cell data were available in 102 patients (n=102) and were used for descriptive purposes only, as >85% of the patients lacked such information.

Statistical Analyses

Data were analyzed using the software STATA version 14 (StataCorp. *Stata Statistical Software: Release 14*. College Station, TX. 2015). Basic demographic characteristics of the entire cohort as well as of the CVID-Rheum and ni-CVID groups are listed on table 1. Data on sex and date of birth were available for all patients. Current age, age of onset and age at diagnosis are summarized as medians and interquartile ranges (IQR) as distributions were non-Gaussian. To better delineate the main phenotypic characteristics of patients with CVID-associated rheumatologic disease, they were compared with patients in the noninflammatory CVID group only. The sex and race/ethnicity distributions between the

two groups was compared using the Pearson's chi-square test. Age differences were examined using a Wilcoxon rank-sum test.

Non-parametric tests and logistic regression analyses were used to evaluate the relationship between basic immunophenotype (IgA, IgM, CD19+ B-cells and CD4/CD8 ratio) and CVID-associated rheumatologic disease. Multiple measurements on lymphocyte subset counts and immunoglobulin levels (IgA and IgM) were available for a number of patients in the cohort. However, because of the number of patients missing data on two or more visits was significant (>80%), we decided to limit the analysis to the first measurement available on record. Differences in CD4+, CD8+, CD19+ cell counts, CD4/CD8 ratio and IgA and IgM serum levels were examined using the Wilcoxon rank-sum test as their distributions were non-Gaussian. In addition, we built logistic regression models to test the associations between immunophenotypic measurements and the CVID-Rheum phenotype using univariate models and adjusting by age at the time of the test, as most of these parameters have age-related changes. Of note, only measurements that included the blood test date were used in the multivariate models, thus, accounting for the differences in the number of observations available for unadjusted analyses. Notably, there were large amounts of missing data on flow cytometry and immunoglobulin assessments. For the purpose of this analysis, comparisons were performed assuming that those measurements were missing at random; however, this is an important limitation of this analysis and is considered in the interpretation of the data.

III. RESULTS

Study Population

We screened data on 879 patients. There were 9 patients with a different primary immunodeficiency disorder including transient hypogammaglobulinemia of infancy (n=7), autoimmune lymphoproliferative syndrome (n=1) and X-linked lymphoproliferative syndrome (n=1) who were excluded. (Figure 1).

A total of 870 patients with diagnosis of CVID were listed on the registry database. Inflammatory manifestations were recorded in 274 patients, and 596 had non-inflammatory CVID. The inflammatory CVID group included 51 patients with systemic autoimmunity (CVID-associated rheumatologic manifestations), 85 subjects with organ-specific autoimmunity including 46 individuals with skin, endocrine, neurologic, ocular, gastrointestinal, renal, or cardiac autoimmune disease and 47 patients with autoimmune cytopenias. Additionally, there were 120 patients with other inflammatory manifestations (granulomas, inflammatory lung disease or benign lymphoproliferation) and 87 patients with a history of malignancy on record (lymphoma, leukemia, solid-organ or skin cancer). (Figure 1). There were 55 patients with diagnoses in two or more inflammatory categories.

The main demographic characteristics of the cohort are displayed on Table 1. The median age of patients in the cohort was 41 years (IQR 28 yr.). There were 502 females (57.7%) and 368 males (42.3%). The cohort was predominantly White-Caucasian (74.2%). There were 40 patients of other ethnicities that included African Americans (n=18), Hispanics (n=24), Asians or Pacific Islanders (n=6), Native Americans (n=1), Mixed ethnicity (n=2). Race/

ethnicity information was unknown in 20% of patients (n=173). The median age of disease onset was 14 years (IQR 26 yr.), and median age of diagnosis was 24 years (IQR 31.7 yr.). However, information on age of onset and age of diagnosis was missing in 50% and 28% of patients respectively. Thirty-nine patients had reportedly died by 2016.

Ethnicity information was recorded in 44 (86%) patients in the CVID-associated rheumatologic disease group and 455 patients (76%) in the non-inflammatory CVID group. Among patients with available data, as in the general cohort, the ethnicity of both groups was predominantly White/Caucasian (72.5% in the CVID-associated rheumatologic disease group and 71.3% in the non-inflammatory CVID group). However, the proportion of non-white patients was higher in the CVID-Rheum group (16% vs. 6.6%) and this difference was statistically significant ($p<0.05$). Of note, we lacked race/ethnicity information in 173 patients (20%), and those individuals without available data were excluded from this comparison.

