

# ETIOPATHOGENIC AND CLINICAL CORRELATIONS BETWEEN LICHEN PLANUS AND ASSOCIATED DISEASES

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## Summary

**Background:** Lichen planus (LP) is a chronic and idiopathic inflammatory disease. The association between lichen planus and hepatitis or various autoimmune diseases has been reported, but nationwide studies of the relationship of lichen planus with associated diseases have demonstrated contradicting results.

**Objectives:** Our study aims to investigate the correlation between lichen planus and associated diseases.

**Material and method:** Our study was performed on 84 patients diagnosed with lichen planus. Data were obtained from the 'Sf. Spiridon' Clinic of Dermatology, Iasi, Romania from 2015 to 2017.

The study of etiological circumstances was based on anamnesis, general physical examination, clinical form of disease and interpretation of paraclinical results. The positive diagnosis was based on clinical appearance, subjective symptoms and histopathological results.

**Results:** Lichen planus had an incidence of 2% among dermatological conditions. The sex distribution revealed a female predominance (60,7%). The median age was around 60 years. The prevalence of liver damage in patients with LP was 22,61%, from which 73,68% had chronic viral infection. Among patients with LP, there were significant associations with autoimmune thyroiditis, vitiligo, rheumatoid arthritis and alopecia areata. On gender-stratified analyses, the association with autoimmune diseases was significant only in female patients (94,11%). Most cases with LP and autoimmune diseases have also associated hepatitis C. In terms of correlation between clinical forms and etiology, eruptive LP was commonly associated with metabolic disorders, while localised LP was more frequently associated with neuropsychiatric disorders.

**Conclusions:** Lichen planus is associated with various seemingly unrelated diseases. Physicians who care for patients with lichen planus should consider screening patients with lichen planus for autoimmune, metabolic and neuropsychiatric disorders. Regarding the etiology of lichen planus, our study supports the immunological hypothesis.

**Key words:** lichen planus, etiology, hepatitis C, autoimmune diseases.

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## Introduction

Lichen planus is a chronic inflammatory disorder, idiopathic, self-limited, that sometimes can relapse, and which affects the skin, mucosas, hair follicles and nails. The most common symptom is the rash that consists of firm,

reddish-purple bumps that are most likely to have mild pruritus.

This disorder does not have racial predisposition and can affect both genders. The adult incidence is around 0,2–1% and in children is 1-4% [11]. Approximately 75% of the patients develop oral mucosal lesions.

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It's a disease of the middle-aged, with onset in the fifth to sixth decades of life and can also have familial character.

### *Etiopathogeny*

Clinical observations have suggested a relationship between exposure to some exogenous agents (viruses, drugs, allergens) and the development of lichen planus.

Many risk factors have been incriminated, such as:

*Infectious factor* – Of the many potential exogenous factors, a particular contribution was attributed to the possible role of viruses, especially hepatitis C virus. In multiple case-control studies, HCV prevalence (3.5–38%) was 2 to 13.5 times higher in patients with lichen planus than in control groups.

Among the different types of lichen planus, the oral form is the most common in HCV infection [1]. HCV-RNA was identified by PCR in 93% of oral lichen planus lesions, suggesting HCV replication in lichen planus lesions, but these PCR results were not confirmed by other studies [17].

In patients receiving anti-HCV therapy, initially interferon and ribavirin, subsequently protease and polymerase inhibitors, the effects on the cutaneous-mucosal lesions of lichen planus varied. In some cases, lesions have improved, while other patients have experienced an exacerbation of the disease. [18]

In addition, there were reports of lichen planus occurring in children 40 days after the hepatitis B vaccination.

There have been reports of cases of lichen planus that appeared on skin areas that were recently affected by herpes simplex virus or varicella-zoster virus. Also, a link between oral lichen planus and human papillomavirus was brought into attention, due to the fact that CD8+ T lymphocyte clones specific for HPV type 16 were identified in the oral lesions. [24]

Among the aforementioned infections affecting lichen planus, *Helicobacter pylori* has recently been proposed as an important etiologic factor. During the evolution of a gastritis or peptic ulcer, *Helicobacter pylori* induces interleukin 1 $\beta$  și TG F $\beta$ , proinflammatory cytokines that are also involved in the pathogeny of lichen

planus. *Helicobacter pylori* eradication could be followed by alleviated skin lesions. [12]

*Genetic predisposition* – familial lichen planus has been reported with a incidence that ranges from 1% to 15% for all types of lichen planus. Genetic predisposition can influence the cutaneous-mucous reactivity towards the etiological factors. [23]

*Neuropsychic factor* – it has been noticed that oral lichen planus often occurs in patients who suffer from anxiety or depressive symptoms, being triggered by a psychoaffective shock. Afterwards, the symptoms are aggravated by stress, trauma and local factors. Lichen planus is frequently associated with peripheral neuritis, syringomyelia, bulbar palsy and paravertebral tumors. Sometimes, the lesions are following the course of a nerve (zosteriform lichen planus).

