Antigen mimicry followed by epitope spreading: A pathogenetic trigger for the clinical morphology of lichen planus and its transition to Graham Lassueur Piccardi Little Syndrome and keratosis lichenoides chronica - Medical hypotheses or reality? *

Mimetismo antigênico seguido de espalhamento de epítopos: agente desencadeador patogênico da morfologia clínica do líquen plano e de sua transição para a Síndrome de Graham–Little-Piccardi-Lassueur e para a ceratose líquenóide crônica – Hipótese médica ou realidade?

Georgi Tchernev [1] Pietro Nenoff [2]

Abstract: Literature data analysis, providing an exact explanation of the lichen planus pathogenesis, as well as its transition into other rare forms such as Keratosis lichenoides chronica or Graham Lassueur Piccardi Little Syndrome are scant, or totally missing.

The chronological course of the disease, known in the literature as lichen planus, varies. Some patients develop Lichen planus or lichen nitidus and there is no logical explanation why. It is also not clear why single patients initially develop ulcerative lesions in the area of the mucosa and only in a few of them these lesions affect the skin.

Antigen Mimicry and Epitope Spreading could be the possible pathogenic inductor in cases of lichenoid dermatoses, as well as the cause for their transition into ulcerative, exanthematous or other rare forms.

The *Epitope* Spreading is probably not the leading pathogenetic factor in lichen planus but a phenomenon which occurs later.

This manuscript analyzes some basic pathogenic aspects and presents some possible medical hypotheses regarding the heterogenic clinical picture and pathogenesis of lichen planus and lichenoid like pathologies of the skin which, in the near future should be analyzed in details in order to clarify several dilemmas the clinical dermatologist has to face.

Keywords: Apoptosis; Epitopes; Immunity; Infection; Lichen planus; Molecular mimicry

Abstract: Análises das informações disponíveis na literatura que forneçam uma explicação precisa sobre a patogênese do Líquen Plano, assim como sobre sua transição para outras formas raras da doença, como Ceratose Liquenóide Crônica ou Síndrome de Graham-Little-Piccardi- Lassueur , são raras ou inexistentes.

O curso cronológico da doença, conhecida na literatura como Líquen Plano, varia. Alguns pacientes desenvolvem Líquen Plano ou Líquen Nítido e não ha uma explicação lógica do por quê. Também não está claro por que alguns pacientes inicialmente desenvolvem lesões ulcerativas na área da mucosa e em apenas alguns deles essas lesões afetam a pele.

Mimetismo Antigênico ou Espalhamento de Epítopos poderiam ser fatores patogênicos indutores em casos de Dermatoses Liquenóides, e também fatores responsáveis pela transição para a forma ulcerativa, exantematosa ou outras formas raras da doença.

Espalhamento de Epítopos provavelmente não é o principal fator patogênico envolvido no Líquen Plano, mas um fenômeno de ocorrência posterior.

Esse manuscrito analisa alguns aspectos patogênicos básicos e apresenta algumas hipóteses médicas sobre o quadro clínico heterogênico e a patogênese do Líquen Plano e de patologias da pele do tipo liquenóide. Essas patologias devem, em um futuro próximo, ser analisadas minuciosamente a fim de esclarecer vários dilemas que o dermatologista clínico tem de enfrentar.

Palavras-chave: Apoptose; Epitopos; Imunidade; Infecção; Líquen plano; Mimetismo molecular

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[1] M.D. Ph.D. Spezialist in Dermatology and Venereology. Department of Dermatology, Venereology and Dermatosurgery, MVZ - Kirchheim, Germany.
[2] Laboratory for Medical Microbiology Partnership Dr Jürgen Herrmann, Prof. Dr Pietro Nenoff & Dr Constanze Krüger Straße des Friedens - Mölbis, Germany.

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INTRODUCTION

A number of clinically diverse, poorly understood, and relatively uncommon skin diseases are linked together by the presence of a pattern of common histopathological elements that traditionally has been referred histologically as the "lichenoid tissue reaction" or clinically to lichenoid-like pathologies of the skin.