There was a statistically significant female predominance in the CVID-Rheum group

Patients with CVID-associated rheumatologic disease comprised 5.9% of all CVID patients and 18.6% of inflammatory cases. (Table 1). To delineate the main phenotypic characteristics of patients with CVID-associated rheumatologic disease, they were compared with patients in the non-inflammatory CVID group only. Patients with cancer, organ-specific autoimmunity, autoimmune cytopenias or other inflammatory manifestations without a rheumatologic disease were not included. There were 596 patients in the non-inflammatory group and 51 with CVID-associated rheumatologic disease (Table 1) for a total of 647 subjects. There was a female predominance in both groups with a female:male ratio of 1.28 in the non-inflammatory CVID group and 3.25 in the CVID-associated rheumatologic disease group. The difference in sex distribution between the two groups was statistically significant ($p<0.01$) (Table 1).

Inflammatory Arthritis is the most common CVID-associated rheumatologic manifestation, followed by autoantibody-associated conditions

A total of 129 patients had associated CVID autoimmune complications defined as the presence of one or more of: autoimmune cytopenias in 47 patients, organ-specific autoimmunity (skin, endocrine, neurologic, ocular, gastrointestinal, renal, or cardiac autoimmune disease) in 46 patients, and systemic autoimmunity (CVID-Rheum group) diagnosed in 51 patients. The two most common rheumatologic conditions were inflammatory arthritis and Sjogren's syndrome (primary or secondary) listed in 18 and 11 patients respectively (Table 2). There were 8 patients with Systemic Lupus Erythematosus (SLE). Several types of vasculitis were reported in 9 subjects and 6 more had other rheumatologic disorders including mixed connective tissue disease (n=3), undifferentiated connective tissue disease (n=1), Behcet's syndrome (n=1), rheumatic fever (n=1), and chronic nonbacterial osteomyelitis (n=1). Of note, all major autoantibody-associated disorders (e.g. inflammatory arthritis, SLE, Sjogren's syndrome) had a strong female predominance as it is seen in rheumatologic disorders not associated with CVID. A summary of the total frequency of CVID-associated rheumatologic conditions as well as their sex distribution is included in Table 2.

CVID-associated rheumatologic diseases overlap with other inflammatory CVID complications in about one-third of the patients

A total of 18 patients with CVID-associated rheumatologic disorders (35%) had an additional inflammatory manifestation. There were 8 patients with a rheumatologic disorder and organ-specific autoimmunity. Organ-specific manifestations in these patients included optic neuritis, uveitis, inflammatory bowel disease (IBD) and autoimmune cytopenias that were likely part of the broader systemic disorder or, in the IBD case, secondary to it. Nine patients had a rheumatologic disorder and other inflammatory manifestation (granulomatous disease, inflammatory lung disease or both), and 6 patients with a rheumatologic disease also developed cancer (papillary thyroid carcinoma, non-Hodgkin lymphoma, T-cell lymphoma, laryngeal carcinoma, breast cancer, and 1 patient with an unspecified malignancy).

No immunophenotypic differences were found between patients with CVID-associated rheumatologic disease and those with non-inflammatory CVID

Peripheral CD19+ B-cells, CD4/CD8 ratios and serum immunoglobulin concentrations (IgA and IgM) were compared between patients with CVID-associated rheumatologic disease and non-inflammatory CVID.

CD19+ B-cell counts were available in 25 patients (49%) in the CVID-Rheum group and 264 (46%) in the ni-CVID group. CD4/CD8 ratio was calculated in 26 patients (51 %) in the CVID-Rheum group and 264 (46 %) in the ni-CVID group. Immunoglobulins (IgM and IgA) were recorded more frequently and were available in 41 and 39 patients in the CVID-Rheum group, respectively, and in 464 individuals (80%) in the ni-CVID group. (Figure 2).