*Drugs* – many drugs have been involved in the development of lichenoid drug eruption with a cutaneous or mucosal involvement (especially the oral mucosa) [3]. The onset may occur months to years after the patient started on the offending drug, in contrast to the typically shorter latencies seen with other types of drug reactions [6]. Among the most commonly involved drugs are ACE inhibitors, gold salts, antimalarials and thiazide diuretics.

*Metabolic factor* – association of diabetes mellitus [2] and dyslipidemia [16].

*Chronic graft-versus-host disease* – may emerge after a quiescent interval of around four months, but it can also appear after 40 days. It involves donor antihost-specific T cells and autoimmunity.

*Cellular and molecular immunologic mechanisms* are essential in the development of this particular disease. First of all, there is an increase of Langerhans cells in epidermis, followed by superficial perivascular inflammatory infiltrate, containing lymphocytes and histiocytes.

There is a T cell-mediated autoimmune reaction against basal epithelial keratinocytes, that are exposed to potentially cell death-inducing factors, produced by the cells of the inflammatory infiltrate (cytokines). Lymphocytes from the inflammatory infiltrate recognise a specific antigen from the involved keratinocytes associated with major histocompatibility complex class I. The antigen's nature is unknown. Perhaps it is a autoreactive peptide, an exo-

genous antigen such as an altered protein, a drug, an allergen or an infectious agent. [23]

Immunofluorescence studies suggest the involvement of the humoral immunity, taking into consideration the fact that colloid body depositions of IgM (also, occasionally IgG and IgA) were discovered.

What causes most cases of lichen planus remains unclear. One theory is that lichen planus is an autoimmune disease, meaning the person's immune system reacts as though the skin and other parts of the body are foreign. This theory is backed-up by the association of lichen planus with other autoimmune diseases, such as: primary biliary cirrhosis, active chronic hepatitis, Gougerot-Sjögren syndrome, dermatomyositis, systemic lupus erythematosus, morphea, bullous pemphigoid, vitiligo, alopecia areata, autoimmune thyroiditis, ulcerative hemorrhagic rectocolitis, myasthenia gravis, Biermer's anemia, Addison's disease and others. Bullous lichen planus can coexist with cancer.

## Material and method

The study was conducted in the Dermatology Clinic of the Emergency Clinical Hospital "Sf. Spiridon" from Iasi between 2015 and 2017 on 84 patients hospitalized with lichen planus.

Patients were selected on the most rigorous clinical and laboratory criteria; the histopathological examination was performed in most patients by analysis of the biopsy fragment.

The study of etiological circumstances was based on anamnesis, general clinical examination, clinical form of disease and interpretation of paraclinical results.

Discussion of the results allowed us to make some differentiated etiopathogenic considerations according to some important aspects.

The correlation of all these changes has attracted our attention to the dominant intervention of the immunological mechanisms in the maintenance of the cutaneous pathological process.

The positive diagnosis was based on clinical appearance, subjective symptoms and histopathological examination.

The local clinical examination was the way to differentiate the clinical forms of lichen planus.

The histopathological examination was performed in most patients, confirming the diagnosis of lichen planus.

## Results and discussions

The lichen planus accounted for 2% of all dermatological pathologies that required hospitalization at the Dermatology Clinic of the Emergency Clinical Hospital "Sf. Spiridon" in Iasi between 2015 and 2017.

The gender distribution of the lichen planus revealed female sex predominance of 60.7, compared with 39.28 men, with a gender ratio of 1: 1.5. Of all cases of oral lichen, 75% were women.

In terms of age group distribution, most cases fell into the 5-6 decades of life. Patient had ages ranging from 12 to 90 years old, with an average onset age of 60 years old.

The prevalence of the disease in children was 4.76%, slightly higher than the prevalence reported in the literature (1–4%). We did not identify any cases of family aggregation.

