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Humoral immunological parameters in Italian patients with oral lichen planus

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SUMMARY

Serum humoral immunological parameters were determined in 25 patients with atrophic-erosive forms of oral lichen planus (OLP) (Group 1), in 28 patients with reticular-plaque-like lesions of OLP (Group 2) and in 21 healthy patients without oral lesions (Group 3). Comparing patients affected by atrophic-erosive forms of OLP (Group 1) with normal controls (Group 3), increased levels of serum IgG approaching the statistical significance were found (Kruskal-Wallis test p=0.0572). It was also found a significantly higher value of kappa (Kruskal-Wallis test p=0.0017; Mann-Whitney test with Bonferroni's correction p<0.001) and lambda (Kruskal-Wallis test p=0.0346; Mann-Whitney test with Bonferroni's correction p=0.013) light chains in patients with atrophic-erosive OLP (Group 1) as compared with normal controls (Group 3). However these higher levels were probably caused by strong prevalence of chronic liver diseases (40%), in patients with atrophic-erosive variety of OLP. No one of these patients was affected by autoimmune liver disease. No differences were noted between atrophic-erosive OLP (Group 1) and hyperkeratosic OLP (Group 2). This study does not confirm the suggestion that patients with OLP may have a generalized immunologic disorder and it also add some evidences that the role of humoral immunity in the pathogenesis of OLP is probably secondary to the cell-mediated reaction against basal keratinocytes.

KEY WORDS:

Lichen planus, oral, immunoglobulins, autoimmunity

RÉSUMÉ

Les principaux aspects de l'immunologie humorale ont été évalués dans deux groupes de malades porteur d'un lichen plan de la muqueuse buccale, 25 à formes atrophiques-érosives (Groupe 1), 28 à formes en réseaux ou en plaques blanches (Groupe 2), et chez 21 sujets sains. Au terme de cette étude les différences les plus remarquables sont les suivantes: le taux des IgG sériques est nettement plus élevé chez les sujets du Groupe 1 ce qui est presque significatif par rapport au Groupe 3 (p=0.0577). L'analyse statistique a surtout révélé des différences significatives entre le Groupe 1 et le Groupe 3 (contrôle) en ce qui concerne les taux sériques des chaînes Kappa (Kruskal-Wallis test p=0.0017; Mann-Whitney test corrigé par Bonferroni

p < 0.001) et des chaînes Lambda (Kruskal-Wallis test p = 0.0346; Mann-Whitney test corrigé par Bonferroni p = 0.013). Aucune autre différence significative entre les trois groupes n'a été observée. Nous pensons que ces résultats sont probablement dus à la présence d'une hépatopathie chronique non auto-immune qui a été diagnostiquée dans 40 % des cas du Groupe 1. Cette étude ne confirme donc pas la thèse selon laquelle les sujets atteints de lichen plan buccal pourraient avoir une défaillance de l'immunité humorale. Elle nous permet de penser que le rôle de cette dernière dans la pathogénèse de la maladie est probablement secondaire à la réaction cellulaire dirigée contre les kératinocytes.

MOTS CLÉS:
Lichen plan, bouche, immunoglobulines, auto-immunité

INTRODUCTION

One of the most controversial topic on oral lichen planus (OLP) is if it is maybe considered or not as an autoimmune disorder. Data which agree with this hyphotesis seem to be the chronic course, female patients prevalence and the association with well-known autoimmune diseases (Tan, 1974; Aronson et al., 1978; Graham-Brown et al., 1982; Cusano and Errico, 1984). Moreover, a recent study has shown a depressed-concavalin-A induced suppressor activity of pheripheral blood mononuclear cells in OLP patients and these evidences would seem to suggest that a reduced self-tolerance could be involved in the pathogenesis of OLP (Sugerman et al., 1992). Considering that a defect in T-suppressor circuits is involved in the pathogenesis of autoimmune diseases, it's possible that exists an autoimmune component in the pathogenesis of OLP.

On the other hand, autoimmune pathologies traditionally are associated with a hypergammaglobulinaemia and serum autoantibodies (Scully and El-Kom, 1985). Several investigations have shown increased levels of immunoglobulins (especially IgG) in erosive OLP (Mahood, 1981; Schroeder, 1981; Sklavounou et al., 1983; Lundstrom, 1984; Sun and Liang, 1986) but other authors have not found significant alterations in serum concentration of any immunoglobulins in patients with OLP (Griffith et al., 1974; Scully, 1982; Shuttleworth et al., 1986).

