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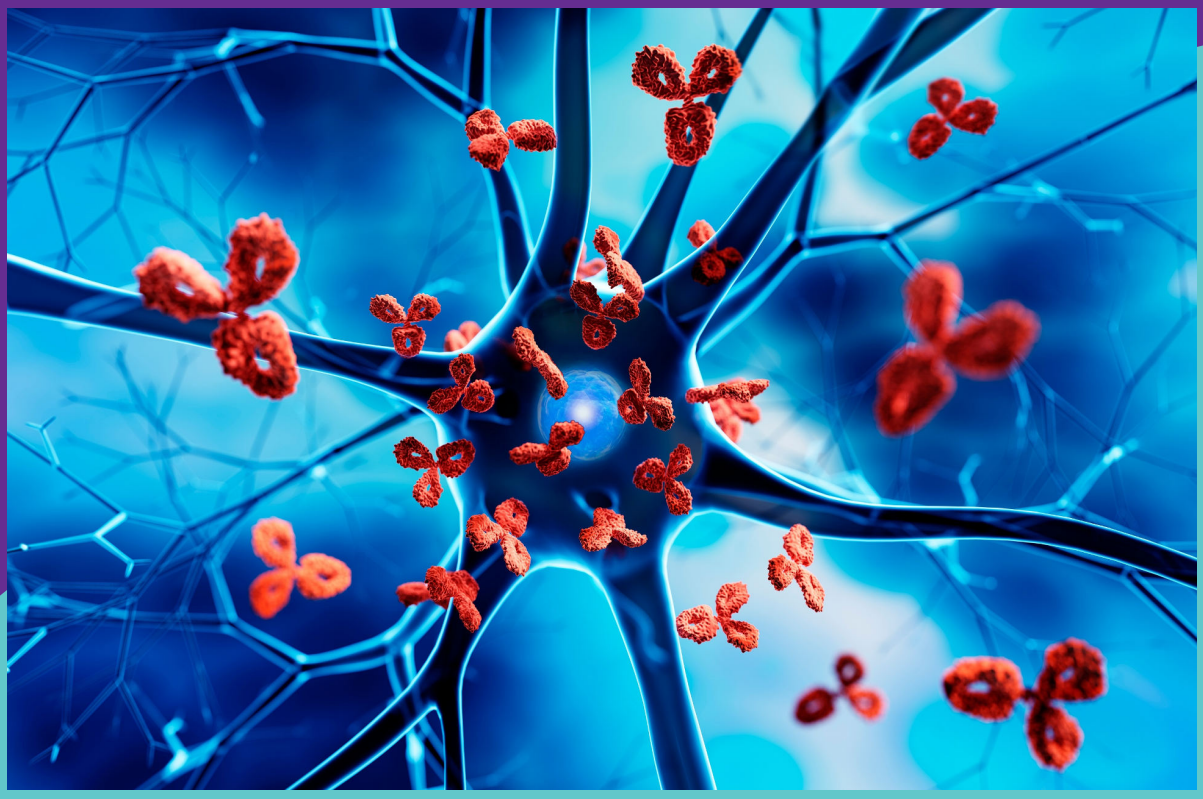

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ERAD, 2023, Volume 2, Issue 1, pages 1-3

Expert Opinion

Is immunofluorescence about to disappear in clinical laboratories?

Running title: autoantibody testing: the role of immunofluorescence

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Abstract

In recent years an emerging question was raised. Is indirect immunofluorescence for autoantibody testing going to decline or even to disappear? Evolution of autoantibody testing has emerged. methods such as double immunodiffusion and counter-immunoelectrophoresis have been progressively abandoned in favor of much more reliable and reproducible methods. An important step towards the possible replacement of IIF has been made with the introduction of fully automated methods. But are those new technologies appropriate. In this article, we discuss the pros and cons of the evolving issues and we raise some more questions which need to be addressed.