Mucosal lesions usually accompany the cutaneous lichen planus. The oral mucosa is preferentially interested (30–70% of cases) [9]. Within the studied group, 16.66% of the cases presented mucosal lesions associated with cutaneous lesions, the oral mucosa being mostly affected. Most common, the lesions were located in the jugal mucosa. Mucosal lesions in absence of cutaneous lesions were present at a rate of 13.09%.

On the genital mucosa we identified lichen lesions in 13.09% of cases. Vulvar localization was the most common. The vulvar lichen planus was exclusively found in adults.

According to statistics, the lichen affected nails in 10% of cases. [10] Within the study group, 3.75% of the cases associated nail lesions. We also identified some cases of cutaneous lichen planus with follicular lesions (6.25%).

Most patients with cutaneous lichen planus (97.5%) accused high-pruritus, which made it easier to establish a positive diagnosis.

The unfavorable disease progression with frequent recurrences was present in 37.5% of cases, although the lichen planus is known to be an autoimmune disease.

### *Infectious factor*

The likening of the lichen planus and the hepatitis virus infection was first reported by Rebola in 1978, and since then numerous studies have been carried out on this subject.

The results obtained in attempting to associate lichen planus lesions with the presence of viral markers of hepatitis virus infection were contradictory, ranging from 1–2% to 70–80%, largely depending on the geographical area in which they were performed [4] [19].

There seems to be an increased prevalence of this association in Southern Europe and the Middle East, while in the UK and the North American population, the correlation is rather frequent with primitive biliary cirrhosis.

By clinically, statistically and investigatively studying the 15 cases of lichen planus associated with viral diseases, we allow some commentary on the etiopathogenicity, the clinical and evolutive aspects, as well as the association of this disease with one of the viral disorders.

In recent years, studies from Taiwan, Brazil, Israel, Saudi Arabia, Turkey, Iran and Thailand have revealed a statistically significant association between lichen planus and HVC infection. However, seroprevalence of hepatitis C in patients with lichen planus in the group we studied was 11.9% (Fig. 1).

The association with viral etiology disorders was present in 17.85% of all cases. The predominance of association with chronic hepatitis C virus (66.66%) was seen in the group of patients with lichen planus associated with viral etiology (fig. 2).

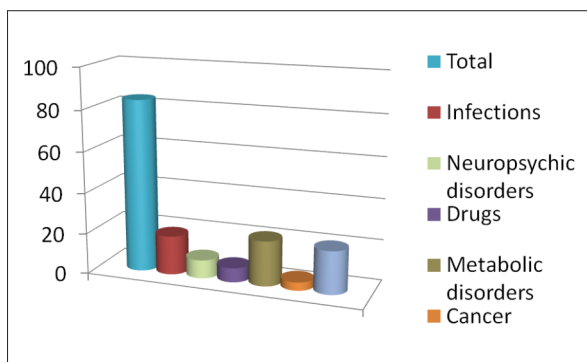


Fig. 1 Prevalence of diseases commonly associated with lichen planus in the studied group.

Studies have reported the existence of liver dysfunction in the patients even in the absence of symptomatic hepatopathy, this association being subsequently enrolled in lichen planus-hepatitis syndrome.

The role of viral hepatitis B in the occurrence of this syndrome is supported by the following: presence of markers of hepatitis B virus infection in 21% of patients with lichen planus; research by a group of researchers in 1990 revealed a double statistical risk of the occurrence of the lichen planus on Ag HBs carriers; the occurrence of basal anti-cellular antibodies of non-keratinized epithelites in hepatitis B-induced liver diseases; signs of lichen planus-like rash after HBV vaccination, or after human anti-HBV immunoglobulins.

Although some cases of lichen have been described in children about 40 days after the second vaccine injection against hepatitis B, we have not identified any such association. Instead, we identified a few cases with a lichen planus associated with chronic hepatitis with HBV (fig. 2).

In 22.61% of cases of lichen planus there were disruptions in liver function. If for the correlation between lichen skin lesions and the presence of hepatic impairment, general opinions are divided, most authors agree on the association between the lichen planus of the oral mucosa and the hepatitis virus infection, especially HCV [7].

This interrelation was especially demonstrated for the erosive form of the lichen planus of the oral mucosa, which may also be associated with gastritis with hypochlorite, chronic thyroiditis. [13]

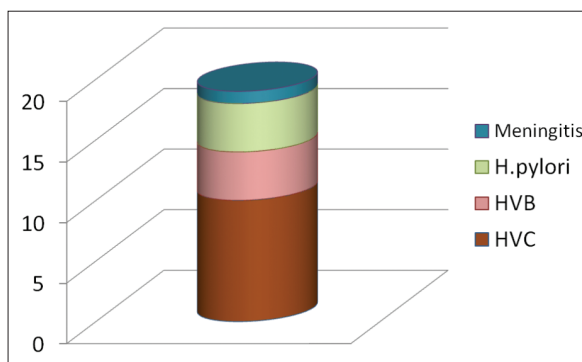


Fig. 2 Infectious etiology associated with lichen planus in the studied group.