Median CD19+ B-cell counts were 160 cells/uL (IQR 235.4 cells/uL) in the CVID-Rheum group and 238 (IQR 308) in the non-inflammatory CVID group. Non-parametric testing showed a borderline significant difference between groups ($p=0.045$). Logistic regression models failed to demonstrate significant associations between CD19+ B-cell numbers and the CVID-Rheum phenotype in an unadjusted model ($n=290$ OR=0.99, 95% CI (0.99, 1.00)) or after controlling by age at the time of the test ($n=254$ OR =0.997, 95% CI (0.99, 1.00)).

Median CD4/CD8 ratio was 1.53 (IQR 1.3) in the CVID-Rheum group and 1.62 (IQR 1.27) in the noninflammatory CVID group and the difference between groups was non-significant ($p>0.05$). Additionally, there were no statistically significant associations between the CD4/CD8 ratio and the odds of having the CVID-Rheum phenotype in the unadjusted model ($n=290$ OR=0.97 95% CI (0.71, 1.33)) or after adjusting by age at the time of the test ($n=250$ OR=0.92 95% CI (0.68, 1.26)).

Median IgA values were 23 mg/dL in the CVID-Rheum group (IQR 100 mg/dL) and 26.5 mg/dL (64 mg/dL) in the non-inflammatory CVID group ($p=NS$). IgM median values were 30 mg/dL in patients with CVID and rheumatologic disease (IQR 44 mg/dL) and 34.8 mg/dL (IQR 59.2 mg/dL) in the noninflammatory group. There were no statistically significant differences in median IgA or IgM serum levels between the two groups ($p>0.05$). Additionally, there were no significant associations between serum IgA levels ($n=481$

OR=1.00, 95% CI (0.99, 1.00)) or IgM levels (n=481 OR=0.99 95% CI (0.99,1.00)) and the odds of having the CVID-Rheum phenotype after controlling by age at the time of the test.

Memory B-cells subpopulations counts in patients with CVID-associated rheumatologic disease

Total memory B-cell counts were available in 53 (8.9 %) patients in the ni-CVID group and 3 in the CVID-Rheum group (5.9%). Switched memory B-cells (CD27+ IgD-) were measured in 65 (11%) patients in the ni-CVID group and 4 (7.8%) in the CVID-Rheum group and IgM+ memory B-cells (CD27+ IgM+) in 49 individuals (8.2%) in the ni-CVID group and 2 (3.9%) in the CVID-Rheum group. Values of total memory (CD27+) and IgM+ (CD27+ IgM+) memory B-cells in the CVID-Rheum group were lower than the median values of the ni-CVID group (Figure 3) in the few patients with available measurements. However, due to the reduced number of available observations it is unknown whether this is an incidental finding or a characteristic of patients with CVID-associated rheumatologic disease.

IV. DISCUSSION

This is the first study to detail the phenotypic characteristics of patients with rheumatologic disorders in a large group of patients with CVID. Our results highlight the coexistence of these two groups of diseases, describe the spectrum of rheumatic manifestations occurring in the largest registry of CVID patients in the U.S., and study associations of CVID-associated rheumatologic disease with additional CVID comorbidities and selected immunophenotype parameters.

There were significant differences in selected demographic features between the patients with CVID-associated rheumatologic disease and patients with non-inflammatory CVID. Specifically, although there were large amounts of missing data, the proportion of non-white patients in the CVID-Rheum group was more than twice the percentage of non-white patients seen in the ni-CVID group among patients with available observations. It is important to mention that the registry is a group of selectively reported cases that may not reflect the general CVID patient population. However, considering associations between other systemic autoimmune disorders and ethnicity (e.g. higher prevalence of SLE in blacks and Hispanics or, of RA among Native Americans),(23, 24) it would be worthwhile to examine whether there are racial variations in the development of specific CVID phenotypes.

Importantly, although CVID affects both sexes equally, there was a significant female predominance among patients with CVID and rheumatologic manifestations, a phenomenon also described among CVID patients with other forms of CVID-associated autoimmunity(7) and a well-known feature of patients with rheumatologic disorders without CVID.(25) This observation brings into question whether sex-related factors play a role in the development of systemic autoimmune in CVID patients as they do in non-CVID patients with autoimmune disease.