The pathogenic chains taking place in the induction of lichen planus (LP) and its subforms have always been subject to controversial discussions which have not found a definite solution. [1]

In most LP or Lichenoid like pathologies of the skin und oral/genital mucosa, the targeted antigen is unknown, with cross-reactivity between environmental antigens and self antigens been suspected (Figure 1). [2] The two events, known as *Antigen Mimicry* and *Epitope Spreading*, could be the possible pathogenic trigger in lichenoid dermatoses, as well as the cause of their transition into other rare forms.

The immunological pathogenic cascade provoking typical lichenoid infiltrates includes not only the activation of CD4+ and CD8+ T-cells, but also the secretion of interferon gamma and the expression of ICAM-1 and FAS-L from the keratinocytes in the epidermal layer of the skin. The further T-cellular mediated apoptosis reaction induces the typical clinic morphology of lichen planus with its characteristic, violet papules (Figure 1A).[1,2]

We suggest that the development of the different forms of lichen planus is the final effect of *Antigen Mimicry*, which occurs during disturbed inner homeostasis or inadequate maintenance systematic and local therapy. [3] The recurrent infections and the polymedication, are probably the cause for immune response expansion towards the cutaneous structures, imitating or exhibiting close morphology to bacterial, fungal or viral structural elements.[3] Within the primary destructive inflammatory processes, unmasking of proteins in the area of the skin happens, preconditions for the extension of the immune response are indirectly created and, consequently, for the development of heterogenic clinical picture, too (Figure 1C). [3,4]

The relationship between psychological status of patients and hormonal profile, and consequently cytokine profile is unclear.

Several researches observing the previous mentioned dependence and its importance are missing. The detailed observation and study of this hypothesis is forthcoming.

Known and proven pathogenetic aspects

The familiar genesis of lichen planus is well known, but also - to some extent - contestable. A significant relation with certain HLA phenotypes is considered to be possible, but it cannot be proved in most of the cases. The association of lichenoid dermatoses with autoimmune diseases, such as multiple sclerosis, lupus erythematosus, vitiligo, ulcerous colitis, alopecia areata, primary biliary cirrhosis and diabetes mellitus has been described in the literature.[5,6]