Knowledge of etiological factors is important for preventing disease progression and for treatment.

#### *Autoimmune diseases associated with lichen planus*

Cellular immunological mechanisms are essential for the onset of this disease. Initially, we are witnessing an increase in the number of Langerhans cells in the epidermis, followed by a perivascular superficial infiltrate consisting of lymphocytes and histiocytes.

In the lichen planus there is a T lymphocyte cytotoxic reaction, directed against epithelial keratinocytes. Lymphocytes from the infiltrate present in the lichen planus are CD8 + cytotoxic and CD45RO + (memory) and express the  $\alpha\beta$ TCR (T cell receptor). They recognize a specific antigen associated with the major class I histocompatibility complex of the keratinocytes involved. The nature of the antigen is unknown. It may be a self-reactive peptide, an exogenous antigen such as an altered protein, a drug, a contact allergen or an infectious agent.

Immunofluorescence studies reveal the implication of humoral immunity, with globular deposits of IgM (occasionally IgG and IgA) corresponding to colloid corps [21]. Also in support of the intervention of an autoimmune mechanism comes the observation that reveals a high serum titre of autoantibodies anti-desmoglein 1 and 3 in patients with oral erosive lichen planus, compared to subjects with reticular lichen planus [5]. But of course, this increase of the autoantibodies may be due to the erosive nature of the lichen planus.

Other research shows that serum TNF $\alpha$  is significantly increased in patients with lichen planus. Also, the increase in MMP-1 and 3 metalloproteinases has been noted in patients with oral erosive lichen planus, thus intervening in basal membrane damage and in induction of apoptosis. [22]

The immunological hypothesis is also supported by the possibility of association of lichen with autoimmune diseases, such as: primitive biliary cirrhosis, chronic active hepatitis, Gougerot-Sjögren syndrome, dermatomyositis, erythematosus lupus, morphea, pemphigoid bullous eruptions, vitiligo, alopecia areata, autoimmune thyroid disorders, ulcer

rectocolitis haemorrhagic, myasthenia gravis, Biermer anemia, Addison's disease, etc. [8]

We have identified an association between lichen planus and autoimmune diseases in 25% of cases (Fig. 1), a high value compared to recent study data that suggests that lichen planus is associated only occasionally with autoimmune conditions, which supports the hypothesis of autoimmune etiopathogenesis.

Regarding age distribution of lichen planus and associated autoimmune diseases, there is an increased prevalence in decades 5 and 6 of life, with the net predominance of female gender (fig. 3).

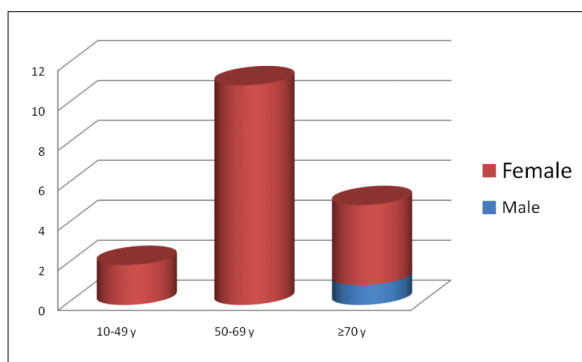


Fig. 3 Age group distribution of cases of lichen planus and associated autoimmune diseases

The study of the incidence of immune manifestations associated with lichen planus according to the clinical form of the disease is illustrated in table 1.

We see the association of autoimmune diseases in all forms of lichen planus. The incidence of immune manifestations in the cutaneous lichen planus has been much higher. It results from our study that such manifestations are rarely associated with the oral erosive lichen planus.

In the oral erosive lichen planus, the incidence of immune manifestations over the oral reticular lichen planus was higher.

The nature of the immune manifestations included in the order of frequency: 37.5% thyroid involvement, 20.83% vitiligo, 12.5% rheumatoid arthritis, 12.5% alopecia areata/ otitis, systemic scleroderma 8.33%, morphea 4.16% and Duhring-Brocq dermatitis 4.16%.



The results of our study are consistent with some literature data confirming the existence of autoimmune manifestations within the lichen planus [14].

