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Editorial

Launching Excellence in Rheumatic and Autoimmune Diseases (ERAD): Instead of a prologue

Running title: ERAD

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Keywords- autoimmune diseases; autoimmunity; rheumatology; rheumatic diseases;

This new journal does not intend to be another on-line journal on the topics of rheumatology and autoimmune diseases. There are so many of those recently launched that is less likely that we need them all to cover the increasing needs of the scientific community.
Our Journal has some features unique when is compared to the other Journals.It is operating under the platinum open access. Thus, the authors experience all the advantages of the open access platform but without paying any fees for process or publication of their paper. To recruit and peer-review papers, we get a lot of help from our Editorial Board members.

The Journal does not limit publication of any specific type of paper. It welcomes original and review papers as all other Journal in the field but can publish also papers of the highest caliber that other journals avoid such as clinical cases, letters to the editor, and commentaries. The journal pays special attention to the work submitted by young investigators, such as educational notes. It also welcomes brief clinical images which have educational value.

Equally important is the way these papers are published. After going through meticulous peer-review assessment, the accepted papers are formatted and published on-line within days after acceptance, making this Journal one of the fastest platforms for dissemination of knowledge in the field of autoimmunity. The modern website of the Journal is also a graphics and the website of the papers in a modern way, simple and more friendly to new users is also

In this issue, we have several papers of great interest in the form of commentaries, clinical cases, clinical images and letters to the Editor.

Enjoy the reading!

Dimitrios P. Bogdanos
Editor-in-Chief

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Commentary

The role of autoantibody markers in predicting interstitial lung disease in patients with systemic sclerosis: the Larissa experience in Thessaly, Greece

Running title: Autoantibody markers of ILD in systemic sclerosis

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Abstract

This commentary underlines the need for continuous research on interstitial lung disease related to autoimmune rheumatic diseases. Amongst the numerous unmet needs, there is the urgent demand for better stratification of patients in terms of prognosis or response to treatment. Disease-related or disease-specific autoantibodies have been proven useful diagnostic tools but their clinical significance in stratifying patients who are gone have a poor prognosis is still a matter of debate. Autoantibody testing relates to the underlying cause of the disease, which in our case can vary amongst a plethora of autoimmune rheumatic diseases, such as systemic sclerosis, rheumatoid arthritis, mixed connective tissue disease or anti-synthetase syndrome. Better stratification of the patients using prompt biomarkers may assist efforts for very early intervention and better outcome.

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Keywords- Autoantibody; Anti-Jo1; Anti-synthetase Syndrome; Autoimmunity; Interstitial Lung Disease; Myositis; Rheumatic Disease

I. INTRODUCTION

Interstitial lung disease (ILD) is used as an umbrella term for a large group of diffuse parenchymal lung diseases characterized by fibrosis and/or inflammation of the lungs(1, 2). The common denominator of those diseases is that they affect the interstitium. The most common form of ILD is idiopathic pulmonary fibrosis, which has unknown cause, despite extensive investigations, hence the term idiopathic (2). Such investigations can include hematological tests, imaging (X-rays, CT scan including high-resolution CT scan, pulmonary function tests, and lung biopsy(1, 2).

Amongst the various causes of ILD, pathogens including several bacteria, viruses and fungi have been identified, which can cause interstitial lung pneumonia (3). Exposure to environmental factors such as asbestos, coal, silica or grain dust, talc etc. have been considered likely causes of ILD. Drug-induced or drug-related ILD due to antibiotics (such as nitrofurantoin), immunomodulators (such as rituximab), chemotherapy agents (such as bleomycin) or even anti-arrhythmic medications (such as amiodarone) have heavily been described in the literature over the years. In addition, one of the most common causes of ILD is autoimmune rheumatic diseases (ARDs) such as systemic sclerosis (SSc), rheumatoid arthritis (RA), anti-synthetase syndrome (ASS), idiopathic inflammatory myopathies, mixed connective tissue disorders, Sjögren's syndrome and systemic lupus erythematosus. All those been identified as major causes of ILD and pulmonary fibrosis. This explains why ILD patients without a profound causal link must be screened for underlying autoimmune causes.

Despite being extremely complex, a vigorous diagnosis of a specific form of ILD now days is more robust. This is due to practice guidelines for the diagnosis, management and treatment, which are issued by authorative thoracic societies such as the American Thoracic Society and the European Respiratory Society. Those guidelines are based on the rigorous assessment of evidence-based literature but as per other guidelines for other medical conditions cannot be applied to a broad scale i.e in patients all over the word. The epidemiology of ILD differs

throughout the globe, and exposure to a heterogenous group of environmental and occupational triggers prevents from a universal applicability of such clinical practice guidelines. Moreover, there is a huge variation of the diagnostic criteria applied. Also, in several countries there is a limited access to medical care, which is readily available in other countries. Finally, most guidelines and consensus statements have been issued on idiopathic interstitial pneumonias (IIPs), and in particular IPF, which offer no assistance or little help to non-IIPs such as those of relevant to ILD related to ARDs. In recent years, rheumatological societies such as ACR and EULAR with participants from respiratory society bodies have issued guidelines centered on ILD related to ARDs, including treatment recommendations for RA-ILD and SSc-ILD.

Over the years, screening tools for autoimmune rheumatic diseases such as disease-specific or disease-related ARDs autoantibodies assisted efforts to identify causes of ILD, which cannot be attributed anywhere else. This is based on the consensus argument, which is now widely accepted, that the diagnosis of idiopathic ILD must incorporate practices, which are based on the exclusion of ARDs or other causes. This is not always feasible, because at times, ILD precedes long-before the development of overt ARDs. Attempts to document serological evidence of ARDs may assist efforts for prompt diagnosis of the underlying disease of the existing ILD, especially is the evidence in the blood relates to immunological parameters with high sensitivity and specific for ARDs. For example, the presence of autoantibodies which are directed against Scl-70, an autoantibody which at high-titre and in the absence of infections or other causes which can account for its presence is closely linked with SSc, may indeed indicate the development of very very early SSc (VVESSc), even if there are no other clinical features related to the disease itself. This is of paramount importance foe the prompt identification of the underlying cause and the proper management of the disease.

Recently, an international consensus statement introduced the concept of "interstitial pneumonia with autoimmune features (IPAF)", which has been proposed and widely accepted by the European Respiratory Society/American Thoracic Society Task force. This term is widely used currently to describe all those causes of ILD which can be attributed to or related with systemic autoimmune disorders, without meeting criteria for a define ARD. Amongst the three domains included in the classification criteria for IPAF, one is related to serology, one to clinical features and one to morphological features. At least one feature from at least two of the three domains is required for the classification The serological domain incorporates anti-nuclear antibody (ANA) ⩾1:320 with diffuse, speckled, and/or homogeneous patterns or any titer in case of nucleolar or centromere pattern; Rheumatoid factor⩾2 × upper limit of normal; and disease-specific autoantibodies such as anti-synthetase, anti-MDA5, anti-topo I antibodies and anti-centromere antibodies. The clinical domain includes Raynaud phenomenon, unexplained digital edema, Gottron sign, digital ulcers, mechanic hands, palmar telangiectasias, inflammatory arthritis or prolonged polyarticular morning stiffness. The morphological domain consists of chest imaging, histopathological patterns, or other pulmonary physiological features in addition to interstitial pneumonia.

Given that the presence of early stage ILD is difficult to be documented in ARDs, despite vigorous monitoring and thorough assessment, and taking into account that its presence is associated with major morbidity and mortality, as it can be the major cause of death in those patients, it is of paramount importance to identify serological prognosticators of future development of ILD in patients with ARD, with no apparent evidence of existing ILD.

To this end our group has assessed several autoantibody markers, which are potentially linked with the development of ILD in patients with SSc. Others have also done the same in a single center of multi center studies. In our cohort of SSc, which originates from Thessaly in central Greece, we have found interesting features, which are worthy to mention. Our results attracted the attention of several investigators and several investigators now cite our studies over the globe. Before discussing further our findings, we must provide some information regarding the geographic origin of our cohorts. Thessaly (approx. 732,000 inhabitants) is one of the 13 official administrative regions of Greece. It is located in the Centre of the mainland country and is sub-divided into four regional units. Larissa is the most populated and its capital city (281,000 inhabitants) with the same name has two hospitals, one of which is the only university hospital of the region. Magnesia (including the Sporades islands), Karditsa, Trikala are the remaining three regions, each of which has a district hospital. The General University Hospital of Larissa is the only one of those, which has a dedicated in-patient Clinic for the case of patients with rheumatic diseases (Department of Rheumatology and Clinical Immunology). In recent years, the district hospital of Larissa and Karditsa have developed

out-patient clinics for the management of patients with rheumatic diseases. Our department is one of the biggest of its kind in Greece and is the only referral center for rheumatic diseases in Central Greece, over exceeding 9.000 visits per year.

The university hospital is also a tertiary hospital and referral Centre for patients with lung diseases, as it operated a dedicated department for respiratory medicine with in - patient and out-patient clinics overseeing patients from Central Greece. The Department of Respiratory Medicine runs a dedicated out-patient clinic for patient with ILD and a joint out-patient clinic (for the care of patients with ILD-ARDs and patients with IPAF) was established in 2018, to deal with the increasing demands for personalized care. Moreover, the Department of Rheumatology and Clinical Immunology runs specialized out-patient clinics for specific diseases (RA, SSc, SLE etc.), which allows meticulous assessment, and specialized diagnostic and therapeutic management approaches, which cannot be offered in district hospitals. It has also assisted efforts to initiate a plethora of translational studies (4-67).

In 2017, making use of a profile line immunoassay for the detection of autoantibodies, we reported our experience on the presence of SSc-specific or SSc-related autoantibodies in a consecutive cohort of 131 patients with SSc, followed up in our Department (11). Amongst those 111 were females including 49 with diffuse cutaneous SSc and 82 with limited cutaneous SSc. All patients fulfilled the 2013 American College of Rheumatology criteria for SSc. Autoantibody testing was performed by conventional indirect immunofluorescence assay (IIF) using HEp-2 as antigenic substrate and a line immunoassay (Euroline SSc profile IgG assay) which enables testing of 13 autoantigens, namely Topo I (known also as Scl-70), centromere proteins A (CENP-A) and B (CENPB), RNA polymerase III subunits 11 (RP11) and 155 (RP155), fibrillarin, NOR-90, Th/To, PM-Scl100, PM-Scl75, Ku, PDGFR, and Ro52 (from SS-A) (11). Over the 131 SSc patients, 97% had positive ANA by IIF. One hundred twenty-one patients (92.4%) had at least one of the 13 autoantibodies. Excluding anti-Ro52 antibodies (which were present in 22.1% of the patients and are not highly specific for SSc), 89.3% of the patients had detectable autoantibodies against at least one of the remaining 12 autoantigens (11). The most common autoantibodies were those against anti-Topo I (41.2% in undivided SSc, 26.8% in lcSSc and 71.4% in dcSSc), followed by anti-CENP (28.2% in total, 39% in lcSSc and 4.1% in dcSSc), and anti-RP in 14.5% total SSc. In regard to the observed clinical associations of detectable autoantibodies, as it is described previously, anti-Topo I was associated with dcSSc and anti-CENP antibodies with lcSSc. We have also found in that cohort that anti-Topo I antibodies were more frequent in patients with ILD, while anti-CENP were negatively correlated (11).

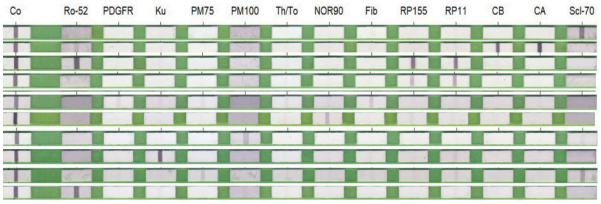

Fig.1. *Multiparametric antibody testing associated with systemic sclerosis using line immunoassay*

In a subsequent study in an extended cohort of 158 SSc patients, we confirmed the observed frequencies of the tested autoantibodies and the association of anti-Topo I antibody positivity with ILD and its negative association with anti-CENP (12). Once again, we have failed to report an association with anti-Ro52 antibodies with ILD (12), contrasting such a finding reported by other studies not only finding that anti-Ro52 is more prevalent in ILD-SSc but is also a marker of poor prognosis. There is no doubt that multiparametric profiling of SSc-specific and SSc-related autoantibodies is of paramount importance for diagnostic and likely prognostic purposes and needs to be advised in case of urgent need of patients' stratification (12). We intend to report similar data on profiling assays in a larger cohort over exceeding 250 patients from our Department and assess whether clinically meaningful association may arise. Currently, we assess all patients with suspected SSc, using this approach (ANA by IIF and subsequent multiparametric test in ANA positive and ANA negative individuals with strong suspicion of SSc). We prefer such testing than that limited to IIF alone or that including ANA by IIF and anti-centromere and/or anti-Topo I alone, without testing other disease related specificities. In our cohort, approximately 13% of the patients had anti-RNA pol III antibodies and anti-Ro52 antibodies were the third most common autoantibodies in SSc(12). One third of the anti-Ro52 antibody positive SSc patients did not have detectable anti-Topo I, anti-CENP or anti-RNA poly III antibodies. In accordance with previous studies, the concurrent presence of anti-Topo I, anti-CENP or anti-RNA poly III antibodies was not found(12). Equally importantly, approximately 20% of our patients had detectable autoantibody reactivity other than anti-Topo I, anti-CENP-A and -B and anti-RNA pol III (11 and 155) making reasonable to assume that testing of other autoantibody specificities could be of diagnostic value, especially if a diagnostic dilemma exists(12). The fact that anti-Topo I is strongly associated with ILD precludes that

this autoantibody testing is a necessary tool for the assessment of ILD(12). More recently, we reported in our cohort an association between anti-C1q antibodies and the presence of ILD in patients with SSc. This finding requires further assessment and external validation(13).