(Submitted 6 June 2023; accepted 20 June 2023)

Keywords- T cell; Thymus; TCR; CD4; CD8; Immunity

I. INTRODUCTION

One of the questions we have been asking ourselves for some years now is whether the indirect immunofluorescence method (IIF) to search for antibodies has had its day and it is time to replace it with other techniques that are more accurate, faster and more automated. There has always been an evolution in the immunological diagnosis of rheumatic diseases: methods such as double immunodiffusion and counter-immunoelectrophoresis have been progressively abandoned in favor of much more reliable and reproducible methods. Radioimmunoassay and immunoenzymatic methods (ELISA) are also recording a progressive and constant decline and will probably be completely replaced within a few years. Only IIF still resists more than 60 years after its introduction in laboratories. No other technique can boast such a long duration in the history of laboratory medicine. Twenty years ago, we had already focused attention on alternative methods to detect antibodies against cellular antigens (ANA - antinuclear antibodies) [1]. The study came to the conclusion that the time was not yet ripe and that the ELISA methods, innovative at the time, did not guarantee the same diagnostic performance as IIF on HEp-2 cells. Eight years later, in 2011, Marvin Fritzler asked himself the same question in an editorial on Arthritis & Rheumatism entitled "The Antinuclear Antibody Test: Last or Lasting Gasp?" [2], concluding that within a few years IIF would be replaced by better performing methods. Today, twelve years later, we are still looking for answers but in this period of time significant

changes and technological innovations have taken place that pose the same question again with more data and more evidence available. Why then should we perhaps shelve this method? The main reasons, known to all those who deal with these diagnostics, are that IIF is a laborious technique, still not standardized, semi-quantitative, lacking in specificity and, above all, dependent in the interpretative phase on the experience of the operator [3]. Moreover, its sensitivity, although high in general, does not allow in some cases to identify some antibodies such as anti-Ro60 which are an important classification criterion of Sjögren's syndrome, anti-ribosomal P in systemic lupus erythematosus, anti-Ro52 in neonatal lupus or anti-synthetase in autoimmune myositis.

An important step towards the possible replacement of IIF has been made with the introduction of fully automated fluoroimmunoenzymatic (FEIA) and chemiluminescent (CLIA) methods. In screening for systemic autoimmune rheumatic diseases these methods are slightly less sensitive but more specific than the IIF HEp-2 method [4, 5]. The reason for the lower sensitivity of the new solid-phase methods is above all linked to the still incomplete panel of antigens compared to that present in a HEp-2 cell. When a method characterized by a much greater number of antigens was used, the sensitivity was in fact comparable to that of the IIF HEp-2, also confirming a clearly higher specificity [6]. These data highlight how new multiparametric systems with superior diagnostic efficiency are starting to act as a concrete alternative to the IIF HEp-2.

Notwithstanding this evidence, a not indifferent role in the opposition to change, it is played by the vast number of studies on the IIF method, its consolidated use over time and above all the fact that clinicians struggle to accept changes on diagnostic aspects with which they grew up and which they have incorporated into many classification criteria of autoimmune diseases. Resistance to change also comes from the world of the laboratory. The recognition of the morphological patterns is still considered very rewarding and professionally qualifying. So much so that in the last survey carried out among Italian laboratories in 2019, as many as 98.2% of them declared that they still use the IIF method [7]. Conversely, in US laboratories it is used by only 55%, signaling a strong propensity to move towards automated solid-phase methods [8]. The choice is dictated by practical reasons: greater speed of execution and reporting, indispensable in particular where the Laboratory services have been strongly consolidated, and elimination of any interpretative aspect (need for training and possible source of legal dispute).

From a clinical point of view, an often-underestimated aspect is whether it is preferable to use more sensitive or more specific methods. Although by definition screening tests should favor diagnostic sensitivity, in a context in which tests are now required by almost all specialists and general practitioners with a very low pre-test probability and in which the target diseases, with the due exceptions, are chronic pathologies with very slow onset and development, false positives have a much greater impact than false negatives. It is now established that in situations of low pre-test probability, immunometric methods perform better than IIF.