What we have noted from the group of diseases associated with cutaneous lichen planus was the prevalence of thyroid involvement (fig. 4).

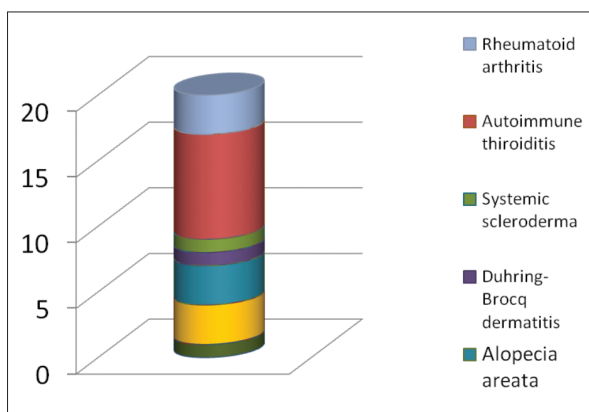


Fig. 4 Autoimmune diseases associated with lichen planus in the studied group.

Since the frequent association of autoimmune thyroid diseases with HLA-B5 antigens is known, and given the results of our study that noted the predominant presence of similar immune diseases, we could suggest that cutaneous lichen has a genetic predisposition that may be associated with HLA-B5, but to better define this relationship, a larger number of patients with

cutaneous lichen planus and an ethnic comparison of the normal control population is needed [20].

It is equally true that not all of the concomitant autoimmune lichen planus have established HLA associations. Thus, we may alternatively admit that they may result from a non-specific, but high immunoreactivity to intrinsic or extrinsic antigens associated with the HLA-B5 positivity.

In the associated lichen planus and viral etiology, the infectious agent may contribute to these manifestations by inducing activation of cytotoxic T lymphocytes directed against epithelial keratinocytes.

These findings suggest that chronic viral infection may facilitate the expression of autoimmune diseases. The presence of concomitant autoimmune diseases with chronic viral hepatitis that has been shown to be common in HCV infection (table 2 and fig. 5) has greater significance in highlighting the induction of the immunological process by the virus than in the presence of non-organ specific antibodies.

#### *Correlations between clinical forms of disease and etiology.*

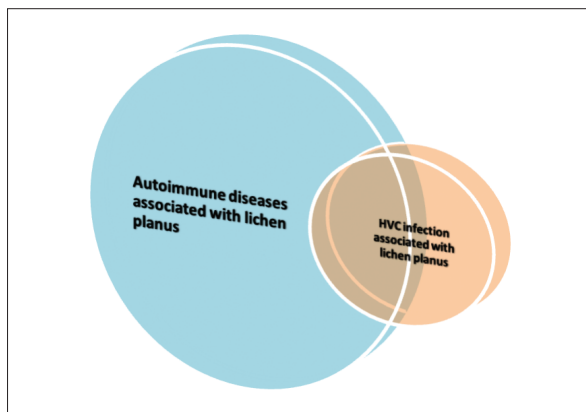
The study of the incidence of affections commonly associated with lichen planus, depending on the clinical form of the disease, is illustrated in table 3.

**Table 1. Incidence of immune manifestations associated with lichen planus according to the clinical form of the disease**

	LP Cutaneous lichen planus		Oral reticular lichen planus		Oral erosive lichen planus		Genital erosive lichen planus	
	Female	Male	Female	Male	Female	Male	Female	Male
Morphea	1	-	-	-	-	-	-	-
Vitiligo	2	-	1	-	1	-	1	-
Alopecia areata / totalis	3	-	-	-	-	-	-	-
Thyroid damage	7	1	-	1	-	-	-	-
Rheumatoid arthritis	2	-	-	1	-	-	-	-
Herpetiform dermatitis Duhring-Brocq	1	-	-	-	-	-	-	-
Systemic sclerosis	1	-	-	-	1	-	-	-

**Table 2. Incidence of immune manifestations associated with lichen planus and chronic viral hepatitis**

	HVC		HVB	
	Female	Male	Female	Male
Morphea	-		-	
Vitiligo	2	-	1	-
Alopecia areata/totalis	1	-	-	
Thyroid damage	3	-	-	
Rheumatoid arthritis	-		-	
Duhring-Brocq herpetiform dermatitis	1	-	-	
Systemic scleroderma	-		-	

*Fig. 5 Prevalence of lichen planus associated with autoimmune diseases and HVC infection.*

The association of lichen planus in all clinical forms with chronic HCV viral hepatitis, neuropsychiatric disorders, metabolic disorders and autoimmune diseases is observed. The greater incidence of metabolic damage associated with lichen planus, compared with the rest of the diseases, is noted. Thus, metabolic disorders are frequently associated with lichen planus, especially with eruptive form, consistent with recent studies that claim their association is common. It is important to note the particular importance of the metabolic factor in the etiology and evolution of the eruptive lichen planus.