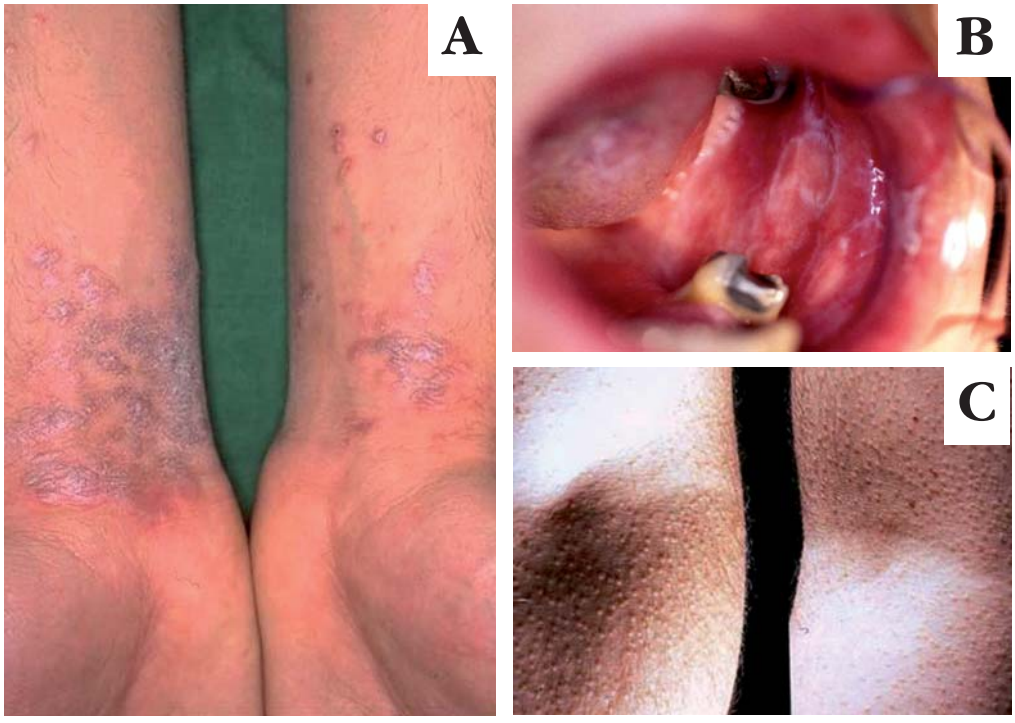

FIGURE 1: A. Typical picture of a patient suffering from lichen planus and the violet papules in the medial area of the distal sector of the forearms.The multi-medication of the patient and the consumption of different narcotic substances probably lies at the basis of the violation of the tissue homeostasis; **B.** Typical Wickham's striae in the area of the buccal mucosa of patient affected by Lichen planus mucosae oris and chronic Hepatitis B Infection. The multiple caries, the availability of tooth fillings and tooth protheses probably violate the integrity of the tissue homeostasis and play an important role during the initial phases of the disease; **C.** Follicular form of lichen planus (Lichen planus follicularis) arisen years after the typical picture with polygonal violet papules located at the places "preferred" by this disease

Their relation, however, with the molecular pathogenesis of lichen ruber is not fully recognized and studied. Diabetes mellitus has been described as a possible result or consequence of a viral infection with further *Antigen Mimicry*, and dermatomyositis (DM) – as a paraneoplastic disease - (the incidence of cancer in patients with DM is about 15-30 %), then, a different meaning must be given to the pathogenetic aspect of lichenoid dermatoses, too. [2,5]

The degree to which the violations of the tissue homeostasis may be viewed as the differentiating moment in the pathogenesis of lichen planus remains unclear. It is possible that the availability of a given genetic predisposition and the incorporation of a certain defined antigen may be considered to be the key factor in the pathogenesis of the disease. The reason for the phenotype manifestation may have a heterogeneous character. It may be due to the temporal weakening of the immune system within the framework of an ordinary infection but it may also be due to permanent disturbances touching upon T- or/and B- cellular immunity or the macrophage system.

All three main components of the immune system: phagocytosis, humoral and cell-mediated immunity are changed in patients with LRP.[6] Changes in the functional activity of phagocytes are manifested by a decreased phagocytic activity of the peripheral blood monocytes towards Staphylococcus aureus and increased production of active oxygen forms during phagocytosis. [6]

The invasive infections with *Staphylococcus* or *Streptococcus* species are often described as the reasons for immunological phenomena. *Post-streptococcus endocarditis*, *glomerulonephritis* and diseases of the joints have – in most cases – a bad prognosis and may be terminated as early as the starting phases of the infections via the implementation of various screening programs.

Changes in the humoral immunity consist in increased serum levels of IgG and IgA, and shifts in the cell-mediated immunity manifested by an increased count of cytotoxic CD4+ T lymphocytes and CD8+; and decreased functional activity of T cells recorded by the proliferative response to phytohaemagglutinin. [6]

Primary T-cellular infiltrates in patients with lichen planus are initially compounded by CD4+, and later, by CD8+ lymphocytes.[1,2] This succession is unclear and refers to changes of the immune response within the evolution of the disease. After the activation of the keratinocytes and the secretion of pro-inflammatory cytokines, the Langerhans's skin cells are activated. Activation of auto-reactive Th-1 T-lymphocytes, which secret interferon gamma (INF-γ), follows. INF-γ induces the pathologic expression of HLA DR, as well as ICAM 1 and FAS-L receptor in the keratinocytes themselves. HLA DR provides an additional capacity to the T-cellular mediated response. ICAM-1 is responsible for the connection with LFA-1 protein: a superficially located T-cellular protein. [2]

The final result of the above described interactions leads to activation of the apoptosis by means of auto-reactive T-cells and the expression of FAS-L on their surface. The perforins affecting the membrane also play an important role during the last part of the immunologic cascade. The previous mentioned interactions are considered to lead the pathogenesis of the disease, but they do not clarify the main pathogenetic cause.