Others have found that anti-Ro52 may indeed have prognostic value for the future development of ILD with poor prognosis, thorough consideration for the assessment of anti-Ro52 testing as a routine in those patients may indeed offer an additional diagnostic and potentially clinical value(68, 69). A multi-national multi-center study including 1,574 patients with SSc has found that anti-Ro52 antibody monospecificity is associated with ILD and poor survival rates(69). A long-term observational Norwegian study has reported that anti-Ro52 (in the absence of arthritis) is one of the strongest predictors of ILD progression in patients with ARDs. Others have failed to corroborate such findings (70). In the absence of well-standardized techniques to test for anti-Ro52 antibodies by molecular-based assays it is difficult to predict the extent of the clinical significance of those (as well as other SSc-related) autoantibodies (9-12, 27, 36, 68-71).

II. CONCLUSION

In conclusion, studies on this topic gained a continuum over the years and will shed a light resolving conclusively this issue.

AUTHORS CONTRIBUTIONS

DPB and LIS had had the original idea and scripted the original draft and subsequent drafts; CL, EP and TS scripted parts of the manuscript and reviewed the literature. EP prepared the artwork All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

1. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. BMJ. 2016;352:h6819.
2. Wijsenbeek M, Cottin V. Spectrum of Fibrotic Lung Diseases. N Engl J Med. 2020;383(10):958-68.
3. Wells AU, Cottin V. Nonspecific interstitial pneumonia: time to be more specific? Curr Opin Pulm Med. 2016;22(5):450-5.
4. Efthymiou G, Dardiotis E, Liaskos C, Marou E, Scheper T, Meyer W, et al. A comprehensive analysis of antigen-specific antibody responses against human cytomegalovirus in patients with systemic sclerosis. Clin Immunol. 2019;207:87-96.
5. Efthymiou G, Liaskos C, Simopoulou T, Marou E, Patrikiou E, Scheper T, et al. Antigen-specific humoral responses against Helicobacter pylori in patients with systemic sclerosis. Immunol Res. 2020;68(1):39-47.
6. Gkiouras K, Grammatikopoulou MG, Bogdanos DP. On the efficacy and safety of rituximab therapy in patients with systemic sclerosis disease: missing points, bottlenecks, over-exaggeration, and discrepancies-comments on the article by Moradzadeh et al. Clin Rheumatol. 2021;40(10):4365-6.
7. Gkiouras K, Grammatikopoulou MG, Simopoulou T, Daniil Z, Bogdanos DP. Comparative effectiveness of mycophenolate mofetil versus cyclophosphamide in systemic sclerosis-related interstitial lung disease. Clin Rheumatol. 2021;40(8):3379-80.
8. Gkoutzourelas A, Barmakoudi M, Bogdanos DP. A Bioinformatics Analysis Reveals Novel Pathogens as Molecular Mimicry Triggers of Systemic Sclerosis. Mediterr J Rheumatol. 2020;31(1):50-70.
9. Gkoutzourelas A, Liaskos C, Mytilinaiou MG, Simopoulou T, Katsiari C, Tsirogianni A, et al. Anti-Ro60 Seropositivity Determines Anti-Ro52 Epitope Mapping in Patients With Systemic Sclerosis. Front Immunol. 2018;9:2835.
10. Gkoutzourelas A, Liaskos C, Simopoulou T, Katsiari C, Efthymiou G, Scheper T, et al. A study of antigen-specific anti-cytomegalovirus antibody reactivity in patients with systemic sclerosis and concomitant anti-Ro52 antibodies. Rheumatol Int. 2020;40(10):1689-99.
11. Liaskos C, Marou E, Simopoulou T, Barmakoudi M, Efthymiou G, Scheper T, et al. Disease-related autoantibody profile in patients with systemic sclerosis. Autoimmunity. 2017;50(7):414-21.
12. Liaskos C, Marou E, Simopoulou T, Gkoutzourelas A, Barmakoudi M, Efthymiou G, et al. Multiparametric autoantibody profiling of patients with systemic sclerosis in Greece. Mediterr J Rheumatol. 2018;29(3):120-6.
13. Liaskos C, Rentouli S, Simopoulou T, Gkoutzourelas A, Norman GL, Brotis A, et al. Anti-C1q autoantibodies are frequently detected in patients with systemic sclerosis associated with pulmonary fibrosis. Br J Dermatol. 2019;181(1):138-46.
14. Marou E, Liaskos C, Efthymiou G, Dardiotis E, Daponte A, Scheper T, et al. Increased immunoreactivity against human cytomegalovirus UL83 in systemic sclerosis. Clin Exp Rheumatol. 2017;35 Suppl 106(4):31-4.
15. Marou E, Liaskos C, Simopoulou T, Efthymiou G, Dardiotis E, Katsiari C, et al. Human cytomegalovirus (HCMV) UL44 and UL57 specific antibody responses in anti-HCMV-positive patients with systemic sclerosis. Clin Rheumatol. 2017;36(4):863-9.
16. Mavropoulos A, Liaskos C, Simopoulou T, Bogdanos DP, Sakkas LI. IL-10-producing regulatory B cells (B10 cells), IL-17+ T cells and autoantibodies in systemic sclerosis. Clin Immunol. 2017;184:26-32.
17. Mavropoulos A, Simopoulou T, Varna A, Liaskos C, Katsiari CG, Bogdanos DP, et al. Breg Cells Are Numerically Decreased and Functionally Impaired in Patients With Systemic Sclerosis. Arthritis Rheumatol. 2016;68(2):494-504.
18. Melissaropoulos K, Kraniotis P, Bogdanos D, Dimitroulas T, Sakkas L, Daoussis D. Targeting very early systemic sclerosis: a case-based review. Rheumatol Int. 2019;39(11):1961-70.
19. Ntelis K, Bogdanos D, Dimitroulas T, Sakkas L, Daoussis D. Platelets in Systemic Sclerosis: the Missing Link Connecting Vasculopathy, Autoimmunity, and Fibrosis? Curr Rheumatol Rep. 2019;21(5):15.

20. Sakkas LI, Bogdanos DP. The Role of B Cells in the Pathogenesis of Systemic Sclerosis. Isr Med Assoc J. 2016;18(9):516-9.
21. Sakkas LI, Bogdanos DP. Infections as a cause of autoimmune rheumatic diseases. Auto Immun Highlights. 2016;7(1):13.
22. Sakkas LI, Bogdanos DP. Systemic sclerosis: New evidence re-enforces the role of B cells. Autoimmun Rev. 2016;15(2):155-61.
23. Sakkas LI, Daoussis D, Mavropoulos A, Liossis SN, Bogdanos DP. Regulatory B cells: New players in inflammatory and autoimmune rheumatic diseases. Semin Arthritis Rheum. 2019;48(6):1133-41.
24. Sakkas LI, Mavropoulos A, Bogdanos DP. Phosphodiesterase 4 Inhibitors in Immune-mediated Diseases: Mode of Action, Clinical Applications, Current and Future Perspectives. Curr Med Chem. 2017;24(28):3054-67.
25. Sakkas LI, Mavropoulos A, Perricone C, Bogdanos DP. IL-35: a new immunomodulator in autoimmune rheumatic diseases. Immunol Res. 2018;66(3):305-12.
26. Sakkas LI, Simopoulou T, Katsiari C, Bogdanos D, Chikanza IC. Early systemic sclerosis-opportunities for treatment. Clin Rheumatol. 2015;34(8):1327-31.
27. Scholz J, Grossmann K, Knutter I, Hiemann R, Sowa M, Rober N, et al. Second generation analysis of antinuclear antibody (ANA) by combination of screening and confirmatory testing. Clin Chem Lab Med. 2015;53(12):1991-2002.
28. Simopoulou T, Grammatikopoulou MG, Gkiouras K, Bogdanos DP. On the diagnostic test accuracy of N-terminal pro-brain natriuretic peptide (NT-proBNP) for pulmonary arterial hypertension in patients with systemic sclerosis. Comment on : "Diagnostic value of cardiac natriuretic peptide on pulmonary hypertension in systemic sclerosis: a systematic review and meta-analysis" by Zhang et al. Joint Bone Spine 2021:105287. Joint Bone Spine. 2021:105317.
29. Bogdanos DP, Daniil Z, Zakynthinos E, Gourgoulianis K, Sakkas LI. When there is a pandemic there is no time to waste: should we have hydroxychloroquine in our armoury against COVID-19 infected patients? Mediterr J Rheumatol. 2020;31(1):94-7.
30. Kourkouni E, Mitsogiannis G, Simopoulou T, Liaskos C, Katsiari CG, Daniil Z, et al. Interstitial Lung Disease in Anti-Synthetase Syndrome. Mediterr J Rheumatol. 2019;30(3):186-9.
31. Gkoutzourelas A, Bogdanos DP, Sakkas LI. Kawasaki Disease and COVID-19. Mediterr J Rheumatol. 2020;31(Suppl 2):268-74.
32. Patrikiou E, Liaskos C, Mavropoulos A, Ntavari N, Gkoutzourelas A, Simopoulou T, et al. Autoantibodies against specific nuclear antigens are present in psoriatic disease and are diminished by secukinumab. Clin Chim Acta. 2020;510:400-7.
33. Angelopoulou F, Bogdanos D, Dimitroulas T, Sakkas L, Daoussis D. Immune checkpoint inhibitor-induced musculoskeletal manifestations. Rheumatol Int. 2021;41(1):33-42.
34. Asteriou E, Gkoutzourelas A, Mavropoulos A, Katsiari C, Sakkas LI, Bogdanos DP. Curcumin for the Management of Periodontitis and Early ACPA-Positive Rheumatoid Arthritis: Killing Two Birds with One Stone. Nutrients. 2018;10(7).
35. Bogdanos DP. Mediterranean Journal of Rheumatology September 2018 Highlights. Mediterr J Rheumatol. 2018;29(3):118-9.
36. Bogdanos DP, Gkoutzourelas A, Papadopoulos V, Liaskos C, Patrikiou E, Tsigalou C, et al. Anti-Ro52 antibody is highly prevalent and a marker of better prognosis in patients with ovarian cancer. Clin Chim Acta. 2021;521:199-205.
37. Bogdanos DP, Sakkas LI. Enterococcus gallinarum as a component of the Autoinfectome: the gut-liver-autoimmune rheumatic disease axis is alive and kicking. Mediterr J Rheumatol. 2018;29(4):187-9.
38. Cantarini L, Rigante D, Vitale A, Napodano S, Sakkas LI, Bogdanos DP, et al. Intravenous immunoglobulins (IVIG) in systemic sclerosis: a challenging yet promising future. Immunol Res. 2015;61(3):326-37.
39. Dardiotis E, Bogdanos DP. Searching for Possible Links between Alzheimer's Disease and Systemic Sclerosis. Mediterr J Rheumatol. 2020;31(4):378-81.
40. Florou DT, Mavropoulos A, Dardiotis E, Tsimourtou V, Siokas V, Aloizou AM, et al. Tetracyclines Diminish In Vitro IFN-gamma and IL-17-Producing Adaptive and Innate Immune Cells in Multiple Sclerosis. Front Immunol. 2021;12:739186.
41. Grammatikopoulou MG, Gkiouras K, Dardiotis E, Zafiriou E, Tsigalou C, Bogdanos DP. Peeking into the future: Transdermal patches for the delivery of micronutrient supplements. Metabol Open. 2021;11:100109.
42. Grammatikopoulou MG, Gkiouras K, Nigdelis MP, Bogdanos DP, Goulis DG. Efficacy of Vitamin D3 Buccal Spray Supplementation Compared to Other Delivery Methods: A Systematic Review of Superiority Randomized Controlled Trials. Nutrients. 2020;12(3).
43. Grammatikopoulou MG, Gkiouras K, Theodoridis X, Asteriou E, Forbes A, Bogdanos DP. Oral Adjuvant Curcumin Therapy for Attaining Clinical Remission in Ulcerative Colitis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2018;10(11).
44. Grammatikopoulou MG, Nigdelis MP, Theodoridis X, Gkiouras K, Tranidou A, Papamitsou T, et al. How fragile are Mediterranean diet interventions? A research-on-research study of randomised controlled trials. BMJ Nutr Prev Health. 2021;4(1):115-31.
45. Kelepouri D, Mavropoulos A, Bogdanos DP, Sakkas LI. The Role of Flavonoids in Inhibiting Th17 Responses in Inflammatory Arthritis. J Immunol Res. 2018;2018:9324357.
46. Maslyanskiy A, Lazareva N, Olinek P, Schierack P, Hentschel C, Cuccato J, et al. Anti-hnRNP B1 (RA33) autoantibodies are associated with the clinical phenotype in Russian patients with rheumatoid arthritis and systemic sclerosis. J Immunol Res. 2014;2014:516593.
47. Mavropoulos A, Varna A, Zafiriou E, Liaskos C, Alexiou I, Roussaki-Schulze A, et al. IL-10 producing Bregs are impaired in psoriatic arthritis and psoriasis and inversely correlate with IL-17- and IFNgamma-producing T cells. Clin Immunol. 2017;184:33-41.
48. Mavropoulos A, Zafiriou E, Simopoulou T, Brotis AG, Liaskos C, Roussaki-Schulze A, et al. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. Rheumatology (Oxford). 2019;58(12):2240-50.
49. Mytilinaiou MG, Bogdanos DP. Primary biliary cirrhosis-specific autoantibodies in patients with systemic sclerosis. Dig Liver Dis. 2009;41(12):916; author reply -7.
50. Pagkopoulou E, Simopoulou T, Maragkouli E, Perifanou-Sotiri S, Kotsakis A, Bogdanos DP. Arthritis and Myositis in a Patient Treated with Programmed Cell Death-1 (PD-1) Inhibitor Pembrolizumab for Lung Cancer. Mediterr J Rheumatol. 2020;31(3):355-7.
51. Rigamonti C, Bogdanos DP, Mytilinaiou MG, Smyk DS, Rigopoulou EI, Burroughs AK. Primary biliary cirrhosis associated with systemic sclerosis: diagnostic and clinical challenges. Int J Rheumatol. 2011;2011:976427.
52. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. Autoimmun Rev. 2017;16(1):10-5.
53. Sakkas LI, Bogdanos DP. Multiple hit infection and autoimmunity: the dysbiotic microbiota-ACPA connection in rheumatoid arthritis. Curr Opin Rheumatol. 2018;30(4):403-9.
54. Sakkas LI, Bogdanos DP, Kousvelari EE. Loss of C9orf72 function leads to autoimmunity. Ann Transl Med. 2017;5(3):60.