However, it should be noted that when we speak of IIF we must consider that we are not referring only to ANA, but also to all the other antibodies that are still being searched for in immunofluorescence, such as the anti-dsDNA antibodies in lupus, the anti-endomysial in celiac disease, anti-gastric parietal cell in autoimmune gastritis, anti-mitochondrial in primary biliary cholangitis, anti-smooth muscle and anti-liver kidney microsomal in autoimmune hepatitis, anti-pancreatic islet in type 1 diabetes, anti-skin in bullous autoimmune dermatitis and anti-adrenal in Addison's disease. Giving up IIF in the diagnosis of rheumatic diseases, which accounts for more than 90% of IIF tests performed in the autoimmunology laboratory, would therefore also involve other diagnostics with an impact that no one has yet taken into consideration at the moment. It therefore appears evident that before discontinuing the IIF method for ANA, screening methods must be made available for all the antibodies that can be found when using the IIF on HEp-2 cells and, more broadly, also for all antibodies that are now being searched for with this analytical method.

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II. CONCLUSION

Finally, as in many other sectors of Laboratory Medicine, the choices will be strongly conditioned by organizational aspects. If readers of IIF slides will fail, the solution will be to eliminate the problem at its source. It therefore seems unlikely that IIF can continue to be considered as the reference method for a long time while new technologies are already available that are much more suitable for the current context of autoimmune diagnostics. These questions, currently still unresolved, will keep us busy in the coming years to ensure that autoimmunology laboratories provide ever more accurate and clinically useful results, adopting the most suitable and most effective methods.

CONFLICT OF INTEREST

The Author declares no conflict of interest.

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ERAD, 2023, Volume 2, Issue 1 pages 4-5

Clinical Image
Pityriasis Lichenoides et Varioliformis Acuta (PLEVA)

Running title: PLEVA

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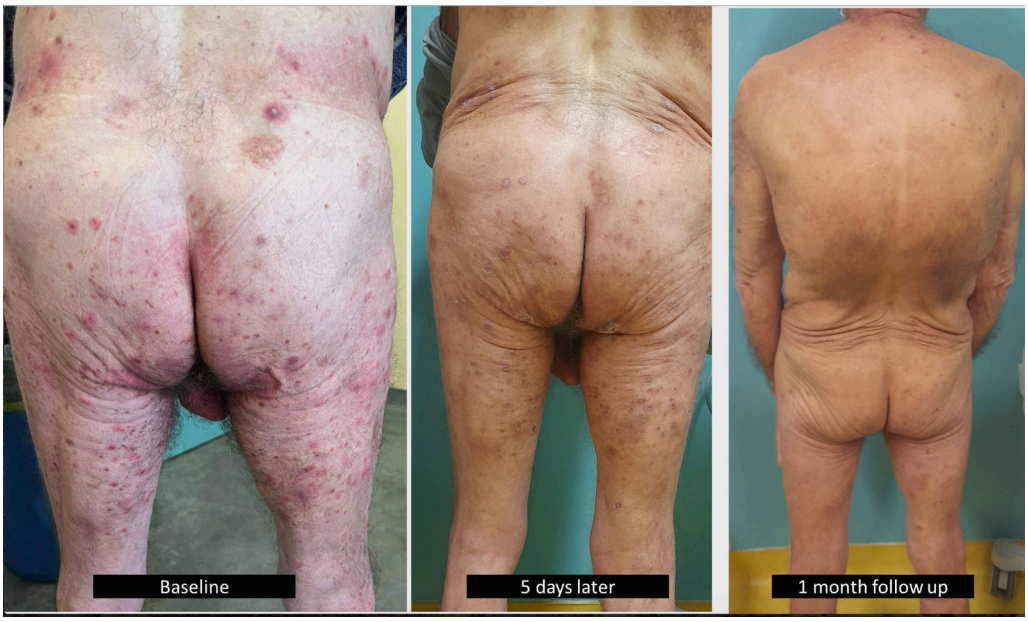
Keywords- acute pityriasis lichenoides; pityriasis lichenoides et varioliformis