The data taken from the anamnesis of patients with lichen planus or its subforms often contain information about serious psychic traumas recently suffered, as well as recent stress situations. Probably, these situations have been accompanied by alterations in the hormonal and also in the immunologic status. In accordance with that, the avoidance of the already mentioned stressing situations or the change of the location of the patients themselves leads, in some cases, to a full remission of the diseases.

Antigen Mimicry as a key factor in the lichen planus pathogenesis?

The concept of *Antigen Mimicry* means the activation of T- or B- cellular immunity with respect to certain cutaneous structures which are similar or analogous to exogenously introduced or secondarily and endogenously originated structures. [7] Different bacterial, viral and parasitic infections, as well as the prescribed medicamentous therapies lead to disorders in the internal homeostasis. [7]

It is generally presumed that they are also the main generators of the next immune response, which can be of different nature.

It is very interesting that drugs and bacterial or viral agents are able to provoke *Antigen Mimicry,* both direct or indirectly. [7]

In the case of viral hepatitis for example, a primary metaplasia of hepatocytes arises, leading to secondary T-cellular immune response. The T-lymphocytes which have crossly reacted attack the skin and they are in position to provoke a lichenoid reaction of different morphology. This is an eloquent example of *Antigen Mimicry* with a primary exogenous viral nature. It is interesting to see how vaccination against hepatitis B also provokes an immunologic response without inducing hepatocyte metaplasia.[5,8,9] This reveals a primary *Antigen Mimicry* of primary exogenous nature. Differences in virulence of hepatic viruses could determine the direct or indirect, secondarily induced *Antigen Mimicry*. When their qualities

or virulence are lower, but their immunogenity is not fully lost, the cutaneous reaction is accepted to be weaker.

The elimination of the respective focus, that is, bacterial, viral, parasitic or pharmacological, in most of cases should be possible and – hypothetically - should lead to a remission of the disease in a high percentage of the patients.[5]

An important factor at this stage should be the removal of the pathogenetic inductor and the application of an aggressive initial therapy. In case of a longer persistence of the inductors of the exogenous *Antigen Mimicry*, the probability of full remission, even when a therapy is applied, decreases. The persistence of T-cellular clones is difficult to control and the necessity of high doses of steroid therapy inevitably increases. In case the inductors of the *Antigen Mimicry* are not identified and are of bacterial, viral or parasitic nature, then the application of such a therapy should generally worsen the patient's prognosis after the dose is reduced. The persistence of the respective inductor is able to lead even to some irreversible morphologic modifications in the tissue homeostasis and, consequently, to an indirectly induced irreversible *Antigen Mimicry*.

For this reason, it is relevant to find not only hidden focuses but also the precise exploration of the significance between them and the patients suffering from lichenoid disorders.

Epitope Spreading and Lichen ruber planus?

The *Epitope Spreading* may be analyzed as a lateral effect of the *Antigen Mimicry* also, provided that it has not been recognized and eliminated as soon as possible. [7] The concept of *Epitope Spreading* is not a leading pathogenetic factor in lichen planus disease but a phenomenon which happens secondarily. *Epitope Spreading* means the development of immune responses with respect to epitopes which are different from the dominant target antigens and they do not react crossly with them. [7] The bullous lichen planus and some rare cases of overlap syndrome – lupus erythematosus/lichen planus or the so called vulvovaginal-gingival lichen planus are probably conditioned by this phenomenon. [10,11] The same is also valid for the overlap syndrome with bullous pemphigoid: lichen planus pemphigoides.[12] During the severe inflammatory reaction which occurs, new antigens become destroyed and "exposed", thus inducing B-cellular immune response.

The antigen specific autoimmune responses within the destructive inflammatory process may spread to different epitopes of one protein (*Intramolecular Epitope Spreading*) or epitopes of other structural proteins (*Intermolecular Epitope Spreading*). [7] Secondary epitopes, which are, understood, hidden epitopes (crypts), or the epitopes, where the immunologic reaction comes later.[7] The strongly immunogenic inductors of *Antigen Mimicry* are able to induce *Epitope Spreading* in a short time also. This fact would lead to a diagnostic mistake of overlap syndromes as well as difficulties in the initial diagnosis. [10,12]

The description of different antigenic determinants in literary data is of no interest to the clinicians because it is a consequence of already known concepts of antigen determinants and *Epitope Spreading*. What is important is the future identification and characterization of the inductors of the *Antigen Mimicry*.

