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ASSESSMENT OF IL-17 IN ORAL LICHEN PLANUS AND IN PEMPHIGUS VULGARIS

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ABSTRACT

Background: the present study was aimed to evaluate the levels of IL-17 as a core cytokine and a diagnostic marker of both OLP and PV for comparison and evaluation regarding saliva and serum.

Subjects and Methods: The present study was performed on a total of 45 subjects divided into 3 groups **Group I Fifteen** patients diagnosed with OLP **Group II Fifteen** patients diagnosed with PV with oral lesions and **Group III Fifteen** healthy patients (control Group). Salivary and serum samples were collected from all participating subjects for determination of IL-17 levels using enzyme-linked immunosorbent assay (ELISA).

Results: Mean IL-17 levels in saliva of OLP group were significantly higher statistically than PV patients and control subjects with p values 0.12 and 0.03 respectively. Serum levels of IL-17 in OLP and PV patients were higher compared to control subjects with a statistically significant p value of <0.001 and 0.013 respectively. IL-17 serum levels were significantly higher statistically in OLP than PV patients with a p value of 0.036.

Conclusion: According to the results the high serum and salivary levels of IL-17 in OLP patients when compared to healthy control group or PV group suggested that it could be used as a diagnostic marker for OLP and could be used to differentiate it from PV.

KEYWORDS: IL-17**,** lichen planus, Pemphigus vulgaris, Serum, saliva.

INTRODUCTION

T-helper cells (Th) have been originally classified into two classes Th-1 and Th-2. Th-17 is a novel class discovered in 2005 ***(Gaffen, 2011).*** Th-17 was verified to play a part in the protection from both intra and extra-cellular agents ***(Lønnberg et al., 2014).*** Differentiation of naive CD4+ T-cells into Th-17 is stimulated by TGF-β and IL-6. This induces IL-17A expression ***(Girolomoni et al., 2012).*** IL-17A is a pro-inflammatory cytokine that belongs to the IL-17 family; comprises IL-17A-F ***(Martin et al., 2013).*** IL-17A plays an integral role in neutrophil recruitment, host defense, and

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immuno-inflammatory pathology ***(Girolomoni et al., 2012).*** IL-17 is mostly secreted by Th17, furthermore by T-reg cells, mast cells NK cells, and neutrophils ***(Adami et al. 2014).*** Both IL-17A and IL-17F bind the same receptor; however, IL-17A impact on gene regulation is stronger by 10–30 times. IL-17B, IL-17C and IL-17D functions are yet poorly demarcated, while IL-17E promotes Th-2 cytokines and limits Th-17 development ***(Gaffen, 2009).*** IL-17 plays a pivotal role in abundant immune-mediated disorders ***(Shabgah et al. 2014 and Yang et al., 2014).***

Lichen planus (LP) is a relatively common muco-cutaneous disease. It affects most frequently the oral mucosa (OLP) ***(Farh and Dupin, 2010),*** it is perceived in two forms; non-erosive (reticular, papules, plaque-like) and erosive forms ***(DeRossi and Ciarrocca 2005).*** The most common form is the reticular one, and is usually symptom free. Erosive LP is less prevalent; however, lesions are painful, thus significant for patients. In several patients, tongue dorsum is ulcerated with resultant severe pain and eating difficulty ***(DeRossi and Ciarrocca, 2005).***

Although both etiology and pathogenesis of OLP is not fully clear, many factors including genetic tendency, stress, some viral and bacterial infections may act as risk factors for OLP ***(Lodi et al. 2000; Sugerman et al. 2002; DeRossi and Ciarrocca 2005 and Moravvej et al., 2007).*** The role of immune system as a key strategic factor in OLP pathogenesis lately has become clearer. In the histo-pathological view, basal cell degeneration and band-like T lymphocytes and macrophages infiltration were perceived. This precise view can be construed as the immune system cell-mediated role in OLP pathogenesis ***(Regezi et al., 2008).***

Shaker and Hassan in 2012 investigated the Potential role of IL-17 in OLP pathogenesis, IL-17 serum levels were found noticeably higher in patients compared with controls. They concluded that IL-17 can contribute to OLP pathogenesis by T cell-mediated reactions enhancement and encouraging release of cytokines.

Cellular apoptosis level was compared in erosive and reticular OLP; results displayed an expressively increased apoptosis and a marked drop in oral epithelium thickness in erosive OLP compared to the reticular type ***(Brant et al., 2008).*** Likewise, atrophic areas were perceived more frequently in erosive OLP, demonstrating advanced inflammation and cell damage. It could be deduced that as IL-17 level rises in inflammatory diseases, it outcomes in extraordinary amounts of pro-inflammatory cytokines release, and consequently in OLP emersion and even its different presentations ***(Brant et al., 2008).***

Pemphigus vulgaris (PV) is a severe life threatening auto-immune intraepithelial blistering disease affecting skin and mucous membranes ***(Scully and Challacombe, 2002).*** In about 70-90% of the cases, oral lesions of PV are the first early manifestations of the disease and they are the only manifestations in nearly 50% of the patients ***(Lamey 1992; Greenberg and Glick 2003; Shamim et al. 2008).***