55. Sakkas LI, Daoussis D, Liossis SN, Bogdanos DP. The Infectious Basis of ACPA-Positive Rheumatoid Arthritis. Front Microbiol. 2017;8:1853.
56. Sakkas LI, Mavropoulos A, Zafiriou E, Roussaki-Schulze A, Bogdanos DP. The effect of Apremilast on signal transduction and IL-10 production in CD39high regulatory B cells in patients with psoriatic arthritis. Mediterr J Rheumatol. 2018;29(1):59-61.
57. Skyvalidas D, Mavropoulos A, Tsiogkas S, Dardiotis E, Liaskos C, Mamuris Z, et al. Curcumin mediates attenuation of pro-inflammatory interferon gamma and interleukin 17 cytokine responses in psoriatic disease, strengthening its role as a dietary immunosuppressant. Nutr Res. 2020;75:95-108.
58. Smyk DS, Koutsoumpas AL, Mytilinaiou MG, Rigopoulou EI, Sakkas LI, Bogdanos DP. Helicobacter pylori and autoimmune disease: cause or bystander. World J Gastroenterol. 2014;20(3):613-29.
59. Smyk DS, Mytilinaiou MG, Milkiewicz P, Rigopoulou EI, Invernizzi P, Bogdanos DP. Towards systemic sclerosis and away from primary biliary cirrhosis: the case of PTPN22. Auto Immun Highlights. 2012;3(1):1-9.
60. Stamatis P, Bogdanos DP, Sakkas LI. Upadacitinib tartrate in rheumatoid arthritis. Drugs Today (Barc). 2020;56(11):723-32.
61. Stamostergiou J, Theodoridis X, Ganochoriti V, Bogdanos DP, Sakkas LI. The role of the Mediterranean diet in hyperuricemia and gout. Mediterr J Rheumatol. 2018;29(1):21-5.
62. Theodoridis X, Grammatikopoulou MG, Stamouli EM, Talimtzi P, Pagkalidou E, Zafiriou E, et al. Effectiveness of oral vitamin D supplementation in lessening disease severity among patients with psoriasis: A systematic review and meta-analysis of randomized controlled trials. Nutrition. 2021;82:111024.
63. Theodoridis X, Pittas S, Bogdanos DP, Grammatikopoulou MG. Social Media as Tools to Study Dietary Habits of Patients with Rheumatic Diseases: Learning from Relevant Work on Inflammatory Bowel Diseases. Mediterr J Rheumatol. 2020;31(4):382-3.
64. Tsiogkas SG, Mavropoulos A, Skyvalidas DN, Patrikiou E, Ntavari N, Daponte AI, et al. Delphinidin diminishes in vitro interferon-gamma and interleukin-17 producing cells in patients with psoriatic disease. Immunol Res. 2021.
65. Tsouris Z, Liaskos C, Dardiotis E, Scheper T, Tsimourtou V, Meyer W, et al. A comprehensive analysis of antigen-specific autoimmune liver disease related autoantibodies in patients with multiple sclerosis. Auto Immun Highlights. 2020;11(1):7.
66. Vranou P, Gkoutzourelas A, Athanatou D, Zafiriou E, Grammatikopoulou MG, Bogdanos DP. Let Food Be Thy Medicine: The Case of The Mediterranean Diet in Rheumatoid Arthritis. Mediterr J Rheumatol. 2020;31(3):325-9.
67. Zafiriou E, Daponte AI, Siokas V, Tsigalou C, Dardiotis E, Bogdanos DP. Depression and Obesity in Patients With Psoriasis and Psoriatic Arthritis: Is IL-17-Mediated Immune Dysregulation the Connecting Link? Front Immunol. 2021;12:699848.
68. Reiseter S, Gunnarsson R, Mogens Aalokken T, Lund MB, Mynarek G, Corander J, et al. Progression and mortality of interstitial lung disease in mixed connective tissue disease: a long-term observational nationwide cohort study. Rheumatology (Oxford). 2018;57(2):255-62.
69. Wodkowski M, Hudson M, Proudman S, Walker J, Stevens W, Nikpour M, et al. Monospecific anti-Ro52/TRIM21 antibodies in a tri-nation cohort of 1574 systemic sclerosis subjects: evidence of an association with interstitial lung disease and worse survival. Clin Exp Rheumatol. 2015;33(4 Suppl 91):S131-5.
70. Lee A, Patterson KA, Tan DJ, Wilson ME, Proudman SM, Stevens W, et al. Anti-Ro52/TRIM21 is independently associated with pulmonary arterial hypertension and mortality in a cohort of systemic sclerosis patients. Scand J Rheumatol. 2021;50(6):469-74.
71. Liu C, Hou Y, Yang Y, Xu D, Li L, Li J, et al. Evaluation of a commercial immunoassay for autoantibodies in Chinese Han systemic sclerosis population. Clin Chim Acta. 2019;491:121-5.

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Commentary

IL-17-mediated depression in psoriatic disease: why the brain is not the only one that matters

Running title: IL-17 and depression in psoriatic disease

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Abstract

This commentary discusses the role of IL-17 in the depression associated with chronic immune-mediated diseases. It uses as psoriatic disease as a model, since there is a consensus regarding the pivotal role of IL-17 mediated immunity in the induction of psoriasis and psoriatic arthritis in a considerable proportion of the affected patients. We argue that if IL-17 plays a role in the induction of depression and/or its progression overtime, patients treated with blockers of IL-17 must show a significant improvement, and that their improvement must be analogous to- or closely related to- the extent of IL-17 inhibition. Though we understand that such a scenario is very simplistic, taking into account the complex interaction between the brain and the affected tissues, we postulate that it can be still possible to dissect the underlying pathophysiological mechanisms, if the focus of the translational research is to be directed towards assessing the IL-17 axis and its relation to brain development and depressive disorders.

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Keywords- Anti-IL17 monoclonal antibodies; Brodalumab; Cytokines; Depression; IL-17; Psoriasis; Psoriatic Arthritis; Secukinumab

I. INTRODUCTION

The role of the cytokine milieu in the induction of depression is a topic, which warranties immediate attention. Patients with chronic inflammatory diseases, such as patients with psoriatic disease, irrespectively of whether they suffer from psoriasis or psoriatic arthritis, experience depressive disorders. Those disorders are not always analogous to the degree of the underlying inflammation, raising concerns as to whether the progress of the disease per se or the underlying cause of the inflammatory disease has an impact in the induction of depression. Amongst the inflammatory cytokines, which are placed on the center of the ongoing research, IL-17 has received special attention (1). Others and we have considered that IL-17 and/or IL-17/IL/23 axis may indeed participate in the development and perpetuation of depression in patients with IL-17-mediated immune/autoimmune disorders (2). We used psoriatic disease as a model to study that hypothesis, as we have been able to witness in clinical and experimental grounds the instrumental role of IL-17 in these disorders (2-12). In fact, we have gone one step further to formulate the hypothesis that depression, obesity and IL-17 are interlinked, at least in psoriatic disease. Our hypothesis was based on solid grounds provided by emerging basic and clinical research [reviewed in].

Herein, we discuss some recent findings that we feel can participate in the ongoing debate.

II. IL-17, TH17 AND DEPRESSION

In a recent study, Kim et al have provided interesting data. These investigators have postulated that stressful events during brain development are associated with increased expression of IL-17. Such an increase may lead to undesirable persistent effects, namely long-lasting depression in young adulthood. To assess their hypothesis, they performed experiments in a murine model asking

whether IL-17 is involved at any stage of chronic depression-like behaviour induced by cumulative mild stress during a critical developmental period.

Over the years, it has become apparent that that IL-17 and IL-17-producing cells are involved directly or indirectly in the induction of major depressive disorders, irrespectively of whether those disorders are associated with immune-mediated and autoimmune diseases or not (13-16). Clinical data provided evidence of higher levels of IL-17 in adult patients with depression compared to healthy controls (14, 17). The percentage of Th17 cells in those patients appears to be higher compared to their control counterparts (18). In experimental animals, Th17 cells are increased (compared to what is expected in normal brains) in the brains of the learned helplessness rodent model (19, 20). Also in experimental depression, data suggest that behavioral changes may intently correlate with the imbalance between Th17 and Treg cell subsets (21). In the clinical setting such a fine balance and in particular its disturbance may play a vivacious role in autism spectrum disorders (22). Also, the imbalance of Th17/Tregs may also participate in the induction and/or progression of depression and anxiety during pregnancy (23). Th17-induced neuronal dysfunction can be irreversible, and this may be important for medications able to inhibit IL-17 or Th17-mediated inflammatory processes (24-26).

III. IL-17, TH17, STRESS AND DEPRESSION

In their murine model exposed to cumulative mild stress (CPMS; cumulative mild prenatal stress, mild maternal separation, and mild social defeat), Kim et al (27) found that their CPMS mice had raised IL-17 levels in the brain and activated microglia. In view of those findings, the Authors speculated that elevated IL-17 levels initiated by cumulative mild stress in early life might represent a likely facilitator in provoking and supporting anxiety- and depression-like behavior in young adulthood. To provide further support for that, they compared the depressive symptoms and the level of IL-17 in the CPMS group with a single or double combinations group of mild stress including mild social defeat stress. Indeed, IL-17 levels in the brain of CPMS mice were higher than single (S) or double stressor groups (PS, MS) (27). Of importance, the extent of depressive symptoms appeared to be correlated with the elevated levels of IL-17 in the brain. Moreover, they have found an increase of Th17 cells in the brains of CPMS mice. Finally, they provided data supporting that nti-IL-17 treatment ameliorates anxiety- and depression-like behaviors in those mice (27). Indeed, when they inhibited IL-17 via anti-IL-17/IL-17A antibody treatment those mice had significantly less anxiety compared the untreated mice. According to the investigators the effect of anti-IL17/IL17A treatment is further indicating that accumulative mild stress in early life is indeed induced by disproportionate IL-17, which is most likely produced by Th17 cells (27). These cells and their produced pro-inflammatory cytokine may provoke a persistent inflammatory response, which can lead to brain damage and induction of depressive symptoms in young adulthood (27).

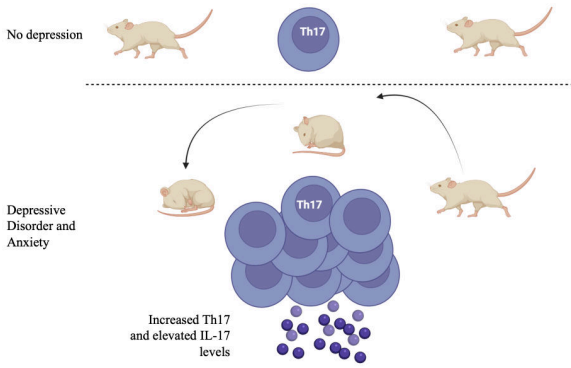

Fig. 1 A hypothesis of Th17/IL-17 mediated depression.

IV. ANTI-IL-17 AND DEPRESSION IN PSORIATIC DISEASE

A recent study has reported data suggesting that coptisine significantly reduces imiquimod-induced psoriasis-like skin lesions, as well as anxiety-like behavior in a murine model (28). This is important because Coptidis Rhizoma, a coptisine-containing herb also known as Huanglian in China, as well as coptisine itself appear to exert anti-neuroinflammatory effects in stress-exposed mice. Coptisine is one of the major alkaloids of Coptidis Rhizoma, a traditional medicinal herb, which is widely used in China to treat a broad range of inflammatory diseases, including immune-mediated skin diseases, such as psoriasis and atopic dermatitis (29, 30).