Moreover, serum autoantibodies were rarely found in OLP patients: antinuclear (ANA) and antismooth-muscles (AMA) antibodies were detected in low title and in a minority of patients, while anti-DNA antibodies were not found (Lundstrom, 1985; Shuttleworth et al., 1986; El-Kabir et al., 1993).

But rarely investigations have systematically related serum immunological parameters with clinical variety of the oral lesions, although recent studies have confirmed the existence of some differences in clinical course between hyperkeratosic forms and atrophic-erosive forms of OLP (Thorn et al., 1988; Gandolfo et al., 1994; Bagan et al., 1993). And it has been suggested that OLP might include more than one genetic and pathological entity with a certain geographic variability (Jontell et al., 1987; Valsecchi et al., 1988; Lin and Sun, 1990; Porter et al., 1993).

The aim of this study was therefore to establish if changes in humoral immunity exist in italian patients with OLP and/or to identify possible humoral immunological differences between patients with atrophic-erosive lesions and patients with reticular-plaque-like lesions.

MATERIAL AND METHODS

Three groups of patients were studied:
a) Group 1 consisting of 25 patients (14 men and 11 women) whose average age was 62 years old (range 28-81) affected by atrophic-erosive varieties of OLP;
b) Group 2 consisting of 28 OLP patients (13 men and 15 women) whose average age was 52 years old (range 24-80) with only reticular-plaque-like lesions of OLP;
c) Group 3 consisting of 21 healthy patients (9 men and 12 women) whose average age was 59 years old (range 24-81) without clinical sign of oral disease.

In all the patients with OLP the clinical diagnosis were confirmed histologically following the WHO (1978) recommendation.

Ten milliliters of venous blood was taken from each person and serum levels of immunoglobulins (IgG, IgA and IgM), light chains (kappa and lambda), C3 and C4 were determinated by the single radial immunodiffusion technique of Mancini. None of the patients was treated for OLP neither they have taken any drugs during the 3 months before the analyses. No patients were suspected of having drug-induced or restoration-related OLP. A full clinical history was obtained from each patient with particular reference to co-existing autoimmune disease.

The data were filed in computerized archives by means of modified data-base which was processed with an hardware PC-AT IBM (Gandolfo et al., 1993).

STATISTICAL ANALYSIS

If the variance was homogenous with the Bartlett test the datum were analysed by one-way parametric analysis of variance. When the variance was dyshomogenous it was used the non parametric Kruskal-Wallis test. This analysis was performed by means of EPI-INFO version 5 (A world processing database and statics program for epidemiology on microcomputers, 1990). For multiple comparisons between groups was used Mann-Whitney test with Bonferroni's correction.

A mean p-value of 0.05 or less was considered significant.

RESULTS

We noted that the serum of patients affected by atrophic-erosive forms of OLP (Group 1) was characterized by an IgG level (mean: 1817.08 mg%) which was higher than controls (Group 3, mean: 1390.63 mg%) and higher than patients affected by reticular and/or plaque-like forms of OLP (Group 2, mean: 1492.31 mg%). This difference has almost reached the statistical significance ($p=0.0572$) (Table I). In the scatter chart diagram of Figure 1 is evident that the IgG values of Group 1 tended to exceed the highest level of the normality range (800-1700 mg%). At the same time, most of the value of Group 2 and Group 3 were within the range. However, the highest IgG levels in Group 1 were found in patients affected by chronic hepatopathies (mean 2680.87 mg%) 5 of which were unnoticed before the oral diagnosis (these patients have been described in details elsewhere) (Gandolfo et al, 1992).