The most common rheumatologic manifestation in this cohort was inflammatory arthritis seen in 18 cases. This is in line with previous studies that also describe arthritides as the most common rheumatologic complication in patients with CVID.(4, 11) We were unable to determine the specific arthritis subtype in all individual cases, but CVID-associated arthritis ranged from mild inflammatory to erosive rheumatoid arthritis and included a few patients with spondyloarthropathies (reactive arthritis and inflammatory bowel disease-associated arthritis) as well as cases of juvenile idiopathic arthritis (JIA). Although arthritides are a relatively uncommon complication of CVID, the coexistence of these two groups of disorders is deeply intriguing. First, the association of antibody deficiency and chronic inflammatory arthritis has been described several times previously.(4, 7, 11, 26) Conversely, an association between inflammatory arthritis and antibody deficiencies in patients without a diagnosed immunodeficiency is also known.(27–30) B-cells are central players in the development of major manifestations of several types of arthritis as they are in CVID. (31–34) Moreover, common inheritance and common genetic associations have been described between certain chronic arthritis, specifically RA and JIA, and primary antibody disorders. (14, 15) Taken together, this evidence brings into question whether these two groups of conditions share a common physiopathology at least in certain arthritis subtypes. Detailed immunophenotyping (e.g. patterns of arthritis, synovial fluid analysis) is necessary in order to define the characteristics of these patients more precisely. Further investigating the link between antibody deficiencies and inflammatory arthritis may inform physiopathology of both inflammatory arthritis and primary antibody disorders.

The spectrum of rheumatologic diseases among patients in the USIDNET cohort included most major systemic autoimmune diseases. Strikingly, SLE and SS, two autoantibody-associated diseases were among the most common, reaffirming that autoantibody-associated disorders may occur even in the setting of deficient immunoglobulin production and that disorders traditionally regarded as hypergammaglobulinemic such as Sjogren's syndrome (about 70% of patients with Sjogren's syndrome present with hypergammaglobulinemia in non-CVID settings)(35, 36) can be seen in CVID. Of clinical importance, since autoantibody profiles are not routinely tested in CVID patients, this observation raises the question of whether CVID patients retain the ability to produce pathogenic autoantibodies and thus, those should be tested. Conversely, we question whether disorders such as SLE, Sjogren's syndrome and certain types of arthritis may coexist with undiagnosed primary antibody deficiencies.

Vasculitides comprised 18% of CVID-associated rheumatologic disorders in this dataset (n=9). Although clinical details were limited, there were records of 1 patient with SLE-associated small-vessel vasculitis and 8 cases without an additional associated rheumatologic disorder including 3 patients with CNS vasculitis, 1 patient with granulomatosis with polyangiitis (GPA), 2 with small-vessel disease, and 2 cases of non-specified vasculitic disorders. A single explanation to this phenomenon in CVID patients is unlikely as vasculitis are a heterogeneous group of disorders that may occur in the setting of malignancies, immunological, infectious and autoimmune disorders. Nonetheless, since certain monogenic immune dysregulation disorders (e.g. RAG deficiency, ADA2 deficiency, STAT 1 gain-of-function mutations) may present with vasculitis and hypogammaglobulinemia,(37–39) we question whether a diagnosis of a vasculitic disorder,

should prompt early work-up to exclude monogenic disorders that feature this complication as a central manifestation.

No significant differences were found in immunophenotypic parameters including CD4/CD8 ratio, IgA and IgM concentrations between CVID-Rheum and ni-CVID patients. Our findings contrast with previous studies where higher IgM levels and increased CD4/CD8 ratio are associated with the development of autoimmune CVID complications.(7–9) Although a significant association between CD19+ B-cell numbers and the CVID-Rheum phenotype was not demonstrated, there was borderline statistically significant difference in CD19+ B-cell counts between the non-inflammatory CVID patients and the CVID-Rheum group and therefore, we cannot decisively conclude that these measurements do not differ. Decreases in B-cell numbers have been described to be associated with the development of CVID-associated autoimmunity (5, 11, 20, 40) Therefore, additional investigations are needed to determine whether these basic immunophenotype parameters could be markers of clinical value in CVID subsetting or as predictors of CVID-associated rheumatologic disease.