At the clinical level, it is well known that patients with psoriatic disease who have elevated IL-17A have also increased risk for depressive and anxiety disorders. A recent clinical report publishing data extrapolated from the

SUPREME study raised further expectation on the likely link between IL-17 inhibition and depression-free symptoms (31). The study reports on the post hoc analysis of 433 patients with psoriasis receiving 300mg secukinumab, a fully human IgG1κ mAb inhibiting IL-17A, in achieving minimal disease activity (MDA). The Authors reported that amongst the clinical factors that positively influenced MDA at Week 16 were absence of depression and anxiety (31). Rivera-Oyola et al reported three patients with moderate-to-severe psoriasis and comorbid depression, who were successfully treated with brodalumab, a fully human IgG2 mAb that binds and inactivates the IL-17A receptor (32). Of interest, in two of those, depression was partially or fully resolved following treatment, suggesting that the blocking of the IL-17 receptor had a direct or indirect effect on their depressive disorder (32).

V. CONCLUSIONS

In conclusion, the effect of IL-17 neutralization in depressive disorders and anxiety related to psoriatic diseases remains elusive. While some data suggest that IL-17A blocking may exert a beneficial effect in ameliorating anxiety and depressive mood, meticulous assessement in clinical and basic research is needed to provide conclusive results. The wide clinical application of IL-17 inhibitors in the routine treatment of psoriatic disease may assist efforts to conclude on this matter in the near future.

AUTHORS CONTRIBUTIONS

EZ and DPB had the original idea and scripted the original draft and subsequent drafts; AID and ST scripted parts of the manuscript and reviewed the literature. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

1. Ghoreschi K, Laurence A, Yang XP, Hirahara K, O'Shea JJ. T helper 17 cell heterogeneity and pathogenicity in autoimmune disease. Trends Immunol. 2011;32(9):395-401.
2. Zafiriou E, Daponte AI, Siokas V, Tsigalou C, Dardiotis E, Bogdanos DP. Depression and Obesity in Patients With Psoriasis and Psoriatic Arthritis: Is IL-17-Mediated Immune Dysregulation the Connecting Link? Front Immunol. 2021;12:699848.
3. Kelepouri D, Mavropoulos A, Bogdanos DP, Sakkas LI. The Role of Flavonoids in Inhibiting Th17 Responses in Inflammatory Arthritis. J Immunol Res. 2018;2018:9324357.
4. Mavropoulos A, Liaskos C, Simopoulou T, Bogdanos DP, Sakkas LI. IL-10-producing regulatory B cells (B10 cells), IL-17+ T cells and autoantibodies in systemic sclerosis. Clin Immunol. 2017;184:26-32.
5. Mavropoulos A, Varna A, Zafiriou E, Liaskos C, Alexiou I, Roussaki-Schulze A, et al. IL-10 producing Bregs are impaired in psoriatic arthritis and psoriasis and inversely correlate with IL-17- and IFNgamma-producing T cells. Clin Immunol. 2017;184:33-41.
6. Mavropoulos A, Zafiriou E, Simopoulou T, Brotis AG, Liaskos C, Roussaki-Schulze A, et al. Apremilast increases IL-10-producing regulatory B cells and decreases proinflammatory T cells and innate cells in psoriatic arthritis and psoriasis. Rheumatology (Oxford). 2019;58(12):2240-50.
7. Patrikiou E, Liaskos C, Mavropoulos A, Ntavari N, Gkoutzourelas A, Simopoulou T, et al. Autoantibodies against specific nuclear antigens are present in psoriatic disease and are diminished by secukinumab. Clin Chim Acta. 2020;510:400-7.
8. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. Autoimmun Rev. 2017;16(1):10-5.
9. Sakkas LI, Mavropoulos A, Bogdanos DP. Phosphodiesterase 4 Inhibitors in Immune-mediated Diseases: Mode of Action, Clinical Applications, Current and Future Perspectives. Curr Med Chem. 2017;24(28):3054-67.
10. Sakkas LI, Mavropoulos A, Zafiriou E, Roussaki-Schulze A, Bogdanos DP. The effect of Apremilast on signal transduction and IL-10 production in CD39high regulatory B cells in patients with psoriatic arthritis. Mediterr J Rheumatol. 2018;29(1):59-61.
11. Sakkas LI, Zafiriou E, Bogdanos DP. Mini Review: New Treatments in Psoriatic Arthritis. Focus on the IL-23/17 Axis. Front Pharmacol. 2019;10:872.
12. Skyvalidas D, Mavropoulos A, Tsiogkas S, Dardiotis E, Liaskos C, Mamuris Z, et al. Curcumin mediates attenuation of pro-inflammatory interferon gamma and interleukin 17 cytokine responses in psoriatic disease, strengthening its role as a dietary immunosuppressant. Nutr Res. 2020;75:95-108.
13. Davami MH, Baharlou R, Ahmadi Vasmehjani A, Ghanizadeh A, Keshtkar M, Dezhkam I, et al. Elevated IL-17 and TGF-beta Serum Levels: A Positive Correlation between T-helper 17 Cell-Related Pro-Inflammatory Responses with Major Depressive Disorder. Basic Clin Neurosci. 2016;7(2):137-42.
14. Nadeem A, Ahmad SF, Al-Harbi NO, Fardan AS, El-Sherbeeny AM, Ibrahim KE, et al. IL-17A causes depression-like symptoms via NFkappaB and p38MAPK signaling pathways in mice: Implications for psoriasis associated depression. Cytokine. 2017;97:14-24.
15. Poletti S, de Wit H, Mazza E, Wijkhuijs AJM, Locatelli C, Aggio V, et al. Th17 cells correlate positively to the structural and functional integrity of the brain in bipolar depression and healthy controls. Brain Behav Immun. 2017;61:317-25.
16. Schiweck C, Valles-Colomer M, Arolt V, Muller N, Raes J, Wijkhuijs A, et al. Depression and suicidality: A link to premature T helper cell aging and increased Th17 cells. Brain Behav Immun. 2020;87:603-9.

17. Chen Y, Jiang T, Chen P, Ouyang J, Xu G, Zeng Z, et al. Emerging tendency towards autoimmune process in major depressive patients: a novel insight from Th17 cells. Psychiatry Res. 2011;188(2):224-30.
18. Beurel E, Lowell JA. Th17 cells in depression. Brain Behav Immun. 2018;69:28-34.
19. Beurel E, Lowell JA, Jope RS. Distinct characteristics of hippocampal pathogenic TH17 cells in a mouse model of depression. Brain Behav Immun. 2018;73:180-91.
20. Fasching P, Stradner M, Graninger W, Dejaco C, Fessler J. Therapeutic Potential of Targeting the Th17/Treg Axis in Autoimmune Disorders. Molecules. 2017;22(1).
21. Hong M, Zheng J, Ding ZY, Chen JH, Yu L, Niu Y, et al. Imbalance between Th17 and Treg cells may play an important role in the development of chronic unpredictable mild stress-induced depression in mice. Neuroimmunomodulation. 2013;20(1):39-50.
22. Moaaz M, Youssry S, Elfatatry A, El Rahman MA. Th17/Treg cells imbalance and their related cytokines (IL-17, IL-10 and TGF-beta) in children with autism spectrum disorder. J Neuroimmunol. 2019;337:577071.
23. Osborne LM, Brar A, Klein SL. The role of Th17 cells in the pathophysiology of pregnancy and perinatal mood and anxiety disorders. Brain Behav Immun. 2019;76:7-16.
24. Siffrin V, Radbruch H, Glumm R, Niesner R, Paterka M, Herz J, et al. In vivo imaging of partially reversible th17 cell-induced neuronal dysfunction in the course of encephalomyelitis. Immunity. 2010;33(3):424-36.
25. Zhang Y, Zhen H, Yao W, Bian F, Mao X, Yang X, et al. Antidepressant drug, desipramine, alleviates allergic rhinitis by regulating Treg and Th17 cells. Int J Immunopathol Pharmacol. 2013;26(1):107-15.
26. Kim JW, Kim YK, Hwang JA, Yoon HK, Ko YH, Han C, et al. Plasma Levels of IL-23 and IL-17 before and after Antidepressant Treatment in Patients with Major Depressive Disorder. Psychiatry Investig. 2013;10(3):294-9.
27. Kim J, Suh YH, Chang KA. Interleukin-17 induced by cumulative mild stress promoted depression-like behaviors in young adult mice. Mol Brain. 2021;14(1):11.
28. Nguyen LTH, Choi MJ, Shin HM, Yang IJ. Coptisine Alleviates Imiquimod-Induced Psoriasis-like Skin Lesions and Anxiety-like Behavior in Mice. Molecules. 2022;27(4).
29. Meng S, Lin Z, Wang Y, Wang Z, Li P, Zheng Y. Psoriasis therapy by Chinese medicine and modern agents. Chin Med. 2018;13:16.
30. Wang J, Wang L, Lou GH, Zeng HR, Hu J, Huang QW, et al. Coptidis Rhizoma: a comprehensive review of its traditional uses, botany, phytochemistry, pharmacology and toxicology. Pharm Biol. 2019;57(1):193-225.
31. Campanati A, Diotallevi F, Radi G, Molinelli E, Brisigotti V, Martina E, et al. Psoriatic patients treated with secukinumab reach high levels of minimal disease activity: results from the SUPREME study. Eur J Dermatol. 2021;31(5):630-7.
32. Rivera-Oyola R, Stanger R, Litchman GH, Thibodeaux Q, Koo J, Fried R, et al. The Use of Brodalumab in Three Patients with Psoriasis and Psychiatric Comorbidities. J Clin Aesthet Dermatol. 2020;13(12):44-8.

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COVID-19 induced autoantibodies are directed against an enormous number of disease-related autoantibodies: the SARS-CoV2 autoantigen-ome era

Running title: Autoantibodies and autoantigen in COVID-19

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Abstract
Autoantibodies are frequently induced during SARS-Cov-2 infection, especially in patients suffered from sever COVID-19. The prevalence of autoantibodies ranges amongst studies but there is a consensus regarding the antigen-specificity of the observed humoral responses. These autoantibodies appear to be directed against known autoantigens, several of which are associated with organ and non-organ specific diseases, while others have not been previously considered significant triggers of autoimmunity and overt autoimmune disease. In this letter, we comment on a recently published study underlying the universal role of SARS-CoV-2 infection as an instrumental initiator for autoantibodies potentially directed against hundreds of autoantigens, several of whom are predictors of future development of an autoimmune diseases. Of pathogenic relevance, the findings of that study undescore a novel pathway used by the virus to initiate autoimmunity and indeed autoimmune disease.

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Keywords- Apoptosis; autoantibody; autoimmune disease; autoimmunity; infection; molecular mimicry; vaccine

Dear Editor,

I. INTRODUCTION

It is well know thar persistent viral infection is a likely trigger of autoimmunity and autoimmune diseases. Epidemiological studies, serological and cellular findings, virological data and findings stemmed from experimental models of autoimmune diseases are supporting this notion, irrespectively of the causative viral trigger or the nature of the autoimmune disease. Early days, several investigators have attempted to provide evidence in support of a direct effect of viral infection in provoking autoimmunity. An example that this machinery is that placing the virus as an instrumental cause of apoptosis of infected cells. Such apoptosis may serve as the impetus for the release of neo-antigens or the relevation of cryptic epitopes. Such a release, in concert with the inflammatory process due to chronic infection, can be sufficient for immunological breakdown and subsequent tissue destruction and organ impairment.

Another mechanism, which has been considered a likely trigger each time a pathogen is linked to autoimmunity is that of molecular mimicry. We and others have produced a wealth of data at the clinical setting in support or against the evidence of that mechanism (1-8). We postulated that specific viruses or microbes are indeed likely triggers of organ specific disease such as those inficting damage to the liver and we have been able to describe pathogen/self mimicking sets of antigenic peptides targeted by cross-reactive humoral and cellular responses in patients at early stages of the disease. Such data have also been obtained by others. Data of such kind have also been described in animal models of the relevant autoimmune diseases.

In the case of COVID-19 related autoantibodies a plethora of published studies have attempted to associate SARS-CoV-2 with autoimmunity, *via* molecular mimicry and immunological cross-reactivity but most of these studies with few exemptions have limited their investigations in the description of amino acid homology sets of SARS-CoV-2 and self protein mimics (9). Such a desciption does not represent clear evidence of the existence of molecular mimicry as most of the relevant sets are totally unreactive and by no means relate to true "antigenic mimicry"(7). Moreover, the presence of immunologal cross-reactivity in COVID-19 patients with detectable autoantibodies does not necessarily means that SARS-CoV-2 is the prime mover of the de novo appearance of autoantibodies as it could be epiphenomenal or short lived (9).