No significative difference was found in medium values of IgA, IgM and C3, C4 complement portions among the 3 observed groups (Table I). At the same time the medium values of the Kappa and Lambda chains in patients with lichen planus (Group 1 and 2) were higher than controls (Group 3) ($p=0.001$ and $P=0.034$ respectively) (Table II). This tendence is graphically visible in diagrams of Figure 2 (Kappa chains) and of Figure 3 (Lambda chains). Comparing the medium values of the 3 groups light chains (Mann-Whitney test with Bonferroni's correction) is evident that patients with atrophic-erosive forms of OLP (Group 1) show significantly higher serum levels of Kappa and Lambda than controls (Group 3) ($p<0.001$) (Table II). On the other hand there are not significative differences either between patients with reticular-plaque-like OLP (Group 2) and controls (Group 3), or between patients with atrophic-erosive (Group 1) and reticular-plaque-like forms of OLP (Group 2) (Table II). However as far as light chains are concerned too, the highest values were found in the 10 patients with chronic hepathopaties (medium value Kappa chain = 204.8; medium value Lambda chain = 216.8). Only one OLP patient had autoimmune disease (vitiligo) and none in the control group.

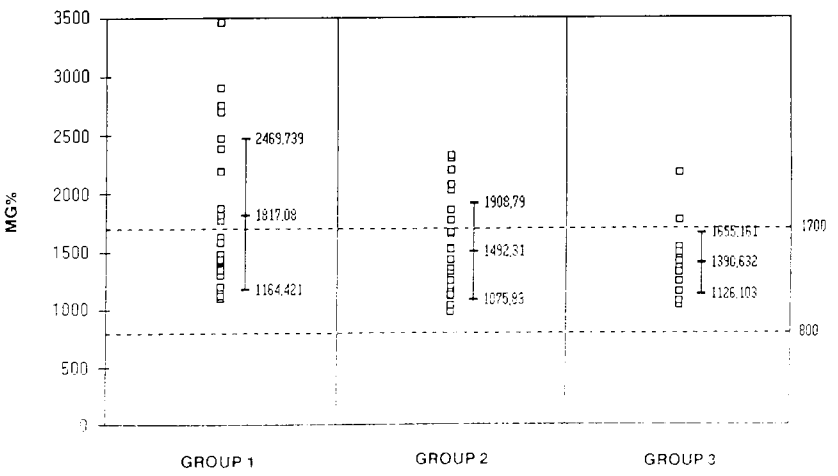

Fig. 1: 1-Serum immunoglobulins levels in the studied groups.
Fig. 1: 1-Taux sériques des immunoglobulines dans les groupes étudiés.

TABLE I
1-Mean values of serum IgG, IgA, IgM, C3, C4, Kappa and Lambda chains in patients with atrophic-erosive OLP (Group 1), reticular-plaque like OLP (Group 2) and controls (Group 3).

Parameters	G@	Mean	Variance	Std Dev	# F (*H)	P
	1	1817.080	425964.160	652.659		
IgG	2	1492.310	173455.579	416.480	*5.722	0.0572
(mg%)	3	1390.632	69975.579	264.529		
	1	367.280	25615.793	160.049		
IgA	2	282.828	23341.362	152.779	2.192	0.1171
(mg%)	3	307.333	17869.133	133.675		
	1	239.840	30602.057	174.934		
IgM	2	222.724	34905.135	186.829	*1.227	0.5413
(mg%)	3	181.333	5839.765	76.418		
	1	144.913	2628.992	51.274		
C3	2	139.556	1605.949	40.074	0.166	0.8485
(mg%)	3	146.632	1655.357	40.686		
	1	42.000	488.909	22.111		
C4	2	42.259	339.046	18.413	*3.523	0.1717
(mg%)	3	33.895	98.433	9.921		
	1	158.360	3795.407	61.407		
Kappa ch.	2	119.667	977.154	31.259	*12.650	0.0017
(UI%)	3	100.125	364.517	19.092		
	1	170.560	7294.257	84.406		
Lambda ch.	2	147.643	4339.571	65.875	*6.723	0.0346
(UI%)	3	114.938	470.329	21.687		

@G: Group
#F : One-way analysis of variance (variance homogeneus at 95% with Bartlett test)
*H : Kruskal-Wallis test (variance not homogeneus)

