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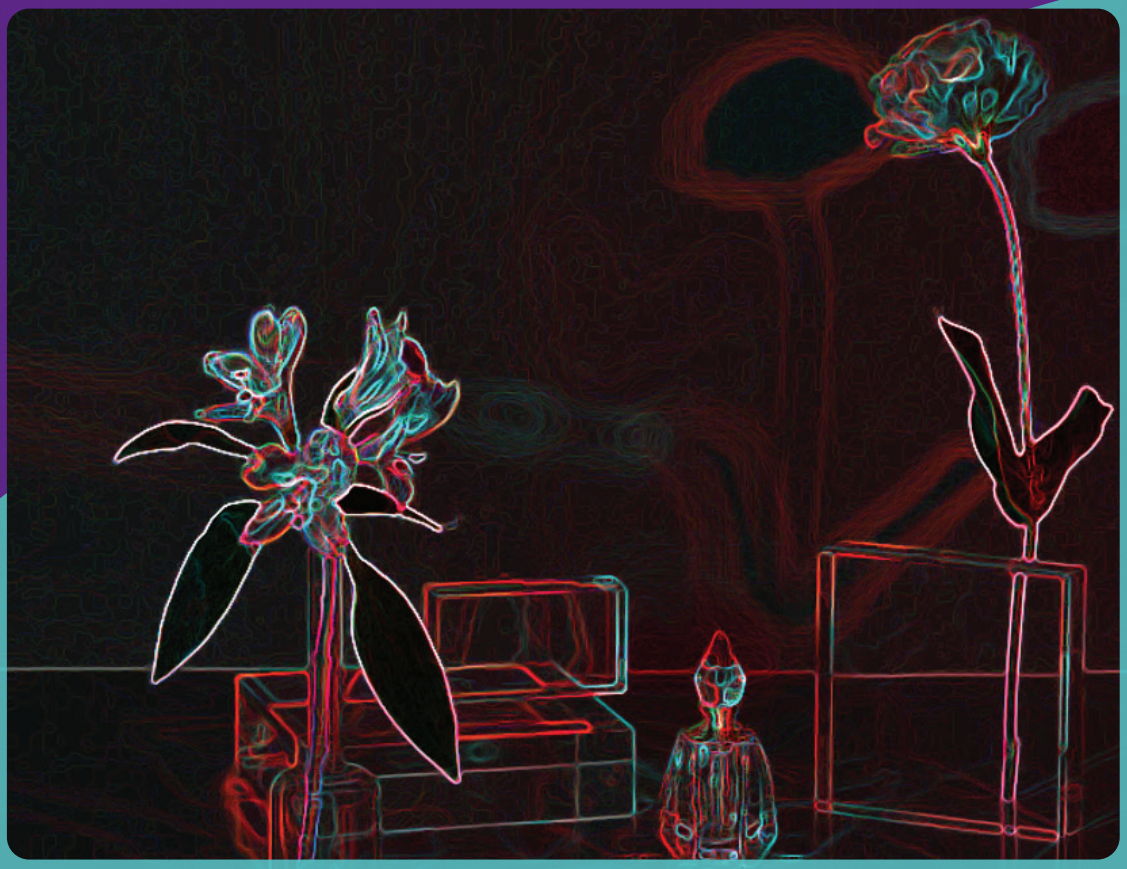

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Excellence in Rheumatic & Autoimmune Diseases ERAD
THE OFFICIAL JOURNAL OF INSTITUTE OF RHEUMATIC AND AUTOIMMUNE DISEASES

Editorial

Excellence in Rheumatic and Autoimmune Diseases (ERAD) is flourishing

Running title: ERAD

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

In no time (just few weeks), we manage to collect papers for our second issue. This has been a great achievement taking into account the wealth of open access journals, which are seeking for new submissions. We deeply appreciate the contributions made by our authors and the extensive pee-review by our members of the Editorial Board and our Reviewers. In this issue, we publish reviews, commentaries, clinical cases, educational notes and clinical images of great interest. The scientific themes are covering all aspects of autoimmunity, ranging from multiple sclerosis to systemic sclerosis and from autoantibodies in cancerous diseases to systemic lupus erythematosus. In our student's corner, we give the opportunity to brilliant biomedical students who work hard to publish their work. We are also seeking for contributions from junior scientists in early stages of their scientific career to use our platform in order to disseminate their work in the world.

Our Editorial Board is continuously updated with experts in the field. We now have several new members from abroad including authorities from Germany, UK, Israel, Italy and even Brazil. We hope that in the near future our Editorial Board will include clinicians and scientists working in autoimmune diseases from countries all over the world. We also give special attention to scientist of the Greek diaspora, who assist our efforts to become leaders in the field.

We are still maintaining our main principles. Platinum open access to all authors. That means authors have all the advantages of an open access Journal but do not have to pay any costs for process and publications of their paper. Our prompt and meticulous pee-review process is run smoothly with the assistance of our members of the Editorial Board and the exhaustive list of our excellent Reviewers. This gives us the opportunity to publish in a fast pace all accepted papers. Our ultimate aim is to have the adequate number of published papers that will allow us the future to apply for inclusion in PubMed. We are sure that with your contribution, we will succeed our goals.

We are grateful for your contribution and support. Enjoy the reading!

Dimitrios P. Bogdanos
Editor-in-Chief

ERAD, 2022, Volume 1, Issue (2), pages 1-3

Excellence in Rheumatic & Autoimmune Diseases ERAD
THE OFFICIAL JOURNAL OF INSTITUTE OF RHEUMATIC AND AUTOIMMUNE DISEASES

Commentary

The role of lung microbiome on multiple sclerosis

Running title: Lung microbiome and multiple sclerosis

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Abstract

Microglia is involved in the pathophysiology of multiple sclerosis (MS) as it is considered the neuroinflammation primer in MS. Several environmental and genetic risk factors possibly contribute to MS. Among them are smoking, and lung infections. Moreover, while the gut microbiome has gained the main focus regarding the ongoing research on central nervous system (CNS) and autoimmunity, a recent study suggests that a connection between the local lung microbiome and the brain, also exists, in which the microglia plays a crucial role. In this commentary, we further discuss the important findings of this study considering the lung microbiome as a modifiable environmental factor, which could provide an alternative method for prevention, management and modification in the course of diseases with autoimmune mechanisms, such as MS.

(Submitted 11 February 2022; accepted 23 March 2022)

Keywords- lung microbiome; autoimmunity; multiple sclerosis; gut microbiome; environmental risk factors

I. INTRODUCTION

Multiple sclerosis (MS) is a common autoimmune disease of the central nervous system (CNS) [1]. The mechanisms that are responsible for the induction of the MS are not yet fully understood [2]. Inflammation, demyelination, ionic imbalance, astrocyte and microglia activation, glutamate excitotoxicity, axonal damage, neurodegeneration are among the pathophysiological processes that are implicated in MS development [3].

Interestingly, microglia is considered as the neuroinflammation primer in MS and constitutes more than one third of early MS lesion's mass [4]. Multiple sclerosis is considered to be a multifactorial disease, where both environmental and genetic risk factors confer susceptibility to its development [5]. Regarding genetics, MS is regarded as a polygenic disease, with a complex genetic pattern [6]. Among the several environmental risk factors that possible contribute to the development of MS are smoking, an Epstein-Barr Virus (EBV) infection, the degree of physical exercise, lifestyle conditions, lung infections, vitamin D deficiency and dietary habits [7, 8]. There is also a complex interplay between the environmental and the genetic factors leading possibly to autoimmunity [9].

The gut microbiome has attracted main scientific attention as a possible regulator of CNS regarding autoimmunity [10].The gastrointestinal tract and especially the intestine seems to have an effect on several human systems, including the immune and CNS systems-[11, 12]. The enteric nervous system has been considered as a second brain, while the gut–brain axis offers the bilateral manner of contact, by which the two organs communicate with each other [13]. As far as MS is concerned, the gut microbiota may be deemed as factors that have an effect on the intestinal milieu and their modification may alter the risk and course of MS [14].

While the gut microbiome has gained the main focus regarding the ongoing research on CNS and autoimmunity [9, 15, 16], a recent study suggests that a connection between the local lung microbiome and the brain, also exists [17]. The recipients of the messages from the lung microbiome are the microglia cells, that are regarded as the neuroinflammation primers in MS [4]. Therefore, according to the study by Hosang et al. (2022), the existence of a lung–brain axis has been reported, and thus, the pulmonary microbiome may have an effect on immunological processes conferring susceptibility to the development of autoimmune disorders, even in the CNS [17].

Given that continuous research into modifiable risk factors for several diseases attracts attention, this finding is of particular interest. More precisely, considering the lung microbiome as a modifiable environmental factor, this could provide an alternative method for the prevention, management and modification of the course of diseases with autoimmune mechanisms, such as MS (e.g. with the use the antibiotics, as in the example of the gut microbiota) [9, 14]. At this point, the differences that exist between the gut microbiota and the lung microbiome should be mentioned [17]. Firstly, lung microbiome is in more direct contact with the external environment and exposed to infectious factors. Secondly, the immune response occurs with small changes in the lung microbiota. Finally, the microbial substances require shorter distance to pass from the lungs to the blood without any flirtation, compared to the gut microbiota. These data may indicate a greater impact of the lung microbiome on autoimmunity, in comparison to the gut microbiota.

The lung microbiome is possible to have an effect on the development of diseases, both respiratory and systematic (e.g. rheumatoid arthritis) [18-21]. Nevertheless, the novel findings of this study by Hosang et al. (2022), are of great importance, in ~~a~~ relation to autoimmunity and development of diseases of the CNS with immunological pathophysiological processes, like MS. Modulation of the lung microbiome and of the multiple factors that affect it, even from early life (infections, use of antibiotics, feeding, mode of birth), or later (smoking) [22], may alter the immune reactivity of the brain [17].