The hypothesis of whether the infectious agents, such as Candida albicans, Proteus mirabilis, Klebsiella, etc. are the initiators of *Antigen Mimicry* and hence of LP heterogeneous clinical picture, remains open (Figure 2).

The interpretation and analysis of this observation is additionally complicated by the fact that most of the patients observed are polymorbid. Their systemic medication has been frequently changed and they are treated at least with five drugs. The role of these medicines as inductors of *Antigen Mimicry* is neither well known nor has it ever been studied.

In other dermatoses, such as bullous dermatoses, for instance, the presence of T-cellular infiltrates in the skin is undervalued and it is considered that they have a secondary importance. Theoretically, they could be analyzed as an initial form of *Antigen mimicry*, where an *Epitope Spreading* and secondary formation of antigens take place. Nevertheless the passive transfer of patients suffering from bullous dermatoses may induce blister formation, which does not serve to prove that it is precisely they which are the main pathogenetic inductor. [7]

Clinician's influence on *Antigen Mimicry* and on the evolution of lichen planus

The persistence of exogenous reversible generators of *Antigen Mimicry* and the lack of adequate initial intensive, clinically oriented symptomatic therapy are able to induce the transfer of the reversible form of *Antigen Mimicry* to irreversible. [7] Frequently, at some highly reputable dermatologic clinics in Europe, adequate therapy without the elimination of the pathogenetic inductor is applied. In practice efforts are directed to focuses of different nature, and the patient's medication is not changed because of the fact that the respective interaction has not been described in literature. This leads to recurrences after some periods of time or in the case of reduction of the immunosuppressive therapy.

In the multidisciplinary clarification of the real

status of the patients, frequently asymptomatic infections such as vaginal candidosis, urogenital infections by Escherichia coli, Klebsiella, Enterobacter are found, as well as chronic persistent bronchitis where gramnegative microorganisms prevail. Their role as a possible cause for the development of the heterogenic clinical picture and of recurrences also has always been devaluated and often rejected (Figure 2). The recommendations given to the patients are incorrect and most frequently are reduced to further ambulatory presentation and clarification of the diagnostic and therapeutic algorithm. The study of the significance of these associations is frequently rejected by the dermatologists themselves.

The study of single multimorbid patients suffering from grave forms of Lichen planus at several dermatologic clinics showed an interesting consecution: that in the cases of persistence of different infectious focuses, irrespective of whether fungal, bacterial or viral nature - the clinical picture of the Lichen planus changes with time to more serious forms (the serious form designates patients with exanthematous lichen planus, ulcerative lichen planus, keratosis lichenoides chronica, complete or incomplete form of Graham-Lassueur-Little-Piccardi-Syndrome) (Figure 2). These changes concern the transitions from located forms, into disseminated or ulcerative forms (Figure 2). It seems that the number of focuses and the number of systemic medication in patients suffering from ulcerative, generalized and complete forms or sub-forms of Graham-Lassueur-Little-Piccardi-Syndrome, Keratosis lichenoides chronica, overlap forms between lichen planus/lupus erythematosus and vulvovaginal-gingival lichen planus forms is higher (Figure 2). [10,11,12]

The above described forms of lichen planus are hard to impact therapeutically and they are frequently resistant to therapies by retinoids corticosteroids, and systematic PUVA. Some patients (having a typical