B-cell memory subpopulations in the CVID-Rheum group were below median values for ni-CVID patients in most of the few patients with available measurements in our study. Although we were unable to determine whether this is a significant finding, this observation is aligned with most other studies describing the immunophenotype of patients with inflammatory CVID, where decreases in memory B-cell subpopulations, especially of switched memory B-cells (CD27+ IgD-) are a consistent feature.(5, 6, 11, 41) Memory B-cell subpopulations abnormalities have also been demonstrated in patients with immune dysregulation disorders(34, 42) and have been used to monitor clinical response to therapies. (20, 43) Moreover, abnormalities of the B-cell compartment are also found in rheumatologic disorders such as RA, SLE, SS and JIA among others.(34, 42) The reason for these abnormalities is unknown in CVID, immune dysregulation, or in rheumatologic diseases, and it is unknown whether the cause is the same in all these disorders. These findings could reflect deficits in memory B-cell production secondary to B-cell differentiation abnormalities, increased cell loss of specific B-cell subpopulations or perhaps, tissue sequestration with redistribution of peripheral B-cells. Regardless, abnormalities in memory B-cells seem to be a consistent marker of immune dysregulation and could prove useful if incorporated into the routine evaluation of patients with CVID and possibly of other B-cell driven diseases (e.g. antibody-associated rheumatologic disorders). The systematic evaluation of the B-cell compartment in these patients may provide mechanistic insights into the specific B-cell abnormalities that drive the development of these conditions.

Because our study is a cross-sectional analysis of a patient registry, it has several limitations. First, since there is no uniform data collection methods addressing musculoskeletal complaints in CVID patients, there is a significant risk of reporting bias limiting our results. Inherent to the study design, there are also risks of selection and recall biases. Importantly, the USIDNET registry is a patient-consented research cohort; it does not include all individuals with CVID in the U.S, and thus, the findings of this analysis do not necessarily apply to all patients with this disease. Additionally, we were unable to establish temporal relationships between time-varying variables (e.g. infections, immunophenotype) and the

development of CVID-associated rheumatologic disorders. Finally, there were large amounts of missing data that precluded the use of certain variables and limit the interpretation of others (e.g. immunophenotype parameters). Nonetheless, the USIDNET registry of CVID patients is a valuable resource that can provide valuable insights into the clinical characteristics of CVID patients with rheumatologic complications and importantly, our study raises several relevant questions worth subsequent exploration. Ultimately, further identifying links between primary antibody immunodeficiencies and systemic autoimmune disorders may allow a better understanding of these two groups of disorders and lay the groundwork for novel phenotyping and therapeutic strategies.

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Figure 1.

Flow Diagram shows selection of patients included in the analysis. Nine patients (n=9) had an additional primary immunodeficiency (PID) diagnosis including Transient Hypogammaglobulinemia of Infancy (n=7), Autoimmune Lymphoproliferative syndrome (n=1) and X-linked Lymphoproliferative Syndrome Type 2 (n=2). There were 274 patients with inflammatory complications of CVID listed. Specific inflammatory complications included systemic autoimmunity (n=51), organ-specific autoimmunity (n=85) including those with autoimmune cytopenias, malignancy (n=87) and other inflammatory complications (n=120) which included granulomatous disease, inflammatory lung disease and non-malignant lymphoproliferation.

Figure 2. Immunophenotypical differences between non-inflammatory CVID and CVID-associated rheumatologic disease groups.

A. CD19+ cell counts by age and disease group. **B.** Comparison of CD19+ B-cell counts between patients with non-inflammatory CVID and those with CVID-associated rheumatologic disease. **C.** CD4/CD8 ratio by age and disease group. **D.** CD4/CD8 ratio values in non-inflammatory CVID and CVID-associated rheumatic disease groups. **E** and **G**: Serum immunoglobulin levels (IgA, IgM) by age and disease group. **F** and **H**: Serum immunoglobulin levels (IgA, IgM) in the non-inflammatory CVID and CVID-associated

rheumatologic disease groups (outliers are omitted). Logistic regression analyses, adjusted by age at the time of the test, failed to reveal any significant associations between CD19+ cells, CD4/CD8 ratio and immunoglobulin levels (IgA, IgM) and CVID-associated rheumatologic disease.