II. CONCLUSION

More data and evidence are required from future studies which should be focused in the role of lung microbiome on CNS autoimmunity and MS. Firstly, it would be interesting if the lung microbiome serves as a modifiable environmental factor for MS. Consequently, the modification of the lung microbiome with a dietary, therapeutic or lifestyle approach (e.g. probiotics, antibiotics, change of crowding conditions, smoking) may be added to the prophylaxis and management of MS. In view of the latter, it should be examined when ~~a~~ microbiome-based intervention would be more effective. Should those be done during early life or later (e.g. after the disease development)? Also, the identification of specific microorganism, the modification of which has the major impact on CNS immune reactivity, would help to make more accurate and targeted studies regarding the role of lung microbiome and MS. Moreover, it would be worth if research could focus on how Disease-Modifying Treatment (DMT) may affect the lung microbiome and thus the possible immune CNS reactivity in MS. Finally, studies on MS preclinical state, although difficult to perform, would give robust data on whether immunological processes of the CNS could be preceded and also alter the lung microbiome.

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AUTHORS CONTRIBUTION

VS conceptualized and wrote the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

ERAD, 2022, Volume 1, Issue (2), pages 4-6

Clinical Case

Severe gout complicated by *Staphylococcus Aureus* abscesses

Running title: *Staphylococcus aureus* abscesses in gout

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Abstract

This clinical report describes a case of a 60-year old patient with a past history of gout treated with colchicine and self-administered betamethasone, who was presented with a severe arthritis, fever, leukocytosis, elevated uric acid levels and inflammation markers associated with bacteremia caused by *Staphylococcus aureus*. Casting abscesses containing both monosodium-urate crystals and *Staphylococcus aureus* were demonstrated flowing from cervical-atlas axis causing odontoid fracture to popliteal regions. Prolonged therapy with multiple antibiotics and hypouricemics successfully treated the infection and prevented further gouty flares.

(Submitted 05 March 2022; accepted 23 March 2022)

Keywords- Abscess; Antibiotics; Allopurinol; Bacteremia; Gout; Infection; *Staphylococcus*

I. INTRODUCTION

A 60-year old patient was hospitalized in 2010 in poor general conditions for severe arthritis involving hands, wrists, elbows, knees and ankles experienced for several weeks. He had history of gout treated with colchicine (low dosage, i.e. 0.5 mg/day due to gastro-intestinal side effects) and self-administered weekly intra-muscular injections of betamethasone 4 mg/day. Clinical examination revealed multiple tophi on the hands, feet, elbows and knees, and massive swelling of the wrists, elbows, knees and popliteal regions. He had fever with chills up to 38°C, neutrophilic leukocytosis with thrombocytosis (WBC 32,460/mcl, PLT 1,026,000/mcl), markedly elevated ESR (96 mm/h), CRP (43.1 mg/dL) and serum uric acid levels (13.4 mg/dl, normal value <7 mg/dl). Blood cultures revealed the presence of *Staphylococcus aureus*.

A surgical aspiration of the material was performed at both legs with the drainage of 400 cc from the right leg and 300 cc from the left leg of a white/yellowish hemorrhagic chalky material containing monosodium-urate crystals. The cultures confirmed the presence of *Staphylococcus aureus*. The patient started experiencing stiff neck and dorsal-lumbar back pain.

Magnetic resonance was performed and revealed diffuse casting abscesses extending from the cervical atlas-axis region to C3-C4 and C5 (Image 1), flowing to the sub-scapular area, shoulders, elbows and wrists. Other flowing abscesses were found flowing from the hips to knees, gastrocnemial region to the ankles. Multifocal extrinsic bone erosions caused by soft tissue masses were observed in all these regions. Computed tomography (CT) showed a fracture of the odontoid-process that appeared dislocated (Image 2), with conglomerated osteolytic lesions with a sclerotic rim in the atlas-axis-C3 and C4 vertebral bodies.

Prolonged therapy with multiple antibiotics (tigecycline, rifampicin, linezolid, doxycycline) successfully treated the infection. In particular, doxycycline 200 mg/day and rifampicin 600 mg/day were prescribed for 6 months.

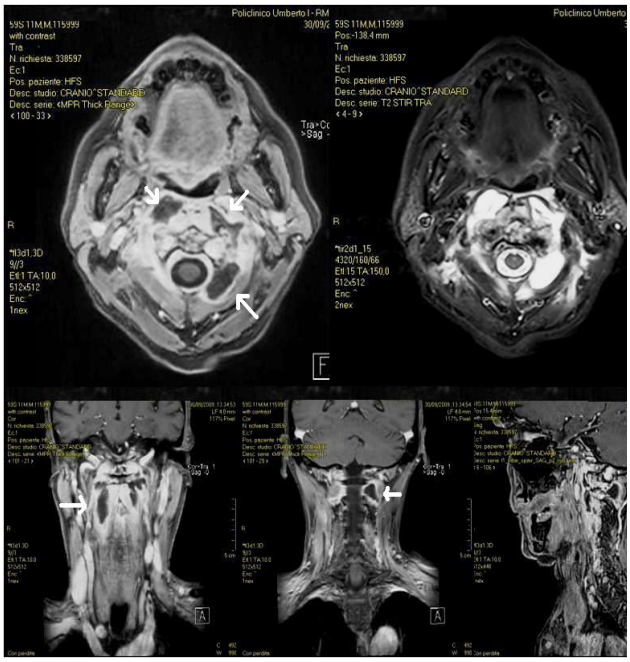

Image 1. Magnetic resonance reveals diffuse casting abscesses extending from the cervical atlas-axis region to C3-C4 and C5.

Colchicine was discontinued and intravenous corticosteroids plus etoricoxib improved the flares of arthritis, but uric acid levels were persistently over 12 mg/dl. Hypouricemic therapy with allopurinol 300 mg/day and losartan were started. To improve the tophaceous lesions and to obtain the prompt lowering of uric acid levels, intravenous rasburicase 7.5 mg was given every two weeks for 4 administrations (1).

Follow-up CT scanning 6-months later showed improvement of the odontoid-process fracture, a marked decrease in the size of the tophaceous masses, stabilization of the bone erosions with marginal sclerosis and periosteal bone formation. Besides general improvement, the disease hesitated in immobilization due to complete ankylosis of knees and ankles bilaterally. Uric acid levels returned into normal (4 mg/dl).

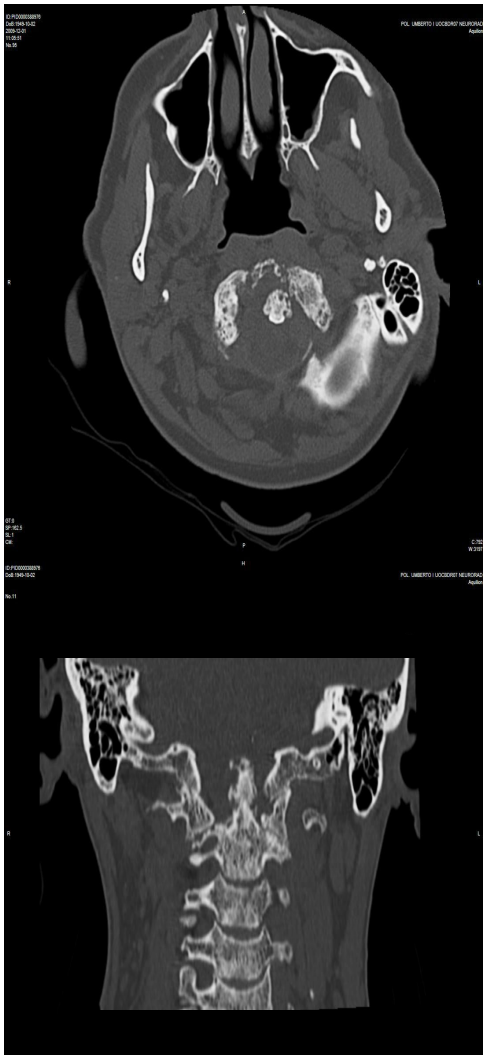

Image 2. Computed tomography shows a fracture of the odontoid-process that appeared dislocated, with conglomerated osteolytic lesions with a sclerotic rim in the atlas-axis-C3 and C4 vertebral bodies.

CONCLUSIONS

It is likely that intra-muscular injections of betamethasone were the access site of the infection and that glucocorticoid (2) had a marked immunosuppressive effect in this patient in which hypouricemic and antibiotic treatments were used in combination to contain the infection and limit the bone damage.

AUTHORS CONTRIBUTION

CP conceptualized and wrote the manuscript. FC revised the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ERAD, 2022, Volume 1, Issue (2), pages 7-8

Commentary

The effect of very low energy diet in fibromyalgia: lost weight, less pain?

Running title: Low-Energy Diet and Fibromyalgia

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Abstract

Increased body weight has been shown to be associated with pain. According to the National Health Interview Survey, approximately one in five Americans have chronic pain, and obesity enhances this risk by 60%. This commentary highlights the promising findings of a recent study reporting on the effect of a Very Low-Energy Diet limited to 800 kcal/day on 195 obese patients with pain and fibromyalgia symptoms for a total of 12 weeks. Stemming from this data, we discuss the direct and indirect implications of the study for the non-pharmaxological management of obese patients with pain and the limitations that came of this study.

(Submitted 23 February 2022; accepted 26 March 2022)

Keywords- diet; fibromyalgia; obesity; pain; very low energy diet; weight

I. INTRODUCTION

Obese individuals are approximately twice as risky to suffer from pain in comparison with those who have a normal body mass index (BMI) (1, 2). Research into the role of nutrition in autoimmune diseases has increased in recent years, with some focusing on low-calorie diets. Several studies have attempted to delineate the effect of weight loss via energy restriction in the relief of pain and in particular on symptoms of fibromyalgia, especially in obese patients who are experiencing such symptoms. The data so far are inconclusive giving a vague picture of what is really going on. While some studies show that weight loss acts as an effective pain relief, others have failed to establish a concrete effect, which could permit subsequent proper counseling aiming at significant weight loss as an indirectmode of action and theraputical management.