A recent study by Wang et al (10) has attempted to provide an holistic new view of the link between SARS-CoV-2, COVOD-19 and autoantibody/autoantigen saga. These authors have placed SARS-CoV-2 in the epicentre of autoantibody development studying the autoantigen-ome of the virus. During infection and in a attempt to survive and arguably to avoid the host's immune-mediated elimination, the virus manipulates its machinery in such a manner that at the end the host's immune response is rather controlled. Attempts of the host to inititate innate and adaptive immunity, whcih could control and preferably eradicate the virus are universal failures. Not only that, but in most cases, intense attempts of the virus to accelate its defensive immunity may indeed provoke cell apoptosis of the host cells, tissue damage and organ failure. In a sense the host destroys its self in a selpf perpetuating manner. A symbiosis between the virus and self is a comprise that the host must accept to survive. According to the authors this sophisticated host-virus symbiosis is achieved by a broad series of significant alterations of host molecules and the reprogramming of host molecular networks, which are perplexed but interconnected in nature. It appears that the infected host cells can/must/do really experience an extreme stress (10). This leads to ther death and the release of neo-antigens, which provokes a perpetuation of immunological phenomena ultimetaly leading to autoimmunity in the form of de novo appearance of autoantibodies.

The investigators have previsouly noted that in response to the virus, the host (amongst others) synthesizes dermatan sulphate (DS), a molecule which participates in wound healing, tissue repair and dead cell clearance (10). This has been instrumental for their research platform and the fruitful completion of their research projects (11). Why? Because DS appears to show high affinity for autoantigens originated from apoptotic cells and host molecules holding peculiar DS-affinity have an excessive predisposition to develop autoantigenic properties. Hence, the use of a platform based on autoantigen-DS affinity studies can eventually lead to the disvovery of a vast number of novel autoantigens (11).

Using this approach the authors have revealed an incredible number of autoantigens targeted by SARS-CoV-2 inititated immune responses (10). Amongst their 751 member autoantigen-ome, 88% are profoundly altered by SARS-CoV-2 infection, either upregulated, downregulated or both (10).

According to the investigators, 369 proteins (56% of their total DS-affinity proteins) are known autoantigens. This has let the authors to logically assume that COVID-19 is a disease, which can potentially provoke autoantibody production and autoimmune disease development (10). A meticulous assessment of their findings is clearly supporting this notion. Forty-two of their autoantigens relate to myelin sheath and could be likely triggers of multiple sclerosis-related autoantibodies or autoantibodies associated with other autoimmune neurological disorders. In a similar vein, 11 autoantigens are originated from stress fibers and 25 are associated with myofibrils, a feature which could explain several "paradoxical" features of COVID-19, from the appearance of anti-smooth muscle antibodies to the development of various muscular and cardiomuscular features of COVID-19, even in the case of less severe patients (10).

II. CONCUSIONS

In conclusion, the provocative data provided by the study of SARS-CoV-2 autoantigen-ome is intriguing (10) and add support to the notion that this is an "autoimmune virus" (12, 13). It remains to be seen whether the gigantic extent of millions of infections may inflect an increase of the incidence and the prevalence of autoimmune disease in the years to come (14).

Reference

1. Bogdanos DP, Choudhuri K, Vergani D. Molecular mimicry and autoimmune liver disease: virtuous intentions, malign consequences. Liver. 2001;21(4):225-32.
2. Bogdanos DP, Rigopoulou EI. Viral/self-mimicry and immunological cross-reactivity as a trigger of hepatic C virus associated autoimmune diabetes. Diabetes Res Clin Pract. 2007;77(1):155-6.

3. Bogdanos DP, Smith H, Ma Y, Baum H, Mieli-Vergani G, Vergani D. A study of molecular mimicry and immunological cross-reactivity between hepatitis B surface antigen and myelin mimics. Clin Dev Immunol. 2005;12(3):217-24.
4. Ehser J, Holdener M, Christen S, Bayer M, Pfeilschifter JM, Hintermann E, et al. Molecular mimicry rather than identity breaks T-cell tolerance in the CYP2D6 mouse model for human autoimmune hepatitis. J Autoimmun. 2013;42:39-49.
5. Gkoutzourelas A, Barmakoudi M, Bogdanos DP. A Bioinformatics Analysis Reveals Novel Pathogens as Molecular Mimicry Triggers of Systemic Sclerosis. Mediterr J Rheumatol. 2020;31(1):50-70.
6. Gregorio GV, Choudhuri K, Ma Y, Pensati P, Iorio R, Grant P, et al. Mimicry between the hepatitis C virus polyprotein and antigenic targets of nuclear and smooth muscle antibodies in chronic hepatitis C virus infection. Clin Exp Immunol. 2003;133(3):404-13.
7. Oldstone MB. Molecular mimicry and immune-mediated diseases. FASEB J. 1998;12(13):1255-65.
8. Polymeros D, Tsiamoulos ZP, Koutsoumpas AL, Smyk DS, Mytilinaiou MG, Triantafyllou K, et al. Bioinformatic and immunological analysis reveals lack of support for measles virus related mimicry in Crohn's disease. BMC Med. 2014;12:139.
9. Damoiseaux J, Dotan A, Fritzler MJ, Bogdanos DP, Meroni PL, Roggenbuck D, et al. Autoantibodies and SARS-CoV2 infection: The spectrum from association to clinical implication: Report of the 15th Dresden Symposium on Autoantibodies. Autoimmun Rev. 2022;21(3):103012.
10. Wang JY, Roehrl MW, Roehrl VB, Roehrl MH. A master autoantigen-ome links alternative splicing, female predilection, and COVID-19 to autoimmune diseases. J Transl Autoimmun. 2022;5:100147.
11. Lee J, Rho JH, Roehrl MH, Wang JY. Dermatan Sulfate Is a Potential Regulator of IgH via Interactions With Pre-BCR, GTF2I, and BiP ER Complex in Pre-B Lymphoblasts. Front Immunol. 2021;12:680212.
12. Dotan A, Mahroum N, Bogdanos DP, Shoenfeld Y. COVID-19 as an infectome paradigm of autoimmunity. J Allergy Clin Immunol. 2022;149(1):63-4.
13. Halpert G, Shoenfeld Y. SARS-CoV-2, the autoimmune virus. Autoimmun Rev. 2020;19(12):102695.
14. Lima M, Aloizou AM, Siokas V, Bakirtzis C, Liampas I, Tsouris Z, et al. Coronaviruses and their relationship with multiple sclerosis: is the prevalence of multiple sclerosis going to increase after the Covid-19 pandemia? Rev Neurosci. 2022.

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Is EBNA1 the molecular mimicry trigger of Epstein-Barr virus associated systemic lupus erythematosus?

Running title: anti-EBNA1 EBV antibodies and SLE

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Abstract

This letter to the editor raises concerns as to whether anti-EBNA1 Epstein-Barr virus (EBV) antibodies could be the viral triggers of systemic lupus erythematosus (SLE). We grow some concerns and comment on that in view of a recent study speculating that indeed anti-EBNA1 antibodies are the likely primary initiators of SLE-specific autoantibodies via molecular mimicry. In our mind, their data are not as convincing as it would be expected to reach a consensus for a decisive role of EBV in provoking SLE.

(Submitted 27 February 2022; accepted 11 March 2022)

Keywords- Antibody; autoantibody; infection; molecular mimicry; virus

Dear Editor,

The group of JA James and JB Hurley has recently published a paper on the role of antibodies specific for EBNA1 of Epstein-Barr virus (EBV) in provoking autoantibodies specific for systemic lupus erythematosus (SLE) (1). To establish an association between a virus such as EBV and disease-related autoantibodies in not an easy task. Especially for EBV this is even harder, as the great majority of adults are infected with EBV and a connection is practically impossible to be established (2-4). To circumvent that, these authors, as well other groups, have decided in the past to perform virological and immunological assessments in pediatric and young patients with SLE. For example, in. one of their previous studies, these investigators have studied children and young adults and found that practically all (99%) of these young SLE patients had seroconverted against EBV compared to just 70% of the control cohort. Their findings were more prominent, taking into consideration that those differences were found in the seroconversion rates against four other herpes viruses; a finding, which makes their discovery pathophysiologically significant.

If their findings hold true (1), it would be of interest to identify, which is the "antigenic sin" i.e. the original viral antigen that provokes the induction of autoantibodies. According to the Authors this antigen must be EBNA1. This is not the first time that such an expectation has been raised. In their more recent paper, the paper that has attracted our attention, Hurley et al report that that IgG anti-EBNA1 antibodies were present in 99.2% compared to 92.8% of their matched controls (1). This statistically significant difference is according to the investigators an indirect proof that autoantibodies characteristic of SLE largely results from an anti-EBNA1 heteroimmune reaction (1). Such associations were not obtained for other EBV antigens.

That anti-EBNA1 antibody responses could be reliable triggers of SLE-specific autoantibodies (and a risk factor of autoimmunity in immunological terms) has been based on previous data supporting various SLE autoantigens cross-react with EBNA1 heteroimmune antibodies, including those against Sm B/B', Ro and C1q (2-5). Such data have been obtained not only in clinical samples but also in experimental animal models of SLE.

We do not feel that a statistically significant difference between two percentages and in particular that of 99.2% compare to that of 92.8% is highly convincing of the true impact of EBNA1 in the risk of EBV in provoking SLE. It

would be preferable if such differences were noted (even by chance) in sequential series of sera, free of the virus, in individuals who acquired subsequently EBV infection and developed SLE compared to those infected without any disease of this kind. In fact, a recent study has been able to provide such data in young military personnel of the US army (6). Amongst those men, EBV has been found to have a significant impact on the development of subsequent multiple sclerosis and the most frequently found peptides reacting of all were those of EBNA (6). Such data is masking a true impact on understanding the decisive role that EBV and EBNA may have as a priori inducer of autoantibodies and autoimmunity. Others and we have repeatedly noted that EBV is a common denominator of several autoimmune diseases ranging from SLE and multiple sclerosis to autoimmune liver diseases (2-5, 7-11).

CONCLUSIONS

In conclusion, EBV is one of the most prominent triggers of autoantibodies during infection. Whether this virus is also a maker of autoimmune disease would not be easy to document. Nevertheless, serological, immunological, virological and experimental studies investigating this topic will solve once for good this matter.

AUTHORS CONTRIBUTIONS

DPB had the original idea and scripted the original draft. EP, CL, GE and CK have drafted parts of the draft and revised the final version. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

1. Laurynenka V, Ding L, Kaufman KM, James JA, Harley JB. A High Prevalence of Anti-EBNA1 Heteroantibodies in Systemic Lupus Erythematosus (SLE) Supports Anti-EBNA1 as an Origin for SLE Autoantibodies. Front Immunol. 2022;13:830993.
2. Draborg A, Izarzugaza JM, Houen G. How compelling are the data for Epstein-Barr virus being a trigger for systemic lupus and other autoimmune diseases? Curr Opin Rheumatol. 2016;28(4):398-404.
3. Draborg AH, Duus K, Houen G. Epstein-Barr virus in systemic autoimmune diseases. Clin Dev Immunol. 2013;2013:535738.
4. Houen G, Trier NH. Epstein-Barr Virus and Systemic Autoimmune Diseases. Front Immunol. 2020;11:587380.
5. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. J Clin Invest. 1997;100(12):3019-26.
6. Lanz TV, Brewer RC, Ho PP, Moon JS, Jude KM, Fernandez D, et al. Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM. Nature. 2022.
7. Dardiotis E, Bogdanos DP. Epstein-Barr Virus: In Search of a Causal or a Casual Relationship Between the Virus and the Disease? Isr Med Assoc J. 2018;20(2):111-3.
8. Rigopoulou EI, Smyk DS, Matthews CE, Billinis C, Burroughs AK, Lenzi M, et al. Epstein-barr virus as a trigger of autoimmune liver diseases. Adv Virol. 2012;2012:987471.
9. Bogdanos DP, Sakkas LI. From microbiome to infectome in autoimmunity. Curr Opin Rheumatol. 2017;29(4):369-73.
10. Patrikiou E, Liaskos C, Mavropoulos A, Ntavari N, Gkoutzourelas A, Simopoulou T, et al. Autoantibodies against specific nuclear antigens are present in psoriatic disease and are diminished by secukinumab. Clin Chim Acta. 2020;510:400-7.
11. Sakkas LI, Daoussis D, Liossis SN, Bogdanos DP. The Infectious Basis of ACPA-Positive Rheumatoid Arthritis. Front Microbiol. 2017;8:1853.

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Commentary

Is there any evidence in support of the protective role of vitamin D and omega 3 fatty acids on the advance of autoimmune disease?

Running title: Vitamin D confers protection from autoimmunity

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Abstract
Vitamin D has long been regarded as an immunomodulator with the potential to suppress autoreactive immune responses. Its role as a possible protective factor for the future development of overt autoimmune disease remains a matter of ongoing debate. In the clinical setting, it is very difficult to dissect the exact role, if any, of vitamin D, either in the induction or in the progression of autoimmune disorders. However, recent evidence has raised great expectations. The VITAL study recruited more than 25,000 older adults in the USA and provided data suggesting that daily supplementation with 2,000 IU/day of vitamin D, or its combination with omega 3 fatty acids for a total of five years induced a significant reduction in the incidence of specific autoimmune diseases. Herein, we further discuss the noteworthy findings of this study and its wider implications for the management of patients at risk of developing autoimmune disorders.