What we have noticed in the group of diseases associated with cutaneous lichen planus was the prevalence of autoimmune diseases. Thus, is important to investigate an eventual

**Table 3. Incidence of affections commonly associated with lichen planus, depending on the clinical form of the disease**

	Eruptive lichen planus	Cutaneous lichen planus	Oral erosive lichen planus	Oral reticular lichen planus	Vulvar erosive lichen planus
HVC	3	4	4	1	1
HVB	1	3	1	1	-
Liver dysfunction	3	1	1	-	-
H. pylori	2	2	-	1	1
Meningitis	-	1	-	-	-
Neuropsychic	1	6	1	2	1
Drugs	3	3	1	2	-
Metabolic disorder	10	7	4	3	3
Autoimmune	4	14	3	1	1
Cancer	-	3	-	-	-

autoimmune pathology in cutaneous clinical forms.

The results of our study are not in line with the literature that chronic HCV viral hepatitis is associated more frequently with oral erosive lichen planus than with other clinical forms of the disease. [15] Within the study group, HCV infection was also present in buccal erosive lichen and cutaneous lichen.

Although, over time, it has been observed that oral lichen planus occurs more often in anxious, depressed patients, within the studied group, neuropsychiatric disorders, especially depressive-type organic disorder, are associated more frequently with cutaneous lichen.

According to the literature, hypertrophic lichen planus is associated with chronic venous insufficiency in most cases (80%).

The etiopathogenic mechanisms of lichen planus are not fully elucidated. In addition, the data obtained in our study is partially contradictory to literature data. These findings underscore the importance of additional studies based on lichen planus etiopathogenesis.

## Conclusions

From the summary of the exposed data and those obtained from the study carried out on the selected lot, some conclusions can be drawn, both theoretically and practically:

The results of the study highlight the association of lichen planus with systemic disorders, as well as their significance in the pathogenesis of the disease. Through the observations made, we have put arguments in support of the immunological mechanisms correlated with the etiology of lichen planus. We considered that the study of clinical forms is important for differential diagnosis, prognosis and treatment of lichen planus.

The etiological circumstances evidenced by anamnesis, by determining the markers of viral infection in the serum and immunological disorder are necessary for the differentiation of the etiological forms of lichen planus, for the prevention of complications and for the establishment of the appropriate treatment.

Lichen planus is a chronic cutaneous-mucosal dermatosis of adulthood, with unknown cause, clinically manifested by a typical monomorphic

eruption and characteristic localization. Known from the time of Hippocrates, the lichen planus has remained permanently in the current due to its still unknown etiopathogenicity, although many etiopathogenic theories have been issued.

By investigating 84 cases of lichen planus we noticed that the disease affects both genders but with a higher incidence in women (60.7%) compared to males (39.28%). Distribution by age group shows a predominance of 5-6 decades of life.

The lesion topography and clinical appearance are able to pinpoint the skin pathogenic phenomenon and provide data for disease progression. The most common clinical form consisted of a typical rash of red-violet, polygonal papules, brilliant in indirect light, covered by a discreet swab, disseminated on the anterior face of the forearms, on the incisor, paravertebral, intense pruritic. The disease has chronic evolution with longer or shorter periods of remission, depending on the treatment applied, the psychoemotional status of the patient and possible comorbidities.

Risk factors intervening in the onset of the disease, identified in the group of patients studied by us are the following, in frequency order: association with metabolic diseases, autoimmune diseases, chronic viral hepatitis, neuropsychotic factor, drugs, *Helicobacter pylori* infection and neoplasia.

By studying the clinical manifestations and correlating them with some clinical and biological parameters, we found that the severity of the clinical manifestations is linearly dependent on the psychoemotional stress and the local traumas, and the presence of the advanced age is a factor of gravity.

From the literature and the data obtained by us, the importance of additional studies on the basis of the etiopathogenesis of the lichen planus is important. The medical, economic and social implications of the increase in the number of patients with lichen planus in recent years are the premises that must sustain medical and educational measures to prevent relapses and complications of this disease.



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Conflict of interest  
NONE DECLARED

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