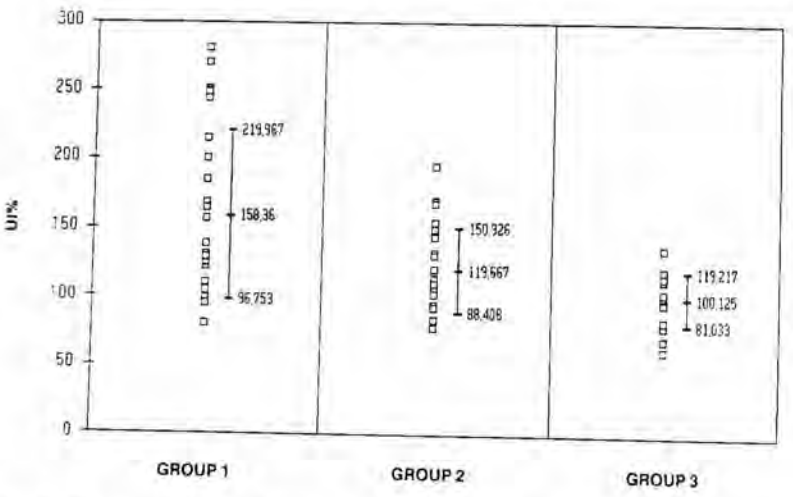

Fig. 2: Serum levels of Kappa chains in the studied groups.
Fig. 2: Taux sériques des chaînes Kappa dans les groupes étudiés.

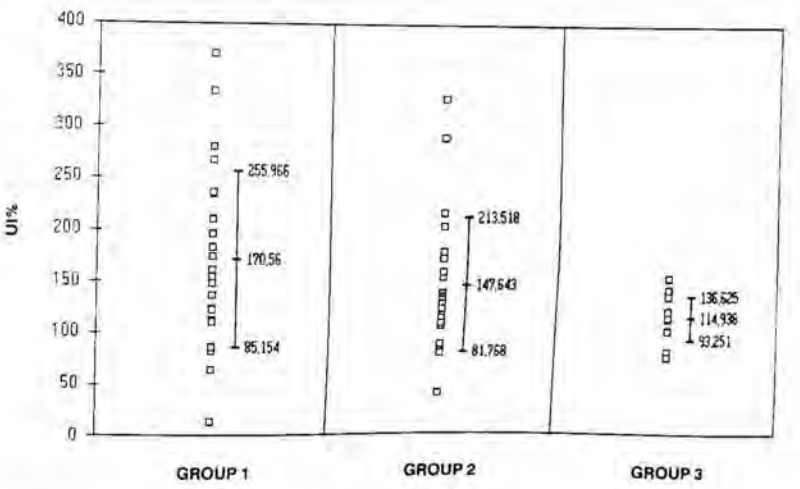

Fig. 3: Serum levels of Lambda chains in the studied groups.
Fig. 3: Taux sériques des chaînes Lambda dans les groupes étudiés.

TABLE II
2-Multiple comparisons between mean values of Kappa and Lambda chains in 3 studied Groups.

	Comparison between Groups	Mean	Z*	P
Kappa chains	1 vs 3	158.360 vs 100.125	3.369	<0.0001
	2 vs 3	119.667 vs 100.125	1.815	NS
	1 vs 2	158.360 vs 119.667	2.261	NS
Lambda chains	1 vs 3	170.560 vs 114.938	2.476	0.013
	2 vs 3	147.643 vs 114.938	1.967	NS
	1 vs 2	170.560 vs 147.643	1.086	NS

*Z: Mann-Whitney test with Bonferroni correction

TABLE III
Reports of serum immunoglobulin levels in lichen planus.

Author		N*	IgG	IgA	IgM
Lehner	(1969)	20	decreased	—	normal
Griffith et al.	(1974)	35	normal	normal	normal
Stankler	(1975)	13	normal	decreased	decreased
Jacyk & Greenwood	(1978)	42	normal	normal	decreased
Mahood	(1981)	31	increased	increased	increased
Scully	(1982)	35	normal	normal	normal
Sklavounou et al.	(1983)	50	increased	decreased	normal
Lundstrom	(1985)	34	increased	normal	normal
Shuttleworth	(1986)	54	normal	normal	normal
Sun et al.	(1986)	46	increased	increased	normal

*N: Number of studied patients

DISCUSSION

Early studies on humoral immunity in lichen planus have reported decreased levels of IgG (Lehner, 1969), IgA (Stankler, 1975) or IgM (Stankler, 1975; Jacyk & Greenwood, 1978) and Stankler (1975) has supported the hypothesis that a humoral immunodeficiency underlies lichen planus. Nevertheless, next studies didn't confirm the above suggestions (Table III), although there are sporadic reports of LP associated with immunodeficiencies (Tan, 1974; Aronson et al., 1978).