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Keywords- Autoantibody; autoimmune disease; autoimmunity; immunonutrition; immunoregulation, nutrients

I. INTRODUCTION

Vitamin D is long regarded as a potent immunoregulator, able to interact with pro-inflammatory and anti-inflammatory cell subsets and mediators (1). Vitaming D and its metabolites are largely derived from the exposure to ultraviolet light on the skin, which converts the prodromal vitamin D to vitamin D_3. In the liver, vitamin D-25 hydroxylase generates the 25-hydroxyvitamin D (25D), which is metabolised to the active form of 1.25-dihydroxyvitamin D (1.25D) which in turn, binds with the vitamin D Receptor (VDR). The fact that T cells, dendritic cells, macrophages and even B cells express VDR has led several investigators to consider 1.25D as an essential factor for the regulation of the immune system (1, 2). Recent evidence suggests that the general population, including patients with autoimmune diseases, either organ-specific or non- specific, experience a significant deficiency of vitamin D, and that the circulating levels of 1.25D may inversely correlate with disease activity (3-6). On the other hand, this deficiency is not always the prerequisite for the development of an autoimmune disease, but can serve as a marker of an autoimmunity-induced consequence or disease progression (6-12). Although debates are still apparent on whether vitamin D deficiency is an epiphenomenon or participates in complex immunological phenomena leading to the induction of autoimmunity, a consensus has been reached regarding the status of most affected patients at the time of diagnosis, the great majority of whom demonstrate low vitamin D levels (6). Unarguably, this has led to the extreme end, an overconsumption of vitamin D supplements irrespectively of whether the affected individual has normal or abnormal vitamin D concantrations (13). In fact, over-the-counter supplements of vitamin D have become so popular, that it has become highly likely for older adults to report consuming vitamin D oral nutrient supplements (ONS) on a

daily basis and for a significant period of time, even in absence of osteopenia or osteoporosis (13).

Since the deficiency of vitamin D_3 is a characteristic feature of patients with autoimmune diseases, the question arises on whether these patients would be protected from the disease, if vitamin D_3 concentrations were normal or elevated (1, 6). Is vitamin D_3 defficiency *per se* adequate for the primary prevention against autoimmune diseases? At what levels would this protection be tenable? These questions have been addressed in various animal models of autoimmune diseases, including autoimmune encephalomyelitis, multiple sclerosis (1), inflammatory bowel diseases, rheumatoid arthritis and type 1 diabetes mellitus (1, 6).

A large primary prevention trial (VITAL), conducted in older Americans was designed to answer these questions (14, 15). VITAL was a randomized, double-blind, placebo-controlled trial of 25,871 men and women across the USA. The study explored whether the daily intake of ONS of vitamin D_3 (2,000 IU) or omega-3 fatty acids could decrease the risk for developing chronic diseases such as cancer, heart disease and stroke in people who do not have a prior history of such diseases (15). The participats were randomized into four arms, with participants receiving a) vitamin D and omega-3 fatty acid ONS, b) vitamin D ONS and a placebo, c) omega-3 fatty acid ONS and a placebo, d) or placebo only. According to the authors "*supplementation with vitamin D at the dose of 2,000 IU/day for approximately five years, alone or in combination with 1 g/day of omega 3 fatty acids (460 mg eicosapentaenoic acid and 380 mg docosahexaenoic acid) led to a lower incidence of confirmed autoimmune disease than placebo*"(14). However, supplementation with omega-3 fatty acids alone failed to lower the incidence of autoimmune diseases, suggesting that it was, in fact, vitamin D ONS rather than omega-3 fatty acids, which accounted for the observed decrease in the the incidence (14).

A sub-analysis of the data provided further clues regarding the relevance of omega-3 fatty acids ONS to autoimmunity prevention. The analysis that included participants with probable autoimmune disease revealed that omega-3 fatty acid ONS reduced the rate of autoimmune diseases by 18% compared to placebo (14). Another interesting point was that when only the last three years of the intervention were accounted for, the group supplemented with vitamin D had 39% fewer cases with a confirmed diagnosis of an autoimmune disease than the placebo group (14). Finally, supplementation with both vitamin D and omega-3 fatty acids decreased the incidence of autoimmune disease by about 30% versus placebo alone. Among the various autoimmune diseases, the incidence of rheumatoid arthritis was approximately 40% lower in the supplementation arms than in the placebo groups. These results must be treated with caution, as less than 40 participants had a definite diagnosis (14).

Furthermore, these findings need external validation. As the trial tested only one dose and formulation of each supplement, it is not clear whether there is a dose-dependent effect, or if the decrease could be noted irrespectively of the dosage of the tested supplements. Moreover, the issue is further perplexed by both the low sample size of patients diagnosed with autoimmune diseases and the uncertainty in the diagnosis of some cases (14). In addition, the duration of the trial may also raise more issues; five years may not be an adequate period, as the preclinical phase of several autoimmune diseases can last for several years, or even decades.

Nevertheless, the findings of this study are of importance for the management of individuals who are at high risk for the development of autoimmune disease, such as family members of patients with autoimmune diseases, or individuals with a genetic background who are prone to develop autoimmune diseases (9). Can we recommend supplementation with vitamin D and omega 3 fatty acids as early as possible and long before the signs of autoimmunity are apparent? Can we recommend in high-risk individuals the regular assay of vitamin D concentrations? Do we need to issue recommendations or guidelines regarding protective measures which could include supplementation with vitamin D and omega 3 fatty acids (9)?

II. CONCLUSIONS

Several areas for improvement are apparent regarding the design and execution of nutrition supplementation trials for the prevention of autoimmune disorders. An adequate sample size and robust diagnostic procedures are needed for future research. Special populations, such as the young and individuals at high risk for developing autoimmunity could also be included in future studies.

AUTHORS CONTRIBUTIONS

DPB and MGM had the original idea and scripted the original draft and subsequent drafts; DA and KG scripted parts of the manuscript and reviewed the literature. All authors approved the final version

of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

References

1. Hewison M. Vitamin D and immune function: an overview. Proc Nutr Soc. 2012;71(1):50-61.
2. Provvedini DM, Tsoukas CD, Deftos LJ, Manolagas SC. 1,25-dihydroxyvitamin D3 receptors in human leukocytes. Science. 1983;221(4616):1181-3.
3. Holick MF. Vitamin D deficiency. N Engl J Med. 2007;357(3):266-81.
4. Hypponen E, Power C. Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr. 2007;85(3):860-8.
5. Patel S, Farragher T, Berry J, Bunn D, Silman A, Symmons D. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum. 2007;56(7):2143-9.
6. Fletcher J, Bishop EL, Harrison SR, Swift A, Cooper SC, Dimeloe SK, et al. Autoimmune disease and interconnections with vitamin D. Endocr Connect. 2022.
7. Dardiotis E, Arseniou S, Sokratous M, Tsouris Z, Siokas V, Mentis AA, et al. Vitamin B12, folate, and homocysteine levels and multiple sclerosis: A meta-analysis. Mult Scler Relat Disord. 2017;17:190-7.
8. Efe C, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, et al. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. Dig Dis Sci. 2014;59(12):3035-42.
9. Grammatikopoulou MG, Gkiouras K, Nigdelis MP, Bogdanos DP, Goulis DG. Efficacy of Vitamin D3 Buccal Spray Supplementation Compared to Other Delivery Methods: A Systematic Review of Superiority Randomized Controlled Trials. Nutrients. 2020;12(3).
10. Smyk DS, Mavropoulos A, Mieli-Vergani G, Vergani D, Lenzi M, Bogdanos DP. The Role of Invariant NKT in Autoimmune Liver Disease: Can Vitamin D Act as an Immunomodulator? Can J Gastroenterol Hepatol. 2018;2018:8197937.
11. Smyk DS, Orfanidou T, Invernizzi P, Bogdanos DP, Lenzi M. Vitamin D in autoimmune liver disease. Clin Res Hepatol Gastroenterol. 2013;37(5):535-45.
12. Theodoridis X, Grammatikopoulou MG, Stamouli EM, Talimtzi P, Pagkalidou E, Zafiriou E, et al. Effectiveness of oral vitamin D supplementation in lessening disease severity among patients with psoriasis: A systematic review and meta-analysis of randomized controlled trials. Nutrition. 2021;82:111024.
13. Haines ST, Park SK. Vitamin D supplementation: what's known, what to do, and what's needed. Pharmacotherapy. 2012;32(4):354-82.
14. Hahn J, Cook NR, Alexander EK, Friedman S, Walter J, Bubes V, et al. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. BMJ. 2022;376:e066452.
15. Manson JE, Bassuk SS, Lee IM, Cook NR, Albert MA, Gordon D, et al. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemp Clin Trials. 2012;33(1):159-71.

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Commentary

Antibody cross-reactivity between casein and myelin-associated glycoprotein results in central nervous system demyelination: Food for Thought on Milk, Diet and Multiple Sclerosis

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Abstract

This commentary discusses a very interesting and well-executed study with clinical correlates, which showed a cross-reactivity pattern between casein, a protein of milk, and myelin-associated glycoprotein, as evidence of a possible involvement in multiple sclerosis pathogenesis. Casein-immunized mice showed antibody-mediated demyelination with complement activation, while casein-antibodies were found in significantly higher levels in patients with multiple sclerosis that in patients with other neurological disorders. These findings highlight that diet could play a determining role in multiple sclerosis, and also provides evidence to suggest that dairy restriction could confer clinical benefits. However, the existing evidence on the association between dairy intake and multiple sclerosis, or the effectiveness of dietary interventions remains contradictory and at preliminary stages. More in-depth investigations of this possible association and studies in the effects of diet in multiple sclerosis patients are needed and more than encouraged.

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Keywords- Autoantibody; Casein; Milk; Multiple Sclerosis; Genetic-Environment Interplay; Autoimmunity; Diet; Microbiome

I. INTRODUCTION

In this era of scientific data abundance and publication bombarding, one can often find too much information on a certain subject, almost never too little. Originality in a concept can be very hard to come across (as I saw in an online academic humour group, "I hate it when a researcher from the 70s steals my novel break-through idea"), and it is very rarely that one reads a scientific article with the profound curiosity I had when reading this research paper by Chunder et al. (2022) (1).

In this study, the researchers built upon a decades-old, somewhat controversial association between bovine milk consumption and the risk of developing multiple sclerosis (MS), and studied casein, the most abundant protein in bovine milk. Firstly, WT B6 mice immunized with casein, and were killed at days 13, 20, 40 and 60 after immunization. Neurological symptoms were recorded. Control mice were either non-immunized or immunized with other bovine milk proteins, and to confirm the pathophysiological mechanisms, a type of mice that is able to produce only IgM-type antibodies was also immunized with casein and examined at 40 days. Only the casein-immunized mice developed neurological symptoms and exhibited progressive demyelination of the spinal cord, without signs of immune cell infiltration. The myelin pathology was indeed shown to be antibody-mediated, as showcased by IgG deposition, especially in mice killed in the later time-points. This was confirmed from the fact that the casein-immunized mice that could not produce IgG, did not exhibit this pathology. Interestingly, the researchers showed that the demyelination stemmed from cross-reactivity between casein and myelin-associated glycoprotein (MAG). The casein antibodies were shown to be harmful for oligodendrocytes via complement activation, leading to morphological changes (shorter branches, fewer processes, cytoplasmic shrinkage) and apoptosis; mice with inactivated complement exhibited significantly less axonal pathology, confirming the complement's involvement.

In order to translate these findings into clinical practice, peripheral blood mononuclear cells from 39 MS patients (subtype not specified) and 23 patients with other

neurological diseases were analyzed; MS patients carried significantly higher titers of anti-casein IgG antibodies. An additional analysis on 10 MS samples showed that these antibodies were truly casein-specific. These samples were then tested for cross-reactivity with MAG before and after casein-antibody adsorption; the samples showed low levels of MAG-reactivity, but nevertheless, a significant decrease was noted after adsorption.

MS is a notoriously multifaceted disorder. Genetic factors definitely play an important role in disease manifestation (2) but they cannot lead to MS on their own. As such, an interplay between genetic susceptibility and environmental factors is thought to trigger the demyelinating processes. Infections have been considered the main "culprit" regarding these environmental triggers (3), but they also do not seem to suffice and more factors seem to be involved. In this sense, diet seems to be much more important than previously thought. A long line of research has shown that dietary factors affect central nervous system (CNS) autoimmunity, since the gastrointestinal system is heavily involved in immune system maturation and tolerance (4). Following this train of thought, the gut microbiome has also gained more and more attention in terms of autoimmunity and is even being considered for therapeutic applications (5).

An association with milk and dairy products consumption and MS was firstly reported decades ago (6, 7). Some researchers wondered if this association with milk was just a reflection of a wider association with a certain lifestyle, i.e. countryside, farms, and milk cows (8). Although an association with country milk production, and nation and local bovine density and MS was reported, this association was weaker than the one found for milk itself, and no association was reported for other animals. One could wonder if maybe infectious agents in bovine milk and cows were to blame for this association, but this study on casein and MAG shows that there is indeed a very plausible connection between demyelination and milk itself. Other proteins of milk have also shown cross-reactivity with different myelin epitopes, and the respective antibodies have been detected in MS (9), also highlighting the possible involvement of milk as a whole in the triggering of autoimmune processes. This was reciprocated by epidemiological studies that linked higher dairy intake during adolescence with MS susceptibility, although one could initially expect to see a protective effect, considering that vitamin D deficiency is regarded a major risk factor for MS and that most dairy products are vitamin D fortified (10).