A recently published observational study conducted in 195 obese patients reporting high levels of pain and symptoms of fibromyalgia determined the effect of weight loss, the time course and improvement course in pain and other symptoms, particularly in the early phase of assessed the effect of a very low-energy diet (VLED) treatment, on symptoms of fibromyalgia such as widespread pain and fatigue, preceding major weight loss (3).

During the first phase of the program, the enrolled obese patients were requested to apply a VLED in the form of whole liquid meal replacement (800 kcal/day or less). This has been asked in view of the fact that total liquid meal replacement appears to reduce meal options, disregards unreported meals and diminishes the risk of unhealthy food intake. It also supports enhanced nutrient absorption and intensifies short- and long-term weight loss. In the present study and throughout the first phase, the primary weight-loss target was to decrease at least 15% of body weight (4,5).

Self-reported physician diagnoses of 16 frequent conditions, including hypertension, dyslipidemia,

osteoarthritis, and depression, were collected through a standardized form. The baseline physical examination indicated four additional metabolic risk factors including high triglyceride levels, low high-density lipoprotein cholesterol levels, high blood pressure and high fasting glucose levels (3)

The findings of the study were noteworthy. At the week-3 visit, the enrolled participants had lost about 2 kg/m2 corresponding to approximately 6% of their body weight. A notable decrease of the their total Firomyalgia Survey Criteria scores was also noted at week 3. Widespread Pain Index scale decreased from (entry level mean, 2.82 [SD, 2.43] to mean. 1.31 [SD, 1.86]; $t = 9.82$;$P < 0.001$) at week-3 and the Symptom Severity scale (entry level mean, 5.57 [SD, 2.14]; decreased in mean, 3.47 [SD, 2.04]; $t = 13.85$; $P < 0.001$) also at week-3. Additionally, the great majority of the participants (89%) showed at least one impoved point, while 72% of them had at least a 30% remission in their experienced symptoms. The most notable findings, at least to our judgement, was that BMI was higher in participants, who had little or no improvement and Physician-diagnosed depression was more common in them. It is also worthy to mention that a higher ratio of female patients had moderate improvement.

There were no significant differences in change in BMI units among the three groups (i.e little/no improvement, moderate improvement and high improvement). Additionally, there was no considerable difference in weight reduction percentages among the three groups. Remarkably, those patients who received VLED showed significant weight loss as well as immediate and notable changes in pain distribution and common pain-related clinical symptoms.

The findings of this study highlight an early correlation between fibromyalgia symptoms and calorie restriction *via* a VLED. It is more likely that health professionals who counsel patients on pharmacological and particularly non-pharmacologic management of pain and pain-related symptoms would value the outcomes of this research.

These promising results must be treated with caution. The design of this study did not include a control group to associate the particular effects of a VLED on these symptoms to the outcomes of a regular dietary treatment. Furthermore, for the fibromyalgia total score or its constituent subscales, no minimal detectable alteration or minimal clinically relevant changes have yet been established.

Nonetheless, the results of this study are of significance for the potential management of individuals who are at high risk for fibromyalgia developemnt, as well as those who are at risk to develop fibromyalgia. The fundamental question remains. Can we conclusively advise in support of a VLED in obese patients with the immediate task to improve their symptoms as early as possible? Can we institute in high-risk obese individuals a calorie restriction diet in order to decline the threat of fibromyalgia induction? And finally, how efficient is really a VLED in those patients, and why non-obese patients may still experience fibromyalgia?

II. CONCLUSIONS

In conclusion, large, independent studies involving thousands of obese people for a long period of time, will provide a clearer knowledge of the actual impact of VLED on fibromyalgia. These studies might evaluate therapies in certain groups, such as those prone to develop fibromyalgia.

AUTHORS CONTRIBUTION

DA drafted the manuscript. DPB revised the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Clinical Image

Granular cell tumor: not to miss

Running title: a rare tongue lesion

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Keywords- Benign neoplasm; Granular cell tumor; Schwann cells; Surgical excision; Tongue;

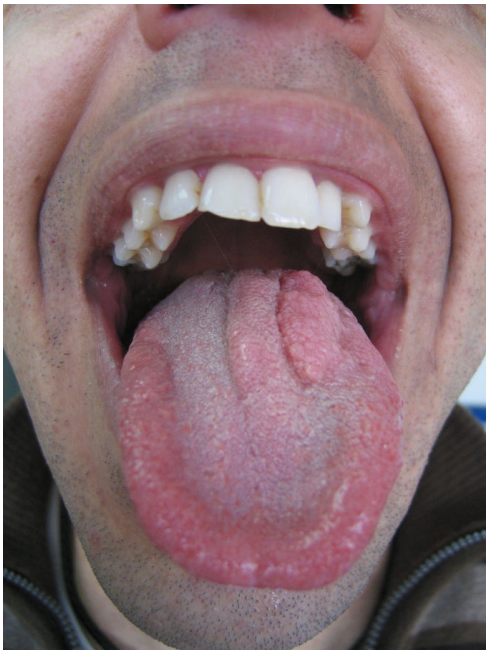

Image 1. Granular cell tumor. Granular cell tumor is an uncommon benign neoplasm that can occur in any part of the body, orofacial region included. It was first described by Abrikossoff in 1926. Rare cases have been reported were the tumor shows malignant behavior. It is believed that granular cell tumor arises from metabolism alterations of Schwann cells. The tumor is usually asymptomatic and appears as a nodule that does not exceed 3 cm. Treatment consists of surgical excision.

AUTHORS CONTRIBUTION
The author prepared the manuscript and the artwork. The author approves the final version of the manuscript.

CONFLICT OF INTEREST
The Author declares no conflict of interest

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Excellence in Rheumatic & Autoimmune Diseases
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Commentary

Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: what we already know and what we would like to know

Running title: Nintedanib in lung fibrosis

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Abstract

Interstitial lung diseases (ILDs) represent a broad category of fibrotic pulmonary diseases and are frequently present in the course of various connective tissue diseases (CTDs), especially systemic sclerosis (SSc) and rheumatoid arthritis (RA). Despite intensive research in the field, pathogenesis is incompletely understood and therapeutic options are limited to immunosuppressants and antifibrotic drugs. The current commentary focuses on a recent publication regarding the efficacy and safety of the anti-fibrotic drug nintedanib in patients with autoimmune related ILD with progressive fibrotic phenotype. We further discuss the important findings of this study and also point to what we still need to know.

(Submitted 11 February 2022; accepted 23 March 2022)

Keywords- interstitial lung disease; pulmonary fibrosis; cutaneous tissue diseases; nintedanib; progressive fibrosing phenotype

I. INTRODUCTION

Interstitial lung disease (ILD) comprises a diverse spectrum of diseases, characterized by fibrosis and/or inflammation of the lungs. ILDs represent a major health problem due to the number of affected patients, along with the incomplete knowledge of pathogenetic pathways, the absence of widely accepted predictors of disease progression and behaviour and the lack of really effective therapeutic agents.

The most common form of ILD is idiopathic pulmonary fibrosis (IPF). ILD frequently complicates connective tissue diseases (CTDs), especially Systemic Sclerosis (SSc), Rheumatoid Arthritis (RA), anti-synthetase syndrome and Mixed Connective Tissue Disease (MCTD) (1). In addition, the entity of idiopathic pneumonia with autoimmune features (IPAF) also raises significant clinical concern (2).

The involvement of the lungs in ILDs is generally described as diffuse fibrosis of the alveolar wall, with or without inflammation, that results in impairment of gas exchange. Moreover, the underlying dysfunction of the immune system in autoimmune diseases is thought to play a significant role in CTD-ILDs. However, CTD-ILDs represent a diverse group of diseases. Different CTDs manifest varying forms of ILD. Patients with SSc and MCTD most commonly present the histological pattern of nonspecific interstitial pneumonia (NSIP), while those with RA frequently have fibrosis with the histological lesions of usual interstitial pneumonia (UIP) (3).

We know from every day clinical practice, as well as from the international bibliography, that within the spectrum of ILDs a subset of patients has, despite treatment, a relentlessly progressive disorder. Those patients develop what is commonly described as a progressive fibrosing phenotype (4). Affected individuals typically present with progressive dyspnea, resulting in respiratory failure which accounts for considerable morbidity and mortality. In SSc, ILD is the first cause of mortality, whilst in all patients with autoimmune diseases represent a significant cause of disability (5).

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Although the concept of progressive fibrosing ILD was initially introduced to patients with IPF, it is now evident that progressive fibrosis can be found in patients with other ILD diagnostic categories, including those with underlying CTD (4). Therefore, the accurate diagnosis and the early identification of disease progression are of outstanding importance, and require multidisciplinary care involving pulmonologists, radiologists and rheumatologists. Corticosteroids and immunosuppressive agents are considered as the mainstay of treatment for CTD-ILDs. Immunosuppressants are currently used for the management of pulmonary fibrosis, however the emerge of antifibrotic drugs provided new hope for affected individuals.

Nintedanib is a tyrosine kinase inhibitor, initially developed as an antitumor agent. It has since been shown to have pleiotropic effects, including anti-fibrotic, anti-inflammatory, and anti-angiogenic activity through inhibition of tyrosine kinases, such as vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), fibroblast growth factor (FGF). It binds competitively to the adenosine triphosphate (ATP)-binding pocket of these receptors and blocks the intracellular signaling, which is crucial for the proliferation, migration, transformation of fibroblasts, and collagen production (6).

In clinical trials, nintedanib has shown efficacy in the treatment of patients with idiopathic pulmonary fibrosis (IPF), thus receiving this indication in the EU and the USA. More recently it has been approved also for SSc-ILD as well as for other chronic fibrosing ILDs with a progressive phenotype. Adverse event profile is mainly characterized by gastrointestinal events.