(submitted 02 January 2023; revised 23 January 2022; accepted 25 January 2023)

A 74-year-old male patient came to the emergency department with an acute eruption consisting of multiple inflammatory papules some of them demonstrating crusting or/and necrosis (Figure 1). The lesions were initially distributed on the trunk and femoral areas and spread to proximal extremities within few days. The patient mentioned a recent upper respiratory infection 15 days before the appearance of the rash and he complained of intense itching. No new medication had been added to his chronic treatment with drugs for arterial hypertension. Blood tests were within normal ranges. He described worsening of the lesions with recent application of combination of topical corticosteroid with an antifungal agent.
Clinical suspicion of PLEVA was raised. After performing a skin biopsy, treatment with doxycycline 100 mg twice daily along with itraconazole 100mg twice daily was initiated-the last for 15 days. Five days later the rash subsided dramatically. On one month follow up he appeared with remarkable improvement and was advised to use doxycycline for at least one more month (Figure 1).



In conclusion, clinical and histologic findings were compatible with the diagnosis of PLEVA, whereas the clinical course and successful response to the applied treatment verified our initial suspicion.

AUTHORS CONTRIBUTION

The authors prepared the manuscript and the artwork. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Commentary

Ginger, a potential inhibitor of neutrophil extracellular traps (NETs)

Running title: Ginger against NETs

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Abstract

Neutrophils are a crucial part of the innate immunity. Initial immune responses against pathogens are primarily neutrophil mediated. Neutrophil extracellular traps (NETs) are expelled following neutrophil stimulation. This process, called NETosis, can be highly protective. However, its' non-specific nature results in upregulation of local pro-inflammatory stimuli and often in tissue injury. NETosis has been suggested to participate in the pathogenesis of many immune-mediated diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and psoriasis. Recently, a phytochemical isolated from ginger root was reported to inhibit NETosis and reduce levels of plasma NETs when administered orally to humans and mice.

(Submitted 23 September 2023; accepted 30 September 2023)

Keywords- NETosis; neutrophils; ginger; 6-gingerol

I. INTRODUCTION

Neutrophils are cells specialized to participate in the initial immune response against pathogens[1]. These granulocytes exert their defensive role through phagocytosis, and production of cytokines or reactive oxygen species. In case of neutrophil stimulation, neutrophil extracellular traps (NETs) are expelled[2]. This process, called NETosis is accompanied by release of granule-components and subsequent exertion of anti-microbial functions against bacteria, viruses, and fungi[3]. While its' effect can be highly protective against pathogens, its' non-specific nature results in upregulation of local pro-inflammatory stimuli and potential tissue injury. Interestingly, prolonged NETosis phenomena can mediate breaks in tolerance of adaptive immunity components and lead to autoantibody production[4]. On the other hand, autoantibodies induce NETosis, thus establishing a feed-forward loop[5].

Subsequently NETosis has been suggested to participate in the pathogenesis of many immune-mediated diseases, including systemic lupus erythematosus (SLE)[6], rheumatoid arthritis (RA)[7] and psoriasis[8]. For instance, NETs have been measured increased in circulatory of patients diagnosed with SLE, have been suggested to associate with autoantibody production, and have been aimed as potential targets of new drugs for the disorder. While development of such targeted therapies has been the subject of thorough research[9], there have been reports of natural herbs exhibiting the capacity to attenuate NETosis and combat pro-inflammatory conditions[10].

Recently, researchers suggested that a phytochemical isolated from ginger root, the 6-gingerol, when administered orally to humans and mice inhibited NETosis and reduced levels of plasma NETs[11]. Specifically, neutrophils were isolated from healthy controls and were stimulated using PMA, or anti-RNP complex, or antiphospholipid syndrome IgG. The ginger solution significantly inhibited NETs production in all scenarios. Intriguingly, when ginger supplements were administered orally to a mouse model of antiphospholipid syndrome blood NET levels and thrombi were significantly reduced. Researchers also examined the effect of ginger consumption on a SLE mouse model and found that post-treatment anti-dsDNA and total IgG antibodies were inhibited. Finally, ginger supplements were also consumed by healthy participants. NETosis by ex vivo stimulated cells and blood NET levels were also hindered.