In this regard, a recent review showed that consumption of dairy products seemed to promote the proliferation of beneficial microbial species, but casein isolates did not induce alterations in microbiota composition (11). This is important since MS patients have been shown to carry a "microbial signature", a distinct pattern in their microbial communities (12), but since casein may not influence gut microbiota, its implication in MS via a different mechanism, such as the aforementioned cross-reactivity with myelin, becomes even more plausible (1).

A wide range of studies have explored vitamins and nutrition supplements as potential therapeutic alternatives in the setting of MS (13). However, reaching a unanimous conclusion as to which diet is effective or which complement confers a benefit is far from near. Interestingly, a lifestyle-questionnaire study with more than 2000 MS patients reported that patients not consuming dairy products were more likely to report a higher quality of life, with reduced disease activity (14). This was contradicted by another similar study, which reported that a higher intake of grains and dairy products was associated with lower disability in MS patients (15). It should be noted however, that both of these studies grouped dairy products together and did not specify further. This could be an important confounding factor, since not all dairy products carry the same protein composition (casein, for instance), or fatty acids, which are heavily discussed in dietary interventions of autoimmunity, and are also known to influence inflammation and gut microbiota (16). Long-chain fatty acids, abundantly found in dairy products, have also been shown to promote pro-inflammatory cells and molecules in animal models of multiple sclerosis; short-chain fatty acids on the contrary, attenuated inflammation (4). Propionate, a short-chain fatty acid was also shown to increase T regulatory cells in MS patients (17). Diets high in fiber, grain, fruits, and vegetables, such as the Mediterranean diet, and diets with almost no dairy intake, such as the Paleolithic diet, have shown promise in the setting MS in some preliminary reports, though the evidence is not strong and more research is needed for definite conclusions to be reached (16). It would be interesting to see if vegan MS patients present a more favorable disease course than animal-protein-consuming ones; one study with a low-fat, plant-based diet showed that patients could adhere to it, but it did not show a significant effect on brain lesions, relapse rates, or overall disability (18).

Moving on, milk has also been associated with several other autoimmune processes as well. Some earlier epidemiological studies claimed that introducing cow's milk-based diet too early in an infant's nutrition increased the risk of diabetes mellitus type 1, with milk proteins being shown as 'diabetogenic' in animal experiments; however, this was not replicated in subsequent studies (19). Dairy

allergy has also been associated with inflammatory bowel disease, and consumption of dairy products can aggravate the disease course (20), while an association of bovine milk proteins with rheumatoid arthritis has been postulated for decades now, with cross-reactivity involved here as well (21). Anti-casein antibodies and anti-lactoglobulin antibodies have also been identified in the sera of patients with active Behcet's disease (22). This variety of associations, albeit not always consistent, highlights that bovine milk might trigger some autoimmune processes, maybe in genetically predisposed individuals, and merits more investigation.

II. CONCLUSIONS

This study on casein and a possible cross-reactivity with MAG has provided further interesting insight on the association of milk and MS. The fact remains however, that these findings need to be replicated and the potential mechanisms need to be more in depth examined; could dairy intake be a causative factor or an aggravating factor? The researchers hypothesize that certain individuals can be sensitized against casein, so that a subsequent casein intake fuels myelin destruction via cross-reactivity with MAG (1). This could have important therapeutic consequences, since patients with MS could potentially avoid relapses with lifestyle and diet changes.

However, as the authors also mentioned, the particular casein antigens need to be more specifically examined, since a multitude of histopathological staining patterns in the immunized mice was reported, hinting towards reactivity with multiple epitopes. Additionally, it will be interesting to study these casein antibodies in all subtypes of MS, since in this particular study the subtypes were not specified, but it is known that the various subtypes differ in terms of pathophysiology and prognosis (23). Additionally, the researchers immunized mice against two other milk proteins (beta-lactoglobulin and alpha-lactalbumin) and did not find similar inflammatory reactions as with casein. However, antibodies against different milk proteins than these have been shown to cross-react with other myelin proteins (9), so whether casein is the main "culprit" behind any possible association of milk and MS remains hitherto unclear.

Drawing from these findings, the overall relationship with milk and dairy products with MS needs to be further investigated, but this is no easy task to accomplish. Firstly, studies examining a causal relationship with dairy intake need to also carefully address potential lifestyle confounding factors that have also shown links to MS, such as smoking and obesity. Then, as the literature currently stands, there is a limited number of high-quality prospective studies or clinical trials on dietary attempts in MS available. These also present a particular challenge on their own, as given the nature of the intervention, no blinding can be performed, and adherence to the regimen is also harder to control and achieve (16). Suitable endpoints are also more difficult to accurately set, since for instance, patients with relapsing-remitting MS, the commonest type, are more likely to be under some sort of immunomodulatory treatments and monitoring the effects of a diet is thus in a way compromised.

It is encouraging, though, to observe the ongoing efforts into approaching a disease more holistically, rather than basing all therapeutic efforts on pharmaceutical compounds and ignoring the impact of lifestyle and other environmental factors in a disease's course. This very well-executed study has provided important "food for thought" on the environmental risk factors of multiple sclerosis and could open a long discussion regarding milk, diet in general, gut microbiota, and autoimmunity, in the scientific community's attempt to find answers, and thus, solutions. One could only encourage similar high-quality efforts in this direction.

AUTHORS CONTRIBUTION

AMA conceptualized and scripted the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

References

1. Chunder R, Weier A, Maurer H, Luber N, Enders M, Luber G, et al. Antibody cross-reactivity between casein and myelin-associated glycoprotein results in central nervous system demyelination. Proc Natl Acad Sci U S A. 2022;119(10):e2117034119.
2. Hadjigeorgiou GM, Kountra PM, Koutsis G, Tsimourtou V, Siokas V, Dardioti M, et al. Replication study of GWAS risk loci in Greek multiple sclerosis patients. Neurol Sci. 2019;40(2):253-60.
3. Marrodan M, Alessandro L, Farez MF, Correale J. The role of infections in multiple sclerosis. Mult Scler. 2019;25(7):891-901.
4. Haghikia A, Jorg S, Duscha A, Berg J, Manzel A, Waschbisch A, et al. Dietary Fatty Acids Directly Impact Central Nervous System Autoimmunity via the Small Intestine. Immunity. 2015;43(4):817-29.
5. Vieira SM, Pagovich OE, Kriegel MA. Diet, microbiota and autoimmune diseases. Lupus. 2014;23(6):518-26.
6. Malosse D, Perron H, Sasco A, Seigneurin JM. Correlation between milk and dairy product consumption and multiple sclerosis prevalence: a worldwide study. Neuroepidemiology. 1992;11(4-6):304-12.
7. Butcher PJ. Milk consumption and multiple sclerosis--an etiological hypothesis. Med Hypotheses. 1986;19(2):169-78.
8. Malosse D, Perron H. Correlation analysis between bovine populations, other farm animals, house pets, and multiple sclerosis prevalence. Neuroepidemiology. 1993;12(1):15-27.

9. Guggenmos J, Schubart AS, Ogg S, Andersson M, Olsson T, Mather IH, et al. Antibody cross-reactivity between myelin oligodendrocyte glycoprotein and the milk protein butyrophilin in multiple sclerosis. J Immunol. 2004;172(1):661-8.
10. Munger KL, Chitnis T, Frazier AL, Giovannucci E, Spiegelman D, Ascherio A. Dietary intake of vitamin D during adolescence and risk of multiple sclerosis. J Neurol. 2011;258(3):479-85.
11. Aslam H, Marx W, Rocks T, Loughman A, Chandrasekaran V, Ruusunen A, et al. The effects of dairy and dairy derivatives on the gut microbiota: a systematic literature review. Gut Microbes. 2020;12(1):1799533.
12. Mirza A, Mao-Draayer Y. The gut microbiome and microbial translocation in multiple sclerosis. Clin Immunol. 2017;183:213-24.
13. Bagur MJ, Murcia MA, Jimenez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, et al. Influence of Diet in Multiple Sclerosis: A Systematic Review. Adv Nutr. 2017;8(3):463-72.
14. Hadgkiss EJ, Jelinek GA, Weiland TJ, Pereira NG, Marck CH, van der Meer DM. The association of diet with quality of life, disability, and relapse rate in an international sample of people with multiple sclerosis. Nutr Neurosci. 2015;18(3):125-36.
15. Fitzgerald KC, Tyry T, Salter A, Cofield SS, Cutter G, Fox R, et al. Diet quality is associated with disability and symptom severity in multiple sclerosis. Neurology. 2018;90(1):e1-e11.
16. Katz Sand I. The Role of Diet in Multiple Sclerosis: Mechanistic Connections and Current Evidence. Curr Nutr Rep. 2018;7(3):150-60.
17. Duscha A, Jörg, S., Berg, J., Linker, R., Gold, R., Haghikia, A. The Effect of the orally applied short chain fatty acid propionate on the immune regulation in MS: results of a human proof-of-concept study (P3.388). Neurology. 2017(88).
18. Yadav V, Marracci G, Kim E, Spain R, Cameron M, Overs S, et al. Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Mult Scler Relat Disord. 2016;9:80-90.
19. Wasmuth HE, Kolb H. Cow's milk and immune-mediated diabetes. Proc Nutr Soc. 2000;59(4):573-9.
20. Judaki A, Hafeziahmadi M, Yousefi A, Havasian MR, Panahi J, Sayehmiri K, et al. Evaluation of dairy allergy among ulcerative colitis patients. Bioinformation. 2014;10(11):693-6.
21. Perez-Maceda B, Lopez-Bote JP, Langa C, Bernabeu C. Antibodies to dietary antigens in rheumatoid arthritis--possible molecular mimicry mechanism. Clin Chim Acta. 1991;203(2-3):153-65.
22. Triolo G, Accardo-Palumbo A, Dieli F, Ciccia F, Ferrante A, Giardina E, et al. Humoral and cell mediated immune response to cow's milk proteins in Behcet's disease. Ann Rheum Dis. 2002;61(5):459-62.
23. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sorensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278-86.

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Case report

Pleuritic pain in a patient with rheumatoid arthritis: *Second time around might be different*

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(Submitted 12 March 2022; accepted 14 March 2022)

Keywords- Rheumatoid arthritis pleuritis, rheumatoid pleural effusion, pleuritic pain, secondary spontaneous pneumothorax

Case Study

A 79-year-old man ex-smoker with a medical history of Rheumatoid Arthritis under corticosteroids and leflunomide presented to the Emergency Department of our tertiary hospital reporting right pleuritic chest pain and mild dyspnea for one week. He didn't report any fever, weight loss, night sweats or hemoptysis. The chest x-ray [Fig. 1] revealed a blunting of the right costophrenic angle and an airspace opacification at the right upper lung field.

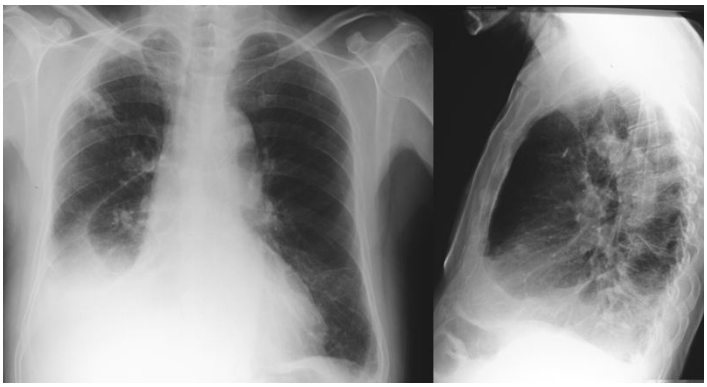

Fig. 1 *X-ray of the first admission showing right pleural effusion*

The subsequent chest computed tomography [Fig. 2] confirmed the existence of right pleural effusion and additionally a thick-walled abnormal gas-filled space within the lung most consistent with a cavitated rheumatoid node.

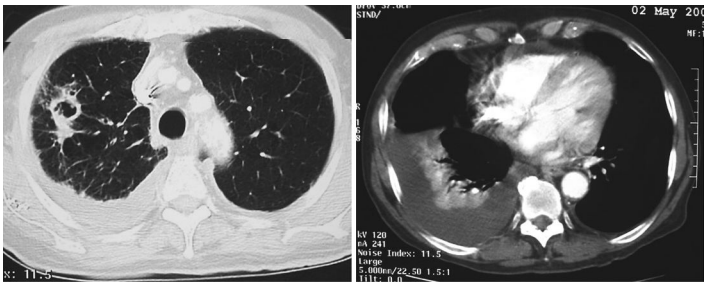

Fig. 2 *Chest computed tomography of the first admission showing a right pleural effusion and a pulmonary cavity in the right lung*

A diagnostic thoracocentesis was performed. The examination of the pleural fluid revealed a predominantly lymphocytic (67%) exudate with low glucose value (18 mg/dl), low pH (7.18), high value of lactate dehydrogenase (768 IU/L) and high value of adenosine deaminase (83.5 U/L). Sputum and pleural fluid microscopic examination and cultures both for common bacteria and acid-fast bacteria were negative. A bronchoscopy was performed, and no evidence of malignancy were found macroscopically or in the cytopathological examination of bronchial secretions. The high adenosine deaminase content was highly suggestive of tuberculosis, mesothelioma, or lymphoma but a full body computed tomography was negative for solid tumor, pleural thickening or enlarged lymph nodes. Cytologic examination of pleural fluid was positive for Naylor's triad that comprises: i) granular/necrotic debris, ii) multinucleated giant cells and iii) spindled histiocytes. In

addition, both serum and pleural fluid rheumatoid factor levels were elevated. Taken together, those findings supported the diagnosis of a pleural effusion related to rheumatoid arthritis, given that other possible causes were previously excluded. After his immunomodulatory treatment was modified, the pleural effusion decreased, and the patient was discharged with a 3-month follow up without any pleural fluid reproduction. However, six months later, the patient presented once again to our Emergency Department with right pleuritic chest pain and dyspnea with acute onset which resembled the symptomatology of the initial visit. The chest x-ray [Figure 3] showed the right visceral pleural edge as a thin white line with no lung markings seen peripherally to this line, while the peripheral space was radiolucent compared to the adjacent right lung.