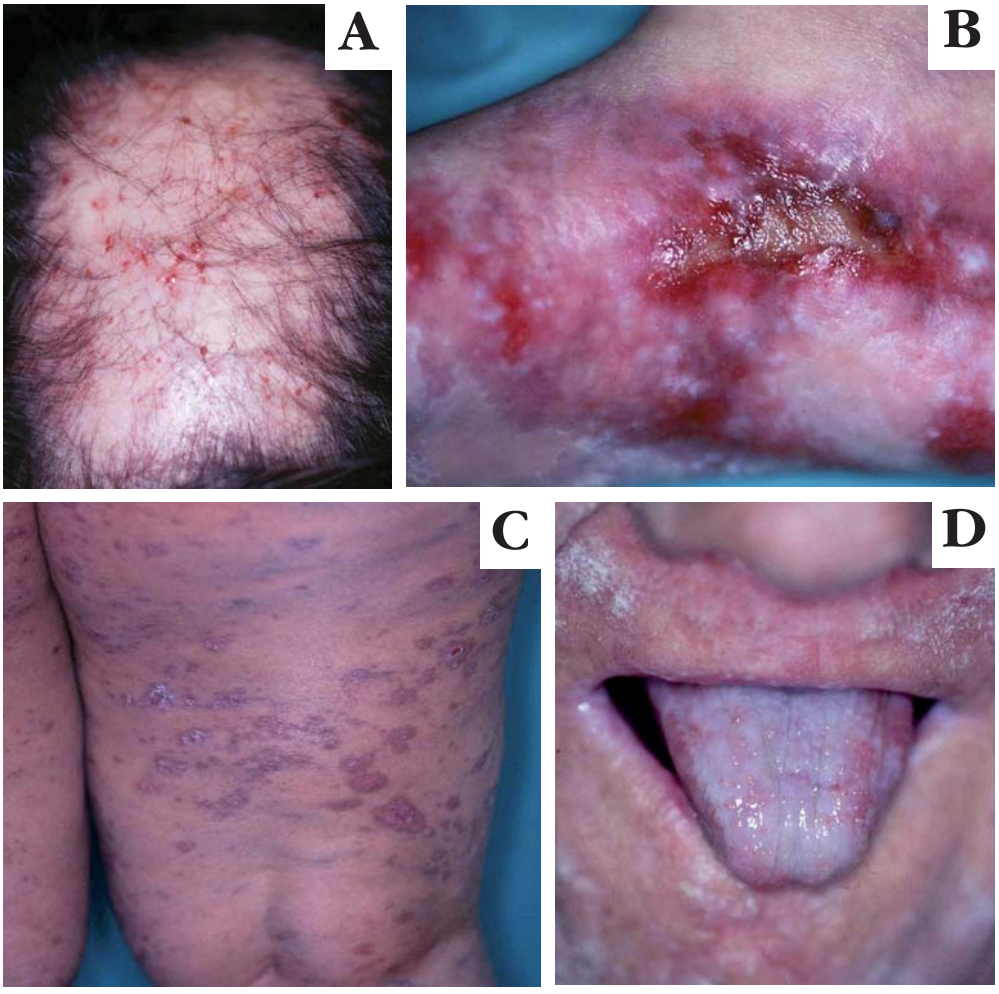

Figure 2: A. A patient suffering from secondarily generated form of Graham Lassueur Little Piccardi Syndrome. Cicatrizing alopecia with parieto-occipital localization. The multimedication of patient with this grave form of lichen planus, as well as the frequent infections, probably are the possible cause of spreading of the immune response to different cutaneous structural antigens; **B.** Ulcerative grave form of patient with Graham Lassueur Piccardi Little syndrome. **C.** Lichen planus exanthematicus, in a female patient who further develops the rare form of Graham Lassueur Little Piccardi Syndrome. Possible cause of spreading of the immune response: urogenital infections with E. Coli, Klebsiella, chronic bronchitis, multi-medication, gastroenteritis, intestinal recurring candidosis; **D.** Lichenoid lesions in the area of the tongue in patient suffering from the rare disease Keratosis lichenoides chronica, which is perceived by several authors as a variant of Lichen ruber

clinical form of Lichen planus and polygonal violet papules in the area of the superior and inferior extremities), during the evolution of the disease can develop a form of GLPLS or KLC (Keratosis lichenoides chronica), which is often resistant to most of the therapeutic agents (Figure 2).