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Interestingly, ginger components have been suggested to inhibit PDE activity[12] and thus reduce immune-mediated cell responses. PDE antagonism leads to accumulation of cAMP intracellularly. PDE4 inhibitors been developed over the last decades and have successfully been used to manage inflammatory-mediated diseases, such as the psoriatic disease[13]. One such example is apremilast which has been FDA-approved for psoriasis and psoriatic arthritis. Whether ginger-mediated inhibition of NETosis both in mice and humans is mainly attributed to this PDE-hampering effect remains to be seen in future research.

II. CONCLUSION

Ginger components seem to effectively restrict the NETs activity. Significantly, observations have now been made in both murine models and humans. Research to assess ginger administration in NET-mediated autoimmune diseases is warranted.

AUTHOR CONTRIBUTIONS

SGT drafted the manuscript. DPB revised the manuscript. The authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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Expert Opinion

The position of autoantibodies in the diagnosis and classification of autoimmune diseases

Running title: autoantibodies in the diagnostic and classification criteria

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Abstract

Autoantibodies are important for the diagnosis and classification of autoimmune diseases. Currently, there is insufficient awareness that autoantibody assays are not standardized. We discuss the issues raised concerning the proper standardization of assays for autoantibody testing. The European Autoimmunity Standardisation Initiative (EASI) promotes the cross-talk between clinicians and laboratory specialists to improve the correct interpretation of autoantibody results.

(Submitted 13 July 2023; accepted 25 July 2023)

Keywords- assay, autoantibody, classification, criteria, EASI, testing

I. INTRODUCTION

Autoantibodies are increasingly recognized as important biomarkers in the diagnosis and classification of autoimmune diseases. Diagnostic criteria are defined to enable clinicians to correctly diagnose a patient based on clinical and laboratory characteristics, while classification criteria are defined to include patients with well-defined clinical and laboratory characteristics in studies. As a consequence, classification criteria are more stringent than diagnostic criteria. Studies with well-defined patient cohorts are not restricted to clinical trials for evaluation of new therapeutics, but also include mechanistic studies to unravel the pathophysiology of the respective disease. It is, however, questionable if classification criteria adequately take into account the heterogeneous nature of autoimmune diseases like systemic lupus erythematosus (SLE). According to the 1997 classification criteria of the American College of Rheumatology (ACR) SLE is classified if at least 4 out of 11 items are met. When considering that these criteria are independent from each other, there may be 330 distinct phenotypes that meet the SLE criteria [1].

Obviously, inclusion of all these phenotypes into a single pharmacological or pathophysiological study will impact a final conclusion. As such, it can also be questioned whether increasing the sensitivity of autoantibody assays will benefit our understanding of the respective disease since the association between autoantibody and disease subtype, like anti-dsDNA antibodies and lupus nephritis or anti-SSA/Ro60 antibodies and cutaneous variants of SLE, may be lost. Besides the dilemma described above, there is insufficient awareness that autoantibody assays are not standardized [2]. In general, the committees involved in the establishment of disease criteria consist only of clinicians lacking experience with the pitfalls of autoantibody assays. This is illustrated by definitions for autoantibody criteria. They may include "at least