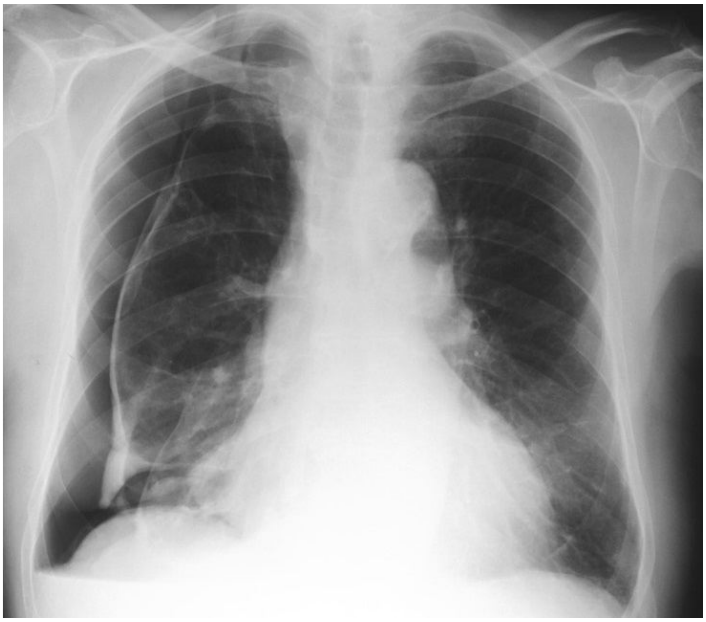

Fig. 3 *X-ray of the second admission showing a pneumothorax of the right hemithorax*

Those radiological findings indicated a right pneumothorax, possibly owing to rupturing of the previously imagined cavitated rheumatoid node. A chest tube was inserted into the right pleural space, the leaked air was effectively drained, and the lung expanded. The patient was stabilized and was discharged from the hospital after few days.

AUTHORS CONTRIBUTION

ZD had the original idea, NGZ scripted the original draft. IED and SIS have drafted parts of the draft and revised the final version. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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Commentary

Metagenome-wide association study reveales disease-specific landscape of the gut microbiome of systemic lupus erythematosus: a constellation of dysbiosis and inflammation

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Abstract

This commentary evidences the role of dysbiosis in patients with systemic lupus erythematosus (SLE). It was shown that specific Streptococcus spp. may exert a pathogenic role by empowering the gut inflammation, especially through the observation of a correlation with acylcarnitine. Nonetheless, geographical differences should be carefully taken into account since genetic, dietary and other lifestyle habits may influence the composition of gut microbiota. More in-depth investigations of this possible association are soon expected.

(Submitted 12 March 2022; accepted 17 March 2022)

Keywords- Autoantibody; Lupus; Gut; Mirobiota; Streptococcus; Genetic-Environment Interplay; Autoimmunity; Diet; Microbiome

I. INTRODUCTION

The intriguing relationship existing between the microbiota and the development of autoimmune diseases still requires to be elucidated. The disruption of the delicate balances among the bacterial species is at the basis of the dysbiosis observed in patients with systemic lupus erythhematosus (SLE) (1). Among the many questions that deserve an answer, certainly it would be interesting to understand whether these changes occur in the stages preceding the development of the disease, or whether they are an epiphenomenon, or a pathogenic mechanism by which the disease develops and maintains itself. Indeed, it was already shown that gut microbiota could play an important role in SLE pathogenesis. Zhang et al. observed in a murine lupus model a marked depletion of Lactobacilli and an increase of *Lachnospiraceae* compared to age-matched healthy controls in young, female lupus-prone mice (2). Hevia and colleagues investigated the presence of gut dysbiosis in SLE patients in remission (SLEDAI score lower than 8) in absence of any immunosuppressant or glucocorticoid treatment during the previous months. A relatively higher abundance of Bacteroidetes was identified in the SLE group. Moreover, a significantly lower *Firmicutes/Bacteroidetes* ratio in SLE individuals compared with healthy controls was detected (3). The high prevalence of Bacteroidetes has been confirmed in the study conducted by Johnson and colleagues, in lupus-prone SNF1 mice with more severe disease (4).

The paper by Tomofuji et al. (5) found an increase of *Streptococcus intermedius* and *Streptococcus anginosus* in patients with SLE.

The microbial pathways related to sulfur metabolism and flagella assembly were altered in the patients with SLE. The authors confirmed the presence of dysbiosis in patients with SLE and observed that there were two metabolites that were more abundant (acylcarnitine and isocitric acid) and significantly positively correlated with *Streptococcus intermedius*.

II. CONCLUSIONS

In conclusion, the presence of these *Streptococcus spp*. should deserve further researches. Indeed, these bacteria are not innocent bystanders (6): in rare circumstances they are known to provoke even severe diseases including endocarditis. The correlation with an inflammatory molecule such as acylcarnitine supports this hypothesis. Nevertheless, the results should be detailed since genetic and dietary habits could influence the outcome of the microbiological analysis. The authors themselves suggest that only some species have the same directional effects between the studies, suggesting that effects of geography, lifestyle and even analytic methods cannot not be rejected.

AUTHORS CONTRIBUTION

CP conceptualized and wrote the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

References

1. Chimenti MS, Perricone C, Novelli L, Caso F, Costa L, Bogdanos D, Conigliaro P, Triggianese P, Ciccacci C, Borgiani P, Perricone R. Interaction between microbiome and host genetics in psoriatic arthritis. Autoimmun Rev. 2018 Mar;17(3):276-283.
2. Zhang H, Liao X, Sparks JB, Luo XM. Dynamics of gut microbiota in autoimmune lupus. Appl Environ Microbiol. 2014 Dec;80(24):7551-60. doi: 10.1128/AEM.02676-14.
3. Hevia A, Milani C, López P, Cuervo A, Arboleya S, Duranti S, Turroni F, González S, Suárez A, Gueimonde M, Ventura M, Sánchez B, Margolles A. Intestinal dysbiosis associated with systemic lupus erythematosus. mBio. 2014 Sep 30;5(5):e01548-14.
4. Johnson BM, Gaudreau MC, Al-Gadban MM, Gudi R, Vasu C. Impact of dietary deviation on disease progression and gut microbiome composition in lupus-prone SNF1 mice. Clin Exp Immunol. 2015 Aug;181(2):323-37.
5. Tomofuji Y, Maeda Y, Oguro-Igashira E, Kishikawa T, Yamamoto K, Sonehara K, Motooka D, Matsumoto Y, Matsuoka H, Yoshimura M, Yagita M, Nii T, Ohshima S, Nakamura S, Inohara H, Takeda K, Kumanogoh A, Okada Y. Metagenome-wide association study revealed disease-specific landscape of the gut microbiome of systemic lupus erythematosus in Japanese. Ann Rheum Dis. 2021 Dec;80(12):1575-1583.
6. Jiang S, Li M, Fu T, Shan F, Jiang L, Shao Z. Clinical Characteristics of Infections Caused by Streptococcus Anginosus Group. Sci Rep. 2020 Jun 3;10(1):9032.

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Clinical Note

New EULAR guidelines on lifestyle changes in patients with rheumatic and musculoskeletal disorders

Running title: Lifestyle and rheumatic diseases

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Abstract

This clinical note underscores the major points of the recent guidelines issued by EULAR regarding lifestyle changes in patients with rheumatic diseases. Amongst other, these guidelines provide practical hints regarding the effect of lifestyle modification, exercise, diet, body mass index, alcohol consumption, smoking, and participation to work in the progression of rheumatic diseases.

(Submitted 12 March 2022; accepted 22 March 2022)

Keywords- Alcohol; Diet; Exercise; EULAR; Guidelines; Lifestyle; Smoking; Vitamin D

I. INTRODUCTION

As a result of thorough review of the existing literature, EULAR recently published recommendations on lifestyle changes (lifestyle behaviors and work participation) that could help prevent the progression of rheumatic and musculoskeletal disorders (1).

Amongst many recommendations, I wish to outline the following:

- Lifestyle modifications, although important for the health of these patients, complement but do NOT replace medication
- Exercise (aerobics and strength training, at least moderate intensity, preferably in a group) is recommended due to its beneficial effects on pain, function and quality of life, especially in patients with osteoarthritis or ankylosing spondylitis.
- A healthy, balanced diet is important; special dieting practices (eg vitamin D, cod liver oil, omega-3 fatty acids, etc.) is unlikely to be associated with better outcomes
- Overweight patients should attempt to lose weight with the assistance of weight loss experts, through diet and exercise.
- Consumption of small amounts of alcohol is unlikely to have negative effects on the outcome of rheumatic diseases. In patients with rheumatoid Arthritis, moderate alcohol consumption is associated with an increased risk of disease or comorbidities. The same applies goes for gout.
- Recommendation for smoking cessation. Smoking has detrimental effects on symptoms, function, disease activity, disease progression and comorbidities in all rheumatic diseases.
- Participation in work is associated with beneficial effects on the health outcome of these patients

II. CONCLUSION

The new EULAR guidelines (1) are providing practical hints for the practicing physician and can assist efforts for counseling of the affected individuals, based on the review of the existing literature.

AUTHOR CONTRIBUTION

SNN scripted the draft. The original idea has been initiated from a post on the author's blog in his native language.

CONFLICT OF INTEREST

The author declares no conflict of interest.

Reference

1. 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases. Ann Rheum Dis. *2022 Mar 8 :*annrheumdis-2021-222020. doi: 10.1136/annrheumdis-2021-222020. Epub ahead of print. PMID: 35260387.

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Clinical Image

Post infectious vasculitis

Running title: infection and vasculopathy

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Received 28 February March 2022; accepted 23 March 2022

Keywords- Adverse reactions; autoimmunity; autoimmune rheumatic diseases; cyclosporine; gum hypertrophy; treatment

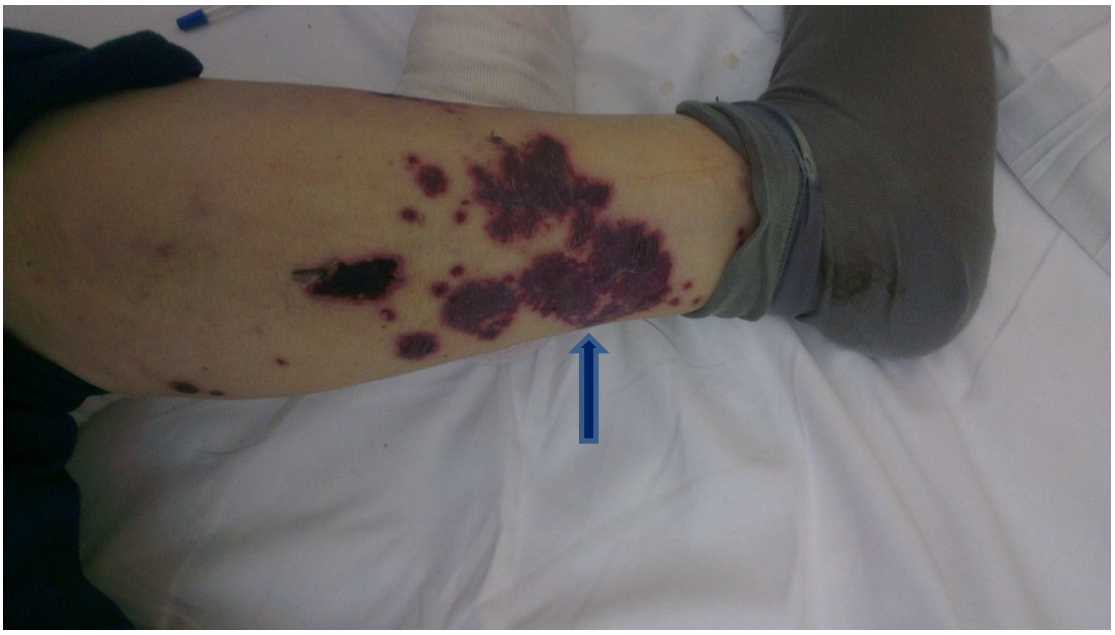

Fig. 1 *Post infectiousvasculitis. Hemorrhagic cutaneous damage fully recovered after antibiotic treatment.*