In the SENSCIS trial, nintedanib reduced the progression of interstitial lung disease in patients with SSc-ILD, as shown by a reduction in the rate of decline in FVC over 52 weeks. In detail, the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (7). Approximately half of the patients received mycophenolate at baseline and nintedanib showed a positive effect versus placebo on the annual rate of decline in FVC regardless of MMF use at baseline; however, overall data supports the concept of combined therapy (8).

The INBUILD trial included 663 patients with chronic fibrosing ILDs and a progressive phenotype. In the overall population, the adjusted rate of decline in the FVC was −80.8 ml per year with nintedanib versus −187.8 ml per year in the placebo group (9). Frequent ILD diagnoses were chronic hypersensitivity pneumonitis (26%) and autoimmune ILDs (25.6%), 19% idiopathic NSIP, 17% unclassifiable idiopathic interstitial pneumonia and 12% other ILDs (10). Although the trial was not designed or powered to identify differences between specific diagnostic subgroups, nintedanib reduced the rate of ILD progression, as measured by FVC decline, irrespective of the underlying ILD diagnosis (10).

Matteson et al (11) currently analyzed the efficacy and safety of nintedanib in patients with fibrosing autoimmune ILDs over 52 weeks. Despite management deemed appropriate in clinical practice, patients fulfilled inclusion criteria for ILD progression within the 24 months before screening. The subgroup of 170 patients with autoimmune disease related ILDs of the initial INBUILD study included patients with RA (89), SSc (39) MCTD (19) and other autoimmune diseases. They were randomly assigned to either nintedanib or placebo. The adjusted rate of decline in the FVC was −75.9 ml per year with nintedanib versus −178.6 ml per year in the placebo group (11). The relative reduction was consistent was previous findings observed in the overall population of the INBUILD study, in the population of patients with SSc – ILD of the SENSCIS trial, as well as with patients with IPF included in the INPILSIS trial. No heterogeneity across the different diagnostic subgroups was detected. It is noteworthy that the INBUILD study was not designed or powered to study patients with individual diseases. When patients were analyzed according to histological pattern, the effect of nintedanib versus placebo was numerically greater in subjects with a UIP fibrotic pattern on high resolution computed tomography (HRCT) compared to those with other patterns; however, no statistically significant heterogeneity was detected (11). Further analysis regarding baseline treatment with disease modifying anti-rheumatic drugs (DMARDs) and/or glucorticosteroids did not indicate significant differences. The adverse events were consistent with previous studies, with gastrointestinal events and particularly diarrhea being the more common. Regarding laboratory detection of liver enzyme elevation were more common in patients receiving nintedanib than in the placebo group, as seen in other nintedanib studies. In 17.1% and 10.2% of subjects in the nintedanib and placebo groups, respectively, adverse events led to permanent discontinuation of the trial drug (11).

II. CONCUSIONS

The current subgroup analysis is really important as it comes from a large, randomized, double-blind, placebo-controlled trial which included patients with progressive

fibrosing autoimmune disease-related ILDs. With the INBUILD trial, the concept of progressive fibrosing ILD was introduced. Fibrosis measured with decline in FVC and/or HRCT findings and worsening of respiratory symptoms at a certain rate was considered as a progressive phenotype that required therapeutic intervention. The results of the clinical studies of nintedanib provided data on reduction of the rate of decline in FVC. The efficacy of nintedanib in slowing the rate of decline in FVC compared with placebo in all diagnostic groups has been demonstrated. The number of patients with SSc-ILD, in both the SENSCIS and the INBUILD trial, as well as those with RA-ILD included in the INBUILD trial are considered rather sufficient. However, more studies are needed to assess its efficacy in patients with other CTD-ILDs, like in those with myositis, SLE and/or Sjogren Syndrome. Moreover, the role of nintedanib in IPAF also needs to be investigated.

Another issue that needs to be assessed in future clinical studies is the treatment strategy, which will determine which treatment option should be come first, the immunosuppressants or the antifibrotic drugs, or if they should be started together. Clinical trials have provided evidence of a level of efficacy of certain immunosuppressants; however, the combination with anti-fibrotics and the appropriate time to do so, remains an unsolved issue.

Regarding safety, adverse events were in large manageable for most individuals. The need of finding promising treatments for patients with pulmonary fibrosis is clearly addressed. Timely identification and management of pulmonary fibrosis are needed to improve outcomes. Further studies that will offer data regarding quality of life, morbidity and mortality are also needed.

AUTHOR CONTRIBUTION

TS conceptualized and wrote the manuscript.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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Clinical Case

Necrotic cutaneous Loxoscelism

Running title: Necrotic cutaneous Loxoscelism

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Keywords- Brown recluse spider bite; cutaneous loxoscelism; necrotic ulcer; dermonecrotic wound

A 56-year-old woman presented with a painful edematous skin lesion due to a spider bite. The evolution of the wound from an erythematous, painful lesion into a necrotizing skin cavity was consistent with the diagnosis of cutaneous loxoscelism. Cutaneous loxoscelism is a medical condition induced by the bite of a spider of the genus Loxosceles, which causes a necrotic ulceration through the enzyme sphingomyelinase D [1]. This is an endemic case of a necrotizing injury bite in areas of the Midwestern and Southern United States, but it is infrequently reported in Greece [2]. Physicians in nonendemic brown recluse regions should be cautious in implicating brown recluses in dermonecrotic wounds in order to initiate appropriate treatment and recommend effective preventative measures.

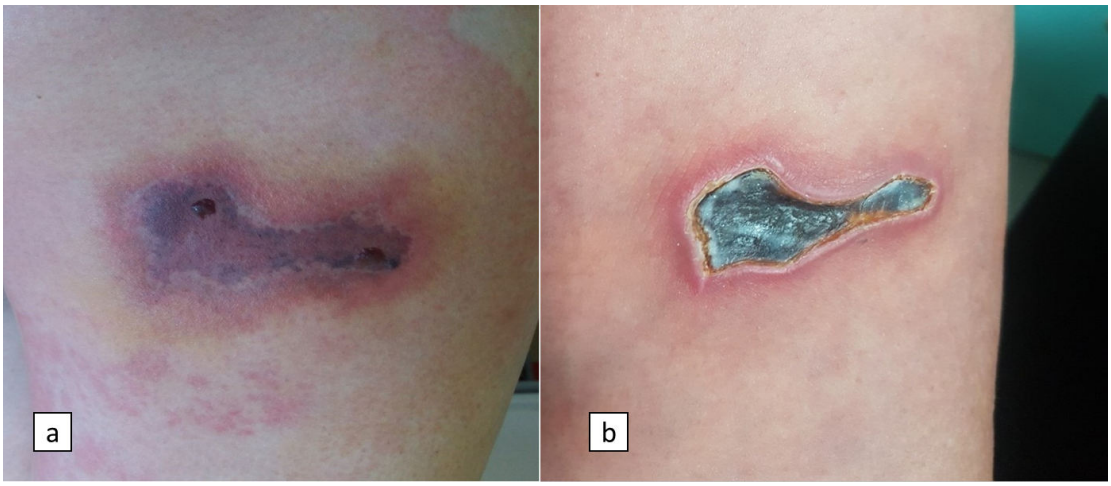

Fig. 1 a. The "red, white and blue" sign which results from reactive erythema, vasoconstriction and thrombosis; b. Necrotizing skin cavity developed 10 days after the brown recluse spider bite.

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AUTHORS CONTRIBUTION

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

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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Educational Note

T cell-lineage fate commitment and development

Running title: T cell development

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Abstract

T lymphocytes establish and maintain immune responses. T cell blood precursors under thymic signaling express TCR and CD4 or CD8 co-receptor and differentiate into naïve T cells. This educational note illustrates the major molecular processes that facilitate development of the double negative pre-thymic cell towards a mature T cell. Basic principles of each model, selective or instructive, trying to elucidate the biologic pressures under which T cell fate is determined are presented. The aim is those in need to better understand the basics of T cell fate choice.

(Submitted 14 March 2022; accepted 29 2022)

Keywords- T cell; thymus; TCR; CD4; CD8; immunity

I. INTRODUCTION

Immune system relies on T lymphocytes to establish and retain immune responses. T cell progenitors stem from bone marrow, migrate to thymus in order to proliferate, be selected and mature and finally, after specific lineage differentiation, are delivered to periphery. Thymic microenviromental signals promote numerous genetic and molecular processes that eventually lead to T cell development. This educational note summarizes key concepts regarding T cell fate choice.

II. T CELL FATE COMMITMENT

In order to facilitate T cell fate commitment and development towards a T cell phenotype, blood progenitor cells migrate to thymus and receive Notch signals (1). Interplay with Notch ligands found in stromal cells of thymus participates in initiation of pro-T cell maturation program (2). Pro-T cell thymocyte maturation has been partitioned in four differential stages of double negative (DN; $CD4^-CD8^-$) cells, which can be separated by relative expression of CD44 and CD25, as follows: $CD44^+CD25^-$ - DN1, $CD44^+CD25^+$ - DN2, $CD44^-CD25^+$ - DN3, $CD44^-CD25^-$ - DN4(3). DN cells can differentiate into αβ TCR single positive ($CD4^+CD8^-$ or $CD4^-CD8^+$) or γδ TCR cells (4). Early thymic T cell precursor (DN1 stage cell) under constant exposure to Notch ligands develops to a DN2a cell and proliferates. At this phase, T cell lineage fate has not entirely been determined, and loss of Notch mediated signaling pathways has the potential to rearrange the developmental program of the cell towards a NK, dendritic or granulocyte cell commitment. Next, pro-T cells transition to DN2b-stage, in which TCR gene rearrangement is undertaken and full T cell lineage commitment is accomplished, a process characterized by substantial changes in chromatin organization (5), and transformation of genome-wide epigenetic marking (6). By the time of DN3a stage, RAG1,2 protein mediated VDJβ gene rearrangement has been completed and a TCRβ chain has been produced (7). Pairing of that TCRβ chain with a pre-TCRα chain, generated by expression of a non-rearranged locus results in the formation of the pre-TCRαβ pair. At this point, β-selection is facilitated and cells carrying mutations that interrupt the function of stimulated-pre-TCR complex-dependent intracellular signaling are doomed to mutational arrest (8). Cells effectively transitioning intracellular signals consequently advance to DN3b stage. During DN4 stage non-rearranged locus expression of TCR-a is interrupted and recombination of the same locus produces the TCRa chain, thus completing the formation of αβ TCR. Simultaneously, thymocytes induce CD8 and CD4 expression, which in term leads to formation of a double positive ($CD4^+CD8^+$) cell population. Transcription factors and their interactions with chromatin

states driving the T cell fate choice are extensively reviewed by Hosokawa H. et al. (9).