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equivalent performance" for solid phase assays compared to HEp-2 indirect immunofluorescence or "with demonstrated >90% specificity" for anti-dsDNA antibodies in the criteria for SLE. Equivalent has not been defined and this low threshold for specificity is really poor for a relatively rare disease. Also, a statement like "performed with a standardized and validated test" for anti-Jo1 antibodies in the criteria for idiopathic inflammatory myopathies (IIM) is difficult to achieve when considering that standard preparations for these antibodies are lacking. Another dilemma with respect to the position of autoantibodies in disease criteria involves the methodology to establish such criteria. The ACR and the European Alliance of Associations for Rheumatology (EULAR), extensively collaborating in the formulation of classification criteria for rheumatological diseases, follow a five-step strategy: enlisting potential items by experts, evaluation of these items in existing study cohorts, defining discriminating items and scoring system, applying the scoring system in a derivation cohort, and finally in a validation cohort. In particular the use of existing study cohorts hampers appropriate inclusion of autoantibodies: no distinction between SSA/Ro60 and Ro52 autoantibodies in the criteria of Sjögren's syndrome, no inclusion of IIM-specific autoantibodies next to anti-Jo1 in the criteria of IIM, and the artificially high ranking of anti-RNA polymerase III antibodies in systemic sclerosis.

I. CONCLUSION

The European Autoimmunity Standardisation Initiative (EASI) has been established to promote the cross-talk between clinicians and laboratory specialists in order to improve the correct interpretation of autoantibody results. In the context of disease criteria, it is evident that EASI may also create more awareness in the community involved in disease criteria that there is lack of standardization of autoantibody assays [3]. Consequently, disease criteria that include autoantibodies may also benefit from the cross-talk between clinical and laboratory experts.

*This is an outline of a lecture given at the 5th Panhellenic Polythematic Congress of Autoimmune Diseases, Rheumatology and Clinical Immunology, 1-3 September 2023, Nafplia, Greece

AUTHOR CONTRIBUTION

The Author drafted the manuscript and revised the manuscript. The Author approved the final version of the manuscript.

CONFLICT OF INTEREST

There is no conflict of interest.

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Clinical Image

Dapagliflozin induced nummular eczema

Running title: Dapagliflozin induced nummular eczema

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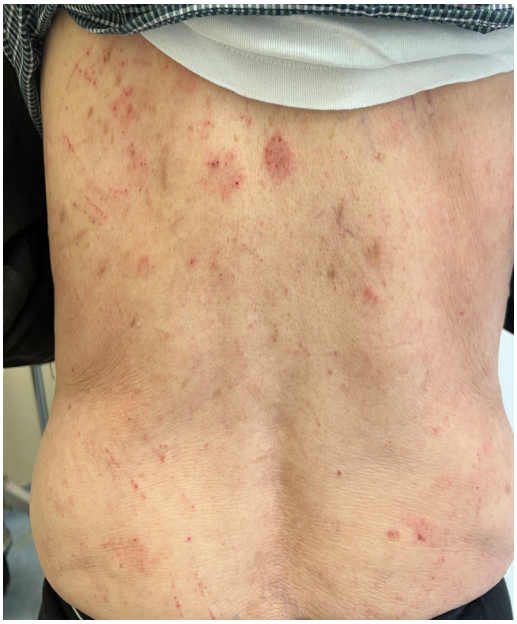
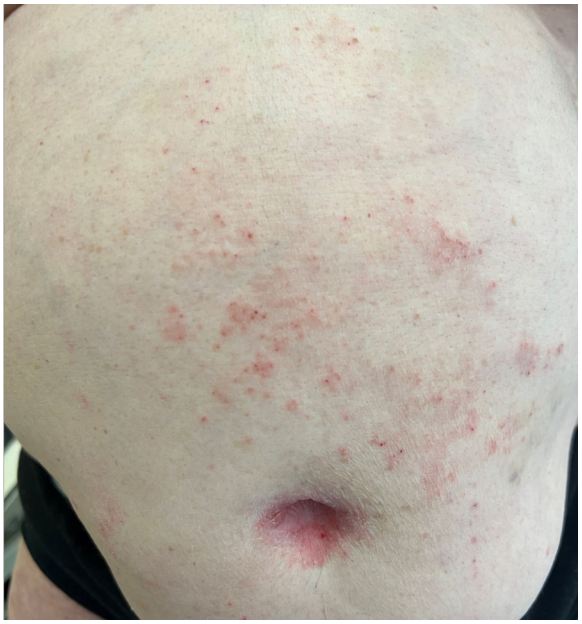
Keywords- drug-induced eczema, lichenification, pruritus, skin rash