In patients suffering from common psoriasis, particularly psoriasis guttata – the clinical form is an alarming sign of the presence of a certain focus, generally it is chronic sinusitis, tonsillitis or dental abscess. Analogous observation is made in the cases of patients suffering from chronic recurrent urticaria. The application of explorative programs leads in the majority of the cases to the elimination of the focus and to the improvement of the clinic picture. Analogous symptoms are observed when the medicines applied are changed. Unfortunately, such programs are not applied to lichenoid dermatoses, or, if held, they do not coincide with the standard diagnostic procedure.

The inopportune suspension of therapy and/or reduction of the dose in case of improvement of the clinical picture of patients suffering from lichen planus is probably able to lead to intensification of the activity of the immune cascades and in this way to indirectly potentiate the inductors of the exogenic antigenic determinants, which are responsible for the induction of *Antigen Mimicry* and *Epitope Spreading.* One of the main tasks of the clinical dermatologist is to establish precisely and eliminate the exogenic antigenic determinants, responsible for the *Antigen Mimicry* and *Epitope Spreading*.

These dogmas are often ignored in dermatologic practices. The exact knowledge and description of the above-mentioned units could lead to the introduction of adequate preventive measures and drastic morbidity decrease of lichenoid subtypes, induced by *Antigen Mimicry*, followed by *Epitope Spreading*.

CONCLUSIONS

1) During our most general observations we came to the conclusion that the serious, generalized lichenoid forms, or the transition from normal to ulcerative, exanthematic or cicatrizing form of lichen planus, the so called Graham Lassueur Little Piccardi Syndrome, or Keratosis lichenoides chronica, are accompanied by a growth of the number of the found focuses in patients who have been clinically observed.[2,4]

Other literary data also indicates that a similar explanation of the pathogenesis is possible.[1]

2) It is also important to register the number of the respective focuses, the activity of the inflammation markers and the clinical picture of the patients. In literature such data is not easy to find. The testing of the immunogenity of bacteria, viruses, and parasites under conditions *in vitro* can provide some information about the extent to which the immune cascade has been activated. The final objectives of this cascade are, however, always different structures, with dermal or epidermal location and the succession of the attacks against them, or impacts of them is unclear.

3) It is known that the elimination of the focuses and the change of the medicines, as a possible "violator" of tissue homeostasis could, hypothetically, lead to a full remission, therefore this must become a task of primary importance for the clinic dermatologist.

The careful filing and study of the evolution of the lichen planus and its subforms in a greater number of patients and for a longer period of time can give and make possible a more precise explanation of the hypothesis we have exposed.

4) The inopportune suspension of therapy and/or reduction of the dose in case of improvement of the clinical picture of patients suffering from lichen planus is probably able to lead to intensification of the activity of the immune cascades and in this way to indirectly potentiate the inductors of the exogen antigen determinants, which are responsible for the induction of *Antigen Mimicry* and *Epitope Spreading.*[2] One of the main tasks of the clinical dermatologist is to establish precisely and eliminate the exogen antigen determinants responsible for the *Antigenic Mimicry* and *Epitope Spreading*.

These dogmas are often ignored in dermatological practices. The exact knowledge and description of the above-mentioned units could lead to the introduction of adequate preventive measures and drastic morbidity decrease of lichenoid subtypes, induced by *Antigen Mimicry*.

5) It can be presumed that the early dermatologic prevention and screening programs applied to patients suffering from lichenoid dermatoses can contribute much more to the patient's health than the determination of the immunologic cascades in the blood and/or apoptotic markers, for example, in the lesional skin. Both of these should be defined as a consequence or the final result of the *Antigen Mimicry* or *Epitope Spreading*, and not as a direct cause of lichenoid diseases. ❑

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ENDEREÇO PARA CORRESPONDÊNCIA / MAILING ADDRESS:
Georgi Tchernev
MVZ Kirchheim GmbH, Department of Dermatology, Venereology and Dermatosurgery, Steingaustr. 13, 73230 Kirchheim unter Teck, Germany
Tel: 0049 7021 9300220
Email: georgi_tchernev@yahoo.de

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