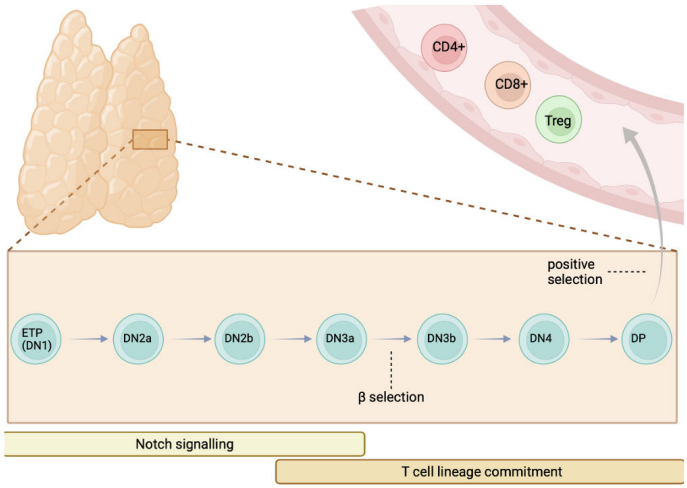

Fig. 1. T-cell lineage development via Notch signaling and T cell lineage commitment

III. POSITIVE SELECTION OF DOUBLE POSITIVE CELLS

Once double positive cells are formed, mechanisms of selection pressures are retained, guaranteeing that only those cells with appropriate functions are permitted to mature and migrate to peripheral tissues (10). The vast majority of double positive thymocytes, express TCRs incapable of self-peptide-MHC complex interactions and subsequently impotent of generating pro-survival signals to sustain cell viability, condemning cells bearing them to a process known as death by neglect (11). On the other hand, high affinity engagement of TCRs to self-peptides provokes sudden apoptotic death, a negative selection procedure securing avoidance of the exacerbation of autoimmunity. TCR interaction with self-peptides in an affinity range between that urging death by neglect and that of negative selection, promotes a process that secures maturation and survival of cells expressing potentially useful TCRs. This process is well-known as positive selection (12). Moreover, double positive cells express both co-receptors CD4 and CD8, whom extracellular domain assists MHC-ligand-TCR interaction and intracellular domain, which relates with protein tyrosine kinase LCK, enhances signals transduced by TCR. CD4 binds specifically to MHC class II, while CD8 to MHC class I. Interestingly, cells expressing TCRs competent to interact with non-MHC specific ligands are not positively selected. As described by Singer A. et al.(13) intracellular levels of LCK are limited and tightly associated to CD4 and/or CD8

molecule function. To promote positive selection adequately intensive TCR signaling requires LCK-assisted signal enhancement. MHC-restricted TCRs, exploiting CD4 or CD8 molecule assistance are able of producing intracellular pro-survival signals, efficient to induce positive selection, whereas non-MHC-restricted TCR bearing cells undergo unavoidably death by neglection. Interestingly, TCR affinity at the higher levels of positive selection encourages clonal deviation, relaying potentially autoreactive T cells towards regulatory (Treg) cell lineage(12). Positively selected population eventually matures in T cells expressing either CD4 or CD8. This process of differentiation depends on MHC class-specific signals.

IV. SELECTIVE AND INSTRUCTIVE MODELS OF T CELL COMMITMENT

The transformation of the thymocyte from double positive to the single positive cell necessitates silencing of transcription of locus for the co-receptor selected to be forsaken and simultaneous genetic events that accompany the CD4/CD8 lineage choice of a T effector type (14). The stochastic selection model dictates that during TCR interaction with self-ligand-MHC complexes, during positive selection of double positive thymocytes, randomly selected locus expression of either CD4 or CD8 is terminated (15). Such a process leads to the formation of a single positive thymocyte bearing a MHC specific class restricted TCR, and a randomly chosen co-receptor, which may match to TCR MCH restriction or may not. A second TCR mediated rescue step guarantees that only maintained cells with a matching co-receptor and TCR are matured and differentiated towards a T cell. Backing for this model has been obtained from co-receptor rescue experiments, in which transgenic co-receptor protein expression rescued T cells bearing co-receptors with inappropriate specificities of MHC-restricted TCRs, signifying that undeniably a second rescue step is taking place (16). However, experimental observation has opposed primary values of the stochastic model (13).

The strength-of-signal instructive model is based on the assumption that TCR specificity induces silencing of expression of mismatching co-receptor. This determines the lineage of double positive cells. More specifically, the cytoplasmic domain of CD4 has been found to bind more LCK than that of CD8 and upon TCR-MHC class II engagement to generate strong signals, while that of CD8 upon TCR-MHC class I interaction to generate weak signals. Relative intracellular signal strength results in inhibited expression of *CD4* or *CD8* gene. Experiments

utilizing chimeric co-receptors consisting of CD8a molecules and the cytoplasmic domains of CD4 set the fundamental principles of strength-of-signal instructive model(17). Expression of engineered CD8-CD4 molecules from MHC class I-restricted double positive thymocytes induced the differentiation of CD4 T cells, that would otherwise—bearing the regular CD8 co-receptor—progress to CD8 T cells. However, experimental work has shown that when ITAMs were altered (in order to evaluate the effect of TCR signaling strength on T cell lineage choice), decrease of signaling intensity did not alter the extent of differentiation towards CD8 or CD4 cells(18). Hence, strength-of-signal model has since been challenged.

Duration-of-signal instructive model could be regarded as a refined version of strength-of-signal model. The core difference differentiating the two is that the first one provisions that duration of TCR stimulation determines the T cell lineage choice. Short TCR stimulation instructs double positive thymocytes to differentiate into $CD8^+$ cells, whereas long TCR stimulation induces $CD4^+$ cell differentiation(19). An explanation of the existence of different duration TCR signals has been attempted to be given by evidence supporting that double positive thymocytes upon TCR stimulation decrease the expression of CD8 co-receptor(20). In case of MHC class I restricted TCR stimulation, CD8 downregulation results in interruption of signaling and in short duration of signals, whereas in case of MHC class II-restricted TCR stimulation, CD8 downregulation does not influence CD4 co-receptor-mediated signaling. Duration-of-signal instructive model also comes with its own drawbacks, and part of its core elements has been also challenged by recent experimental data. Maintaining components of the duration-of-signal instructive model, other models explaining the T cell fate choice, such as the kinetic signaling model have been elaborated(13).

V. CONCLUSION

The processes involved in T cell development and choice of lineage fate have comprehensively been studied. While advances through experimental observations have assisted efforts to uncover the complex mechanisms, in molecular and genetic level, that eventually define whether CD4 or CD8 co-receptor surface expression will prevail, much remain to be explored. Future research to support a definitive model of T cell fate determination is warranted.

AUTHOR CONTRIBUTIONS

SGT drafted the manuscript. DPB revised the manuscript. The artwork was prepared using BioRender under license to DPB. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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Clinical Image

Gum hypertrophy in a patient treated with cyclosporine

Running title: gum hypertrophy and cyclosporine

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

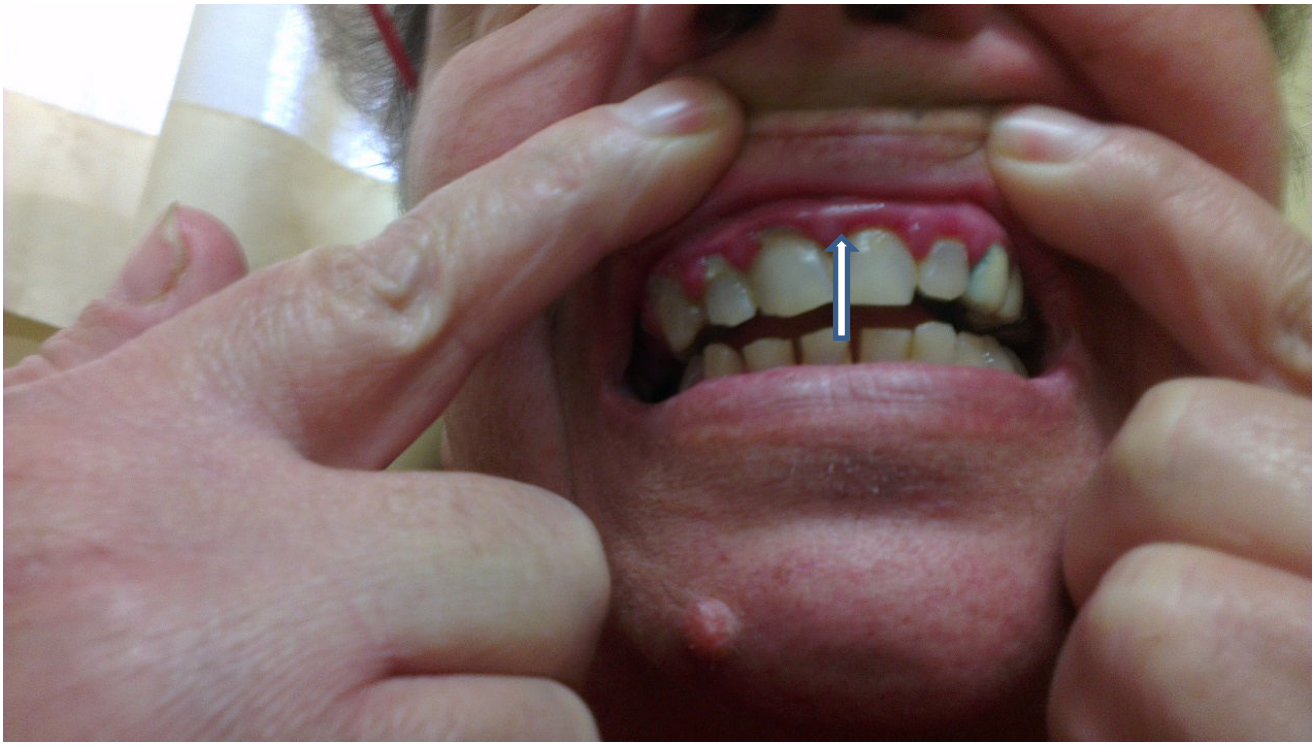

Fig. 1 *Gum hypertrophy. A rare but well-known side effect of cyclosporine*

AUTHORS CONTRIBUTION
The author prepared the manuscript and the artwork. The author approves the final version of the manuscript.