(submitted 03 January 2023; revised 17 January 2022; accepted 19 January 2023)

This is a case of an 85-year-old man who presented with a skin rash which appeared three months ago. The rash which developed on the trunk and the upper and lower limbs was accompanied by intense pruritus and was gradually getting worse. It consisted of red, eczematous nummular lesions and patches with lichenification. Excoriation was also present because of the scratching (Figure 1). The patient suffered from chronic kidney disease and coronary heart disease. From his medical history it was concluded that the patient had started a new drug (dapagliflozin 10mg/day), 10-20 days before the appearance of the rash. Dapagliflozin is a sodium- glucose cotransporter 2 inhibitor and was subscribed to the patient because of his renal disease. Overall, there was a strong suspicion of a drug related skin rash.





The patient was advised to discontinue dapagliflozin in agreement with his nephrologist and was treated with topical steroids and emollients in addition to antihistamines to alleviate pruritus. On his 20 day follow up there was a remarkable improvement of the rash with a few residual lesions on his back.

AUTHORS CONTRIBUTION

The authors prepared the manuscript and the artwork. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The Authors declare no conflict of interest

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Expert Opinion
Epitope specificity of anti-beta2GPI IgG in APS: clinical relevance

Running title: anti-beta2GPI IgG in APS

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Abstract

In the new ACR/EULAR APS classification criteria an entry criterion of at least one positive aPL test is included along with laboratory and clinical criteria, clustered into clinical and laboratory domains (Lupus Anticoagulant [LAC], and aCL and/or anti-β2glycoprotein-I (β2GPI) antibody IgG/M detected by ELISA). Patients accumulating at least three points from clinical and laboratory domains are classified as having APS. We discuss the mounting evidence that the epitope specificity of anti-β2GPI antibodies can offer additional diagnostic and prognostic information.

(Submitted 30 August 2023; accepted 01 September 2023)

Keywords- Antibody, ACR/EULAR, APL, diagnosis, LAC, prognosis

I. INTRODUCTION

aPL represent the example of a laboratory test that moved from dichotomous to quantitative/semiquantitative results consistent with the idea that aPL titer offers more diagnostic/prognostic information for both vascular and obstetric manifestations (1). The inclusion in the new classification criteria of two levels of aCL/aβ2GPI ELISA positivity ("moderate" and "high" titers) and the combined aCL IgG and aβ2GPI IgG positivity is consistent with the higher prognostic value of medium/high aPL levels and the main value of β2GPI-dependent antibodies. The definition of aPL "persistence" (two positive tests at least 12 weeks apart) was not changed in comparison with the previous criteria. The levels for "moderate" and "high" positivity apply to ELISA tests but not to others, e.g., new automated platforms. In particular, the higher sensitivity of chemiluminescence raises the issue of the real diagnostic/prognostic value of results close to the cutoff limits used for the other solid-phase assays.

Comparison studies among the different aPL solid-phase techniques are limited and report a similar specificity of the assays even though discrepancies can be found (personal data).

II. CONCLUSION

There is growing evidence that the epitope specificity of anti-β2GPI antibodies can offer additional diagnostic and prognostic information. For example, antibodies against domain (D)1 display higher diagnostic/prognostic value. While antibodies directed against D4,5 are more frequent in aPL-positive asymptomatic carriers.

*This is an outline of a lecture given at the 5th Panhellenic Polythematic Congress of Autoimmune Diseases, Rheumatology and Clinical Immunology, 1-3 September 2023, Nafplia, Greece

AUTHOR CONTRIBUTION

The Author drafted the manuscript and revised the manuscript. The Author approved the final version of

the manuscript.

CONFLICT OF INTEREST

There is no conflict of interest.

CONFLICT OF INTEREST

The Author declares no conflict of interest.

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