More recently, several authors have shown that an increased level of IgG was common in patients with oral erosive lesions of LP (Mahood, 1981; Schroder, 1981; Sklavounou et al., 1983; Lundstrom, 1984; Sun et al., 1986) and Sklavounou et al. (1983), Lundstrom (1984) and Sun et al. (1986) were also able to demonstrate statistically significant differences between serum IgG in LP and controls. By Lundstrom's opinion (1984), considereing high levels of IgG all the values exceding 15 g/l, approximately one third of the patients in his investigation and previous studies shown an elevation of serum IgG levels. This moderate polyclonal increase of IgG is not typical of any specific immunological disease known.

Some authors (Griffith et al., 1974; Sun et al., 1986) suggested that elevated serum level of IgG may be considered representative of a secondary oral infection during mucosal erosion, while Lundstrom (1984) thought that it may represent a continuous autogenous production of soluble antigens characteristic of many autoimmune phenomena. The primary antigen could be of an exogenous kind but it could adhere and to change the individual's own components. In a second phase, cell-mediated reaction may influence the humoral immunity and lead mainly to elevations of serum IgG.

In our study too, patients with atrophic-erosive varieties of OLP (Group 1) shown an increase of the average serum level of IgG (mean = 1817 mg%) compared to patients affected by hyperkeratosic forms of OLP (Group 2) (mean = 1492 mg%) and to healthy persons (Group 3) (mean = 1390 mg%) and these differences were near to statistical significance ($p = 0.0572$). Nevertheless, 40% of the patients in Group 1 were affected by chronic liver diseases and these patients showed the most elevated values of serum IgG, although none of them was affected by autoimmune liver disease (personal data, not shown). So, the slight polyclonal peak of serum IgG in our patients with atropic-erosive OLP is probably caused by the coexistence of chronic liver diseases given the fact that an hypergammaglobulinemia is a relatively common pattern in chronic liver disorders (Ockner, 1988). Moreover, it is known that in Southern Europe populations oral erosive LP is frequently associated with a liver damage (Ayala et al., 1986; De Olmo et al., 1989; Gandolfo et al., 1994) and on the other hand, OLP does not seem a manifestation of a generalized autoimmune disturbance (Shuttleworth et al., 1986; Scully & El-Kom, 1985).

As far as the other analyzed parameters are concerned, medium values of the light kappa and lambda chains in patients with atrophic-erosive OLP were significantly increased compared with healthy controls (Table II). Nevertheless, also this datum has been probably influenced by a strong prevalence of liver diseases in patients with atrophic-erosive lesions. In fact, it is known that all the serum immunoglobulins have similar structures which were made of two pair of polypeptic chains: 2 heavy chains and 2 light chains. The last two may be antigenically characterized in Kappa and Lambda. The kappa chains are present in about 65% of IgG while the Lambda chains are present in 35%. The same proportion is found in serum IgA and IgM (Paul, 1989). So, it is evident that the synthesis of light chains reflects the synthesis of serum immunoglobulins and when their levels increase (i.e. consequence of chronic liver disease) also the levels of the light chains are higher. On the other hand, we do not think that a higher level of light chains may represents a specific feature of OLP given normal serum levels of principal immunoglobulins and normal ratio Kappa/Lambda in all the studied cases.

In conclusion, our results agree with the latest pathogenetic hypothesis (Walsh, 1990) and confirm that the role of humoral immunity in OLP pathogenesis is probably secondary to cell-mediated reaction against basal keratinocytes and consequent to damage of the lower epithelium and basement membrane zone (Brandtzaeg, 1975; Scully & El-Kom, 1985). This point of view is confirmed by T cell nature of the inflammatory infiltrate and by the non-specific lesional deposits of immune components in OLP, probably representing exudation and deposition of plasma proteins in already damaged tissue, rather than autoantibodies (Scully & El-Kom, 1985; Hedberg et al., 1986; Lin et al., 1988). Moreover, peaks of IgG sometimes detected in patients with atropic-erosive OLP could represent a sign of an associated and unnoticed chronic liver disease rather than a generalized autoimmune process.

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