CONFLICT OF INTEREST
The Author declares no conflict of interest

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Educational Note

T cell activation in cancer

Running title: T cells in cancer

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Keywords- Cancer; CD80/86; dendritic cell; immune activation; MHC; immunity; TCR, tumour

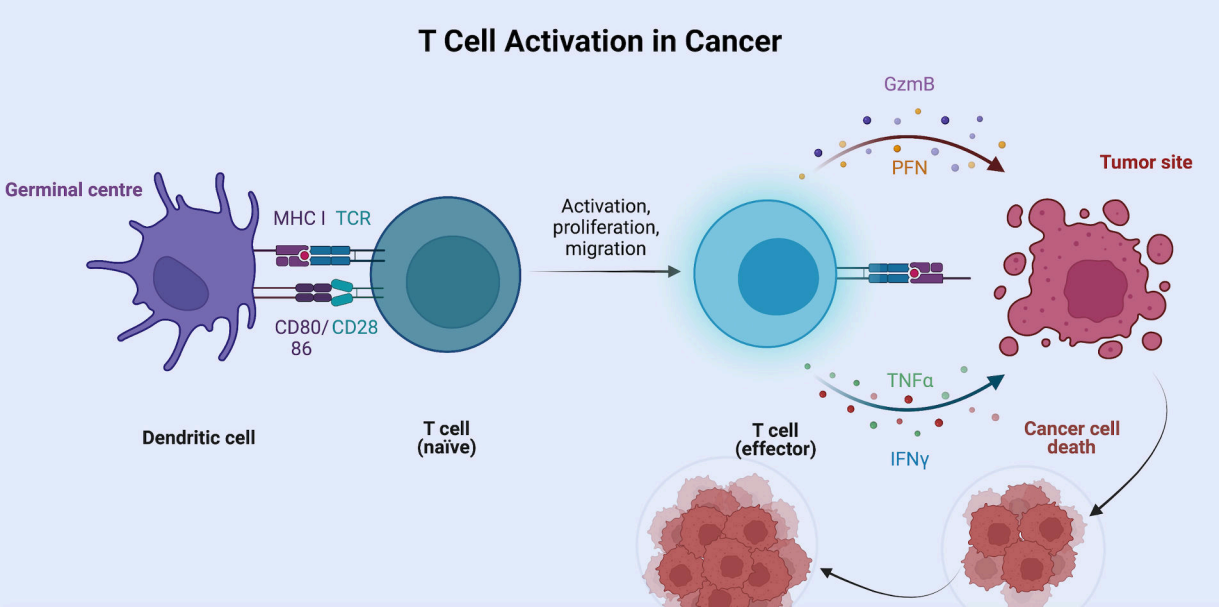

Fig. 1 Mechanisms of T cell activation in cancer. Previous to activation, professional antigen-presenting cells such as dendritic cells must load antigen onto MHC molecules such as MHC-I (for CD8 T cells) to make them equipped for contact with a naïve T cell that exhibits a cognate T cell receptor (TCR). It also grants appropriate co-stimulatory ligands CD80/86 for the corresponding CD28 co-stimulatory receptor, which is expressed in both classes of T cells. Soon after activation, mostly in the lymphoid tissue, T cells are activated when their TCR bind to their cognate antigen presented by dendritic cells. This is done in conjunction to CD28 28 binding with CD80/86. Proliferation and migration of the activated T cells in the site of the tumor is taking place and the self-perpetuated promotion of their enhanced T cell activation and proliferation, is further augmenting the effector function of cytotoxic T cells and their antitumoural T lymphocyte potential. Pro-inflammatory and anti-tumour related cytokine production, such as that of interferon-γ (IFN-γ) nd tumor necrosis factor α (TNF-α) is promoted. Subsequently, more T cells bind to tumour antigens presented by MHC-I in cancer cells through their TCRs. This process leads to the release of perforin and granzyme B, which are known cytolytic mediators and can generate adequate tumour killing (1-3). Prepared using Biorender under license to DPB.

AUTHORS CONTRIBUTION

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

CONFLICT OF INTEREST

The Authors declare no conflict of interest.

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Excellence in Rheumatic & Autoimmune Diseases ERAD
THE OFFICIAL JOURNAL OF INSTITUTE OF RHEUMATIC AND AUTOIMMUNE DISEASES

Clinical Image

Fissured tongue: hints

Running title: scrotal tongue

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Keywords- Down syndrome; Fissured tongue; Geographic tongue; Lingua plicata; Pustular psoriasis; Scrotal tongue

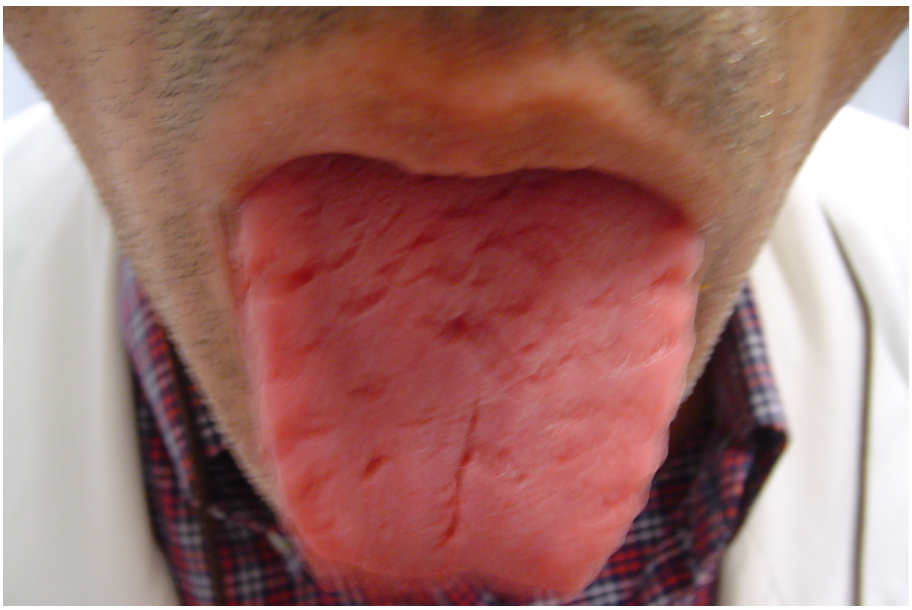

Image. 1 Fissured tongue. Fissured tongue also known as 'scrotal tongue' or 'lingua plicata' is a benign condition characterised by one or more shallow or deep grooves or furrows (fissures) on the top surface of the tongue. It is usually painless unless debris such as food gets trapped within the grooves or when it occurs in association with geographic tongue. Causes of fissured tongue are not clear but it may occur with certain underlying syndromes or may be an inherited condition. It is rarely seen in orofacial granulomatosis, Melkersson-Rosenthal syndrome and Down syndrome. It is can be also associated with geographic tongue and pustular psoriasis. The main complication of a fissured tongue is the development of orofacial granulomatosis (facial swelling) or Melkersson-Rosenthal syndrome (a triad of a fissured tongue, orofacial swelling and facial palsy). A fissured tongue can be the first sign. Fissured tongue is a benign condition that does not require any specific treatment. Patients should brush the top surface of their tongue to remove any debris that may cause irritation or infection.

AUTHORS CONTRIBUTION
The author prepared the manuscript and the artwork. The author approves the final version of the manuscript.