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ni-CVID group	N=53	N=65	N=49
Mean (SD)	18.6 (21.2)	5.6 (7)	7.9 (12.3)
Median (IQR)	11.4 (5,22)	3 (1,7)	4.8 (1.4, 9)
Vasculitis (n=1)	1	0	-
RA (n=1)	5.3	3.9	0.9
UCTD (n=1)	-	24.3	-
SLE (n=1)	2.4	0.4	2

Figure 3. Memory B-cell phenotype.

Total and IgM+ memory B-cells are below median values for patients with non-inflammatory CVID in patients with rheumatologic manifestations. Statistical comparison was not performed as there were insufficient observations in the CVID-rheum group.

Table 1.

Basic demographic and clinical characteristic of the USIDNET CVID cohort

	All CVID patients N=870	CVID-associated rheumatologic Disease N=51	Non-inflammatory CVID N=596	p-value
Gender (n, %)				< 0.01
Male	368 (42.3)	12 (23.5)	261 (43.8)	
Female	502 (57.7)	39 (76.5)	335 (56.2)	
Ethnicity (n, %)				0.02
White/Caucasian	646 (92.7)	37 (84)	425 (93.4)	
Non-white	51 (7.3)	7 (16)	30 (6.6)	
Unknown	173	7	141	
Age in years				<0.000
(median) (IQR)	41 (38)	59 (28)	39 (39)	
Number of patients (n) *	831 *	46 *	583 *	
Age of onset in years				
(median)(IQR)	14 (26)	20 (26.4)	11 (27)	
Number of patients	435	27	272	
Age of diagnosis in years				
(median) (IQR)	24(31.7)	39 (26.6)	19 (32.6)	
Number of patients	625	39	399	
Deceased n, %	39 (4.5)	5 (9.8)	13 (2.2)	< 0.01
Unknown	50 (5.8) **	7 (13.7) **	36 (6) **	

* Excludes deceased patients (n=39)

** Patients with missed survival data (n=50) were assumed to be alive

Non-inflammatory CVID is defined as the absence of autoimmunity, granulomas, inflammatory lung disease, lymphoproliferation or malignancy. CVID-associated rheumatologic manifestations included patients with any diagnosed systemic autoimmune disorder except sarcoidosis. Current age, age of onset, age of diagnosis and time to diagnosis are displayed as median and IQR (interquartile range) as their distributions were not Gaussian. There are significant differences in current age, ethnicity and sex between the CVID-Rheum and ni-CVID groups. Age of onset and age of diagnosis were not compared due to large amounts of missing data (>30%). Although the number of deaths was small (4.5% of the cohort), there were significantly higher proportion of deaths in the CVID-Rheum group compared with the ni-CVID group.

Table 2.

Frequency of CVID-associated Rheumatologic Diseases

Disorder	Number of patients (%)	Females (%)
Total of patients with CVID-associated autoimmune complications	129/870 (14.8)	56.2
Rheumatologic Disease	51/129 (39.5)	76.5
<i>Inflammatory arthritis</i>	18/51	67
<i>Systemic Lupus Erythematosus (SLE)</i>	(35.3)	100
<i>Sjogren's Syndrome</i>	8/51	100
<i>Raynaud's Syndrome</i>	(15.7)	88
<i>Dermatomyositis</i>	11/51	100
<i>Mixed Connective Tissue Disease (MCTD)</i>	(21.6)	100
<i>Undifferentiated Connective Tissue Disease (UCTD)</i>	7/51 (13.7)	0
<i>Behcet's syndrome</i>	1/51 (1.9)	
<i>Rheumatic Fever</i>	3/51 (6)	100
<i>Aseptic Osteomyelitis</i>		0
<i>Vasculitis (GPA, CNS vasculitis, HUVS, other small vessel vasculitis)</i>	1/51 (1.9)	0
		67
	1/51 (1.9)	
	1/51 (1.9)	
	1/51(1.9)	
	9/51	
	(17.6)	

CVID- associated autoimmune complications includes patients with rheumatologic disorders (n=51) and organ-specific autoimmunity (n=85) which includes skin, endocrine, neurologic, ocular, gastrointestinal, renal and cardiac autoimmune conditions as well as autoimmune cytopenias.

Abbreviations: GPA= granulomatosis with polyangiitis (Wegener's granulomatosis). HUVS= hypocomplementemic urticarial vasculitis. CNS= Central Nervous System.