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The Author declares no conflict of interest

Excellence in Rheumatic & Autoimmune Diseases ERAD
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Clinical Image

Granulomatosis with Polyangiitis (Wegener's) with nasal manifestation

Running title: Persistent sinusitis with necrotic intranasal mucosa

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Keywords- Wegener's granulomatosis; necrotic nasal mucosa; nasal obstruction

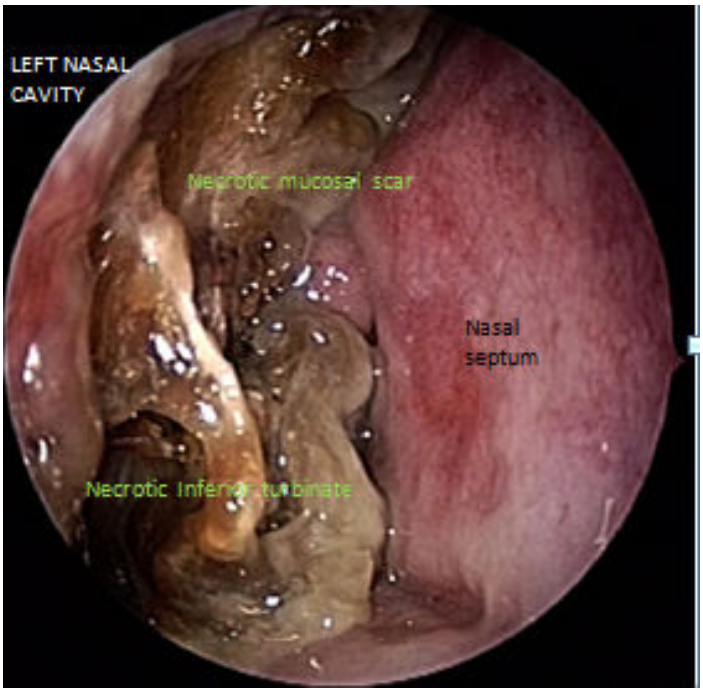

Image 1. The typical manifestation of primary necrotizing vasculitis was persistent nasal obstruction in an adult patient with no history of nasal disorder. In the endoscopic intranasal examination may reveal only diffuse nasal mucosal destruction and in advance manifestation of the disease with necrotic areas. The mucosa may be dry, crusted and the tissue around and underlying the crusts is extremely friable. Perforations of the nasal septum are also common. In this case, manifestation was unilateral co involved inferior and middle turbinate in the left nasal cavity with intact nasal septum. A diagnosis of Granulomatosis with Polyangiitis requires a history of chronic inflammation for at least four weeks which is not due to another cause. Adequate biopsy of representative tissue is important as well as an autoimmune serology manifesting the presence of disease related C-ANCA/anti-PR3 (ANCA)

AUTHORS CONTRIBUTION
The author prepared the manuscript and the artwork. The author approves the final version of the manuscript.

CONFLICT OF INTEREST
The Author declares no conflict of interest

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Review

Autoantibodies as diagnostic markers in cancer

Running title: Autoantibodies in cancer

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Abstract

The emergence of autoantibodies (AAbs) against self-antigens is an old story almost a hundred years old. On the contrary, only recently scientists started to shed light on the antigen-specific immune response in cancerous diseases. During the last decades numerous studies have revealed the significance and applications of autoantibodies in cancer. Cancer-evoked immunity has apparently dual role in either promoting or suppressing the neoplastic progression. Moreover, the implications of AAbs in early diagnosis as biomarkers are continually studied focusing on early detection of cancer and effective management. In this mini review, we mostly elaborate the possible contribution of autoantibodies in the diagnosis of cancer.

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Keywords- TAAs, TSAs, autoantibody, cancer, biomarker

I. INTRODUCTION

Cancer, despise all the scientific developments, remains the second leading cause of death and a still growing public health issue in the whole world.The estimation is that about 1,670 deaths a day are expected to occur in the US (1). Prostate, colorectal, lung, stomach and liver cancer prevail in men while colorectal, lung, breast, thyroid and cervix cancer are the most widespread among women (2).
As such, it is more urgent every day the acquisition of more accurate screening methods for early diagnosis leading to effective treatments and better prognosis. An alternative to the traditional strategies in the battle against cancer is the presence of autoantibodies.

Autoantibodies are immunoglobulins directed against self-antigens (3). The corresponding antigens have an enhanced or abnormal expression in cancer cells than in healthy ones. In 1901 the first report about the AAbs existence came in light and almost 50 years later a report was published about antinuclear antibodies in the serum of patients with Systematic Lupus Erythematosus (SLE) (4–8). These cell-penetrating AAbs which have the ability to intrude into living cells in vitro and in vivo are characteristic findings in autoimmune diseases. A still growing number of AAbs have been discovered against different antigens namely nuclear, cytoplasmic different proteins, cell membrane etc (9).

The whole process of antibody production is still foggy but multiple elements appear to play pivotal roles for example infection, genetic predisposition, ineffective apoptosis and environmental factors etc(9). The pathogenesis of the emergence of the autoantibodies depends on the dysfunction of the immune system in the same platform for autoimmune diseases and cancer. In the context of a defective immune tolerance autoreactive lymphocytes prevail, generate AAbs and cause autoimmunity and cancer with different biologic activities in each entity (10,11). The spontaneous AAbs in neoplasm might represent the effort to fight against tumor progression whereas in autoimmunity it is more of a self tolerance failure and inflammation (12). In 1996 the scientific community acknowledged the report of Baldwin et.al. about the generation of autoantibodies due to tumor-associated antigens (TAAs) presented in cancer cells' surface (10,13). Another class of antigens after epigenetic alterations, mutations or deletions in normal genes so called tumor-specific antigens (TSAs) emerged (14). Escape from immunosurveillance is considered the main

pathophysiological procedure leading to tumor growth but the pathogenic role of autoantibodies is still vague. Researchers strive to exploit AAbs for prompt diagnosis, gain information about tumor progression, target therapies and prognosis to fill the knowledge gap in oncology.

A great number of epidemiological studies focused on the increased or decreased risk of certain types of cancers in autoimmune diseases and on the other hand the promoting role of cancer to induce autoimmunity. So, Rheumatoid Arthritis (RA) has been correlated to increased risk of hematological and solid cancers (15) and on the other side of the spectrum development of Scleroderma in cancer patients having POLR3A mutation (16). AAbs share their presence in cancer as well as in autoimmune diseases like anti-Ro/SS-A and anti-La/ SS-B in patients with Sjogren's syndrome (17) and SLE (18) and in hematological neoplasia as well (12). In cancerous diseases AAbs are frequently detectable after spontaneous B-cell response and might be useful because of their biologic activities to tackle malignancies. Accordingly, in autoimmune diseases AAbs could be useful for diagnosis and disease progression.

In this review, we summarize the current data with regards to the application of AAbs in oncology. There is growing evidence for their ability to contribute as cancer biomarkers in clarification of diagnosis.

2. HUMORAL IMMUNE RESPONSE IN CANCER PROGRESSION

A very significant trait of adaptive immune response in cancer patients is the infiltration of the tumor microenvironment by tumor associated B cells and the consequent immune surveillance within has positive or negative effects in immune responses. In this context, some AAbs promote cancer progression whereas others prevent tumor growth. It has been suggested that there are two potential justifications (19), firstly the presence of the AAbs characterize an immune system in "a good shape" with good prognosis and secondly, they have an immediate impact on the tumor by implicating various mechanisms(20).

In 1970, Sir Frank Mac Farlane Burnet introduced the concept of immune surveillance theory as he proposed that neo-antigens trigger immunological reaction against tumors(21). This function might create better survival rates in different malignancies for instance melanoma (14), Hodgkin lymphoma (22), prostate carcinoma (23), glioblastoma (24), colon carcinoma (25), ovarian (26), gastric (27), pancreatic (28), hepatocellular (29), lung (30), breast cancer (31), tongue (32) cancers. Additionally, some spontaneous induced autoantibodies might constrain cancer tumorigenesis through complement –dependent and antibody-dependent cytotoxicity, antigen-presenting cells(APCs) and T cells activation (33(33) or intervene in functionality of tumor cell surface structures (i.e. receptors). On the contrary, some AAbs may foster malignancy progress. As we aforementioned, cancer and autoimmunity share a plethora of AAbs. Patients with autoimmune diseases might have heightened risk to develop neoplasia and on the other hand cancer patients may easier affected, compared to general population from an autoimmune-related disease.

Patients with Systemic sclerosis (Sc) have been showed that they present high risk for neoplasia especially in breast and lung (34). The published work of the John Hopkins Scleroderma Center database depicted that there is a connection of this augmentation with the presence of autoantibody against RNA-polymerase III subunit (35).Moreover, they revealed mutations in the corresponding gene (POLR3A) strongly suggest the implication in a novel way of cancer in this autoimmune disease (36).In an Italian study, correlation of anti-Scl70 with lung cancer is revealed (37) and additionally Bruni et.al found anti-PM/Scl100 in scleroderma patients with cancer(38).

Another element that is currently under investigation is the subtype of the autoantibody involved in cancer progression. It seems that IgG4 subclass antibodies are taking part in tumor microenvironment and serum IgG4 was inversely correlated with patient survival as Karagiannis et.al suggested in 2013. Their work proposed that IgG4 in Th2-based inflammation may provide a tumor-induced immune escape and a good start for biomarker development and personalized therapeutic approaches (39).

Additionally, a procedure of importance regarding the contribution of AAbs in cancer progression are secreted IgG antibodies from cancer epithelial cells resulting to support promotion and not apoptosis of tumors (40–43).Nevertheless, more effort is needed to elucidate these implications of AAbs in malignancy progression.

3. POTENTIAL EXPLOITATION OF AUTOANTIBODIES AS CANCER BIOMARKERS CONTRIBUTING TO DIAGNOSIS

It is generally accepted that early detection of any type of cancer is the goal of medical approach to mitigate or prevent metastasis and nullify mortality rates. In this context, during the last decades, the generation of AAbs as a characteristic of effective immune surveillance for tumor cells became prominent for cancer screening and diagnosis. The potential implication of autoantibodies as cancer biomarkers have been investigated from many groups since the first antigen, p53, described to trigger AAbs production in breast cancer patients (44). In 1999 Fernandez-Madrid et.al. described antinuclear antibodies in sera of patients with lung cancer and suggested the diagnostic and prognostic value of this finding (45).

The continuously growing interest regarding AAbs as diagnostic tools in cancer has been strengthened by their notable characteristics. On the contrary to the low or even undetectable concentrations of protein biomarkers, B-cell response offers abundant, high affinity antibodies, present in early stages of cancers. Specifically, these biomarkers, as immunoglobulins, are characterized by their stability and persistence in high quantities for prolonged periods in serum samples, due to diminished proteolysis and clearance from the circulation (10,46,47). It is noteworthy that they are easily obtained with minimally invasive technics and they have long half-lives. These traits increase their sensitivity and specificity for diagnosing tumors than antigens. For example, anti-alpha-fetoprotein (AFP) antigen has only 60% and 69% sensitivity and specificity respectively with regards to liver cancer diagnosis compared to AFP antibody sensitivity 89% and specificity 77% (48). Actually, the most intriguing feature of AAbs is their ability to emerge long before the first signs and clinical diagnosis of cancer for months or even years (49).For instance, strong evidence supporting this notion came from studies that revealed the presence of p53 (tumor suppressor protein) AAbs in the sera of smokers and workers in carcinogenic environment prior to development of lung cancer (50,51).Recent studies have elaborated more AAbs in early stages of different types of neoplasia namely prostate (52), ovarian (53), lung (54), gastrointestinal (55), breast (56,57) and cervical (58,59). Having considered all the above cancer serum AAbs might serve as novel cancer biomarkers, after the verification of specific panels with the suitable combination, to indentify tumor signals as early as possible.

Currently, as the research is still ongoing, previous results have made clear that detection of a single cancer biomarker has less value in screening and predict malignancies when compared to panels of circulating autoantibody, especially in tandem with corresponding antigens, which yield to significant diagnostic power. With this approach, to blend together multiple immune responses in a group, it is more thoroughly addressed the diversity of tumor cells antigens. Somiari RI et.al in 2016 and Bassaro L et.al. in 2017 used for this reason an Autoantibody Profiling System-90 containing 90 antigens aiming to detect disease-associated AAbs pertinent to different autoimmune conditions and cancer in human plasma (60,61). Another group employed a panel of four AAbs against human HER2, p53, TOPO2 and IGFBP2(insulin like growth factor binding protein) in breast cancer resulting with 75% specificity and sensitivity(62). More intriguing is the combination of 22-phage-diplayed antigens for prostate neoplasia that achieved 88% sensitivity and 82% specificity (63). The common denominator of the majority of these studies is the insufficient diagnostic sensitivity and specificity which must be addressed by either multiple markers or discovery of novel antibody targets.

Furthermore, scientists strive to exploit novel technologies for AAbs detection. Apart from enzyme linked immunosorbent assay (ELISA) which has drawn a lion's portion in this field for many years along with protein microarrays, novel methodologies have emerged and struggle to insure a place in the future scene. High Throughput methods for autoantibody detection include serological proteome analysis (SERPA)(64,65), Reverse-capture antibody microarray (a modern version of multiplex elisa) (64), Self-assembly microarray(66) , Multiple Affinity Protein Profiling (MAPPing)(67), Phage-display antigen microarrays (Epitomics)(68) and Glycan arrays (67). Moreover, new and unique techniques appear like the nanoplasmonic-based biosensor by Soler M. which offers sensitive and real-time quantification of autoantibodies for the early diagnosis of colorectar cancer (69). It is really pivotal to incorporate high-throughput assays during the exploration procedure to detect specific panels of autoantibodies with specific traits foe early diagnosis. Moreover, validation assays are of paramount importance in order to determine the actual significance of the discovered autoantibodies in clinical practice.(67)

AAbs detection and quantification new methods might be an invaluable diagnostic tool for screening strategies as well for asymptomatic and cancer high-risk groups but with improved sensitivity and specificity in clinical practice.

4. DISCUSSION

It is well-studied up to now that the measurement of spontaneous disease-associated antibodies could provide early detection of neoplasia before the onset of physical symptoms, which would be of paramount importance by offering patients a wider range of options for effective treatment at an earlier stage of disease.

The experience from the autoimmune diseases paves the way to investigate the hidden properties of AAbs. Roughly speaking, some of them could be protective against some cancers while others significantly increase the occurrence of specific cancer types. For example, the risk for expressing lung, pancreatic, hepatic, thyroid, haematological, vulvar neoplasia in SLE patients is heightened comparing to others namely breast, endometrial, ovarian etc.(9). Likewise, patients with RA exhibit increased risk of developing lung cancer as well as leukemia and lymphoma (70) and at the same time a significantly decreased risk for breast, cervical and colon cancer (70,71).

It is more than obvious that there is a still expanding variety of AAbs in cancerous diseases lies on the findings of numerous animal and human studies with more than 120 reported responsible tumor antigens (14) pointing out the unique competence of our immune system to sense the non-

self even among native elements. The pathophysiology of the AAbs' emergence share common features with autoimmune diseases having inflammation in the tumor microenvironment as the cornerstone known already from the 19th century(14).

Experience gained from research have indicated that combination or panels of AAbs are better working as diagnostic biomarkers in lieu of single autoantibodies yet proven from an autoantibody assay, EarlyCDT-Lung.(72) The dissection of single antibody specificities is a difficult task considering the polyclonal nature of B cells by the same manner as autoimmunity(73).

5. CONCLUSIONS

Summarily, in all pathologies early biomarkers represent invaluable tools for the early diagnosis and management. Especially in cancer it is of crucial importance the application of non-invasive, accurate and sensitive methods as early diagnostic tools to detect the emergence of neoplasia.

The study of AAbs against mutated or even normal proteins is alive and kicking. By exploiting the multiple line of evidence from autoimmune diseases research aims at better understanding of the immune response and the intricate nature and specificity of the AAbs against TAAs and TSAs. They might represent promising biomarkers highly stable, circulating for more time than antigens and are present earlier than symptoms for the early diagnosis in cancers(67,74) incorporating the protein array technology and analyzing a great number of proteins simultaneously. There are still open issues regarding the value of AAbs in cancerous diseases but despite many odds, seem to have great potential in early detection and even treatment and prognosis in a personalized way. Maybe the scientific community tackling with autoimmune and cancerous diseases in tandem is ready to kill two birds with one stone.

AUTHORS CONTIBUTION

All authors participated in preparing the final version of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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Clinical Case
A rare case of postpartum pemphigoid gestationis

Running title: Bullous dermatoses in pregnancy

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Case Study

A 34-year-old woman presented with multiple fluid-filled lesions on the body of 20 days duration. Within hours after her second delivery, an itchy rash appeared in the inguinal folds. On the following day, the rash had spread over the abdomen and also the arms, and the patient noticed blisters over the identical sites (Fig.1).

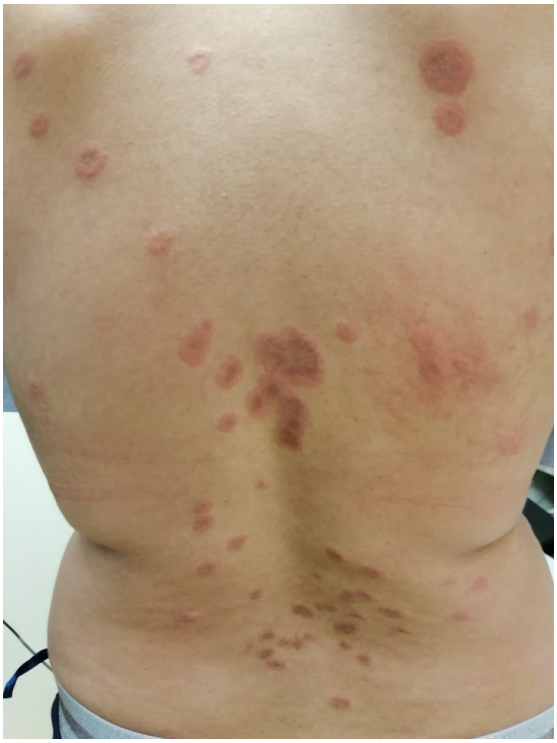

Fig. 1 *Blisters over the patient's back.*

Physical examination revealed bullae in an annular configuration on an erythematous base and urticarial plaques involving her abdomen, back, and forearms (Fig.2).

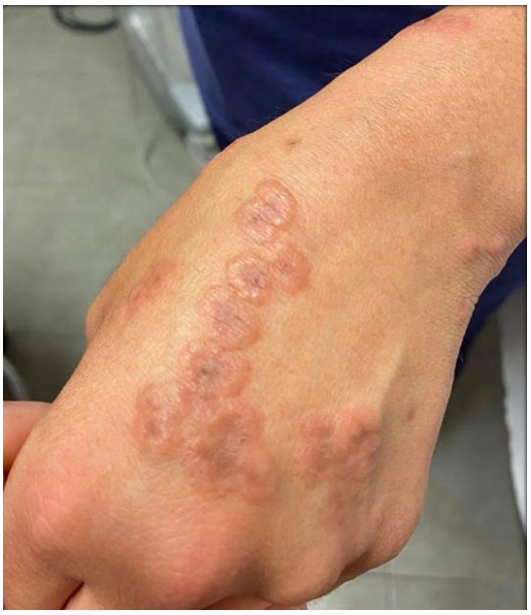

Fig. 2 *Bullae in an annular configuration on an erythematous base*

Histological examinations of biopsy specimens and direct immunofluorescence of perilesional skin confirmed the diagnosis of pemphigoid gestationis. Punch biopsy results showed subepidermal blistering dermatosis with

perivascular infiltrates of eosinophils and lymphocytes. Direct immunofluorescence was negative for IgG, IgM, and IgA, but demonstrated linear deposits of complement component C3 along the dermo-epidermal junction. The patient was started a 10-day prednisone taper starting at 60 mg daily for 7 days and decreasing 10 mg daily every 5 days, without significant improvement of the lesion. In addition to cortisone, the patient was treated with tetracycline antibiotics. Due to the non-response to cortisone, we decided to add cyclosporine 2.5 mg/kg (150-200mg) daily to the patient's treatment. The patient responded well within 2 weeks of starting cyclosporine and her lesions regressed completely.

Pemphigoid gestationis is pregnancy relative autoimmune vesiculobullous skin disease belonging to the group of blistering diseases. Although it's a rare disease, it occurs in just 1 in 50 000 pregnancies, the clinician needs to suspect and diagnose the disease when a pregnant or postpartum woman has itching and blisters.

AUTHORS CONTRIBUTION

All authors participated in the writing of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

PERMISSION TO PUBLISH

The patient provided a written consent for permission of the photos to be published.