Oral manifestations are clinically characterized by blisters with very thin and fragile roof that rapidly rupture, resulting in chronic painful erosions with epithelial remnants at its periphery. The most common picture is that of multiple, large and persistent erosions covered by yellow exudates and tend to extend progressively by peripheral extension with minute tendency to heal ***(Murphy, 2003 and Black et al., 2005).*** Lesions may extend out of lips on the vermillion border forming heavy hemorrhagic crusts. The Nikolsky's sign is positive ***(Scully and Challacombe 2002; Gleaves et al., 2005).***

PV is due to circulating IgG autoantibodies directed against a normal desmosomal cell adhesion glycoprotein, known as Desmoglein (Dsg), present on the cell membrane of keratinocytes ***(Black et al. 2005and Bascones-Martinez 2010).*** It has been demonstrated that early in the course of the disease, when lesions are limited to mucous membranes, patients have antibodies only against Dsg3. Anti-Dsg1 antibodies was found later in the progress of PV

disease, coinciding with skin involvement ***(Scully and Challacombe 2002; Ruocco et al. 2005).***

Although the immune-pathology of PV is clearly related to auto-antibodies, the cellular arm of the immune system is also involved in its pathogenesis ***(Toto et al. 2000 and Veldman et al., 2003).*** Auto-reactive T-cells play a crucial role in the pathogenesis of PV ***(Rizzo et al. 2005 and Satyam et al., 2009).***

IL-17-generating T lymphocytes have been categorized as a novel effector T lymphocyte subset, named Th-17 that is discrete from Th-1, Th-2 and T-reg subsets ***(Stockinger and Veldhoen 2007 ; Mortazavi et al., 2014).*** IL-17 is a CD4+ T cell-originated cytokine, which stimulates the expression of pro-inflammatory cytokines, IL-ß and TNF-α, by macrophages and dys-regulation of this new subset has been revealed to be associated with many autoimmune diseases ***(Raychaudhuri and Raychaudhuri, 2010).*** Hence the cytokines play a significant role in the immune-pathogenesis of PV ***(Masjedi et al., 2017).***

AIM OF THE STUDY

Accordingly the present study was designated to evaluate the levels of IL-17 as a core cytokine and a diagnostic marker of both OLP and PV for comparison and evaluation regarding saliva and serum where the level of salivary IL-17 in pemphigus wasn't clearly investigated before in the past literature.

SUBJECTS & METHODS

1. Study population:

The present study was performed on a total of 45 subjects, 13 males and 32 females. All participants were recruited from the outpatient clinic of Oral Diagnosis, Oral Medicine and Periodontology Department, Faculty of Dentistry, Cairo University; and outpatient clinic of Dermatology Department, Faculty of Medicine, Cairo University.

Inclusion criteria:

Participants were systemically free as evaluated by the aid of Dental Modification of the Cornell Medical Index to standardize their systemic condition ***(Brightman, 1994)***. They had no history, symptoms, and/or signs of infection and allergy. Furthermore, they were selected to be free of any oral lesions other than OPV or OLP which had to have the following criteria;

(i) Painful lesions

(ii) No topical treatment for 2 weeks, and no systemic treatment used for one month before the start of sampling.

Exclusion criteria:

Exclusion criteria: application of any local treatment for lesions during the previous month; those who use corticosteroids or other immune-suppressive drugs, taking any drugs during the previous 3 months; history of allergy to foods or environmental factors, smoking; the existence of any oral lesions rather than OLP or OPV, systemic diseases (cardiovascular disease, kidney, hypertension), pregnancy, breast feeding, children patients, all were excluded from the study. We also excluded patients whose lesion was nearby amalgam restorations.

Ethical procedures:

All subjects were informed about the detailed procedure and they were given written approval consent to sign, and the protocol was approved by the ethics committee of our institution. Patients were treated after the samples had been collected. The study was performed between August 2018 and September 2018. The forty five selected participants were allocated into three groups as follows:

Group I Fifteen patients diagnosed with OLP.

Group II Fifteen patients diagnosed with PV with oral lesions.

Group III included fifteen healthy volunteer subjects with good general health.

The first group involved OLP which was diagnosed clinically and confirmed histo-pathologically according to the modified WHO criteria in 2003 as below: Clinical criteria: presence of symmetric or bilateral reticular or papular lesions with erosive and or atrophic components. Histological criteria: presence of well-defined band-like zones of inflammatory infiltration confined to the superficial part of connective tissue, consisting mainly of mature lymphocytes; signs of "liquefaction degeneration" in basal cell layer, absence of epithelial dysplasia.

The second group involved PV confirmed by biopsy and presence of PV intra-orally and lesions on skin.

Sampling

The un-stimulated whole saliva (UWS) was collected between 10:00 a.m. and 12:00 p.m., and at least 90 minutes after the last intake of drink or food. All subjects were requested to swallow first, tilt the head forward and then expectorate at least 5cc UWS into a sterile centrifugal tube without swallowing. The samples were centrifuged (2000g for 10 min), and the supernatants stored at -20 C until analysis. Blood samples were collected in sterile tubes and allowed to clot at room temperature. Sera were isolated by centrifugation and stored frozen below –20 until assayed for IL-17 level.

IL-17 levels were assessed by using Enzyme-Linked Immuno Sorbent Assay (ELISA) kits, Cat No E0063H for the invitro quantitative detection of IL-17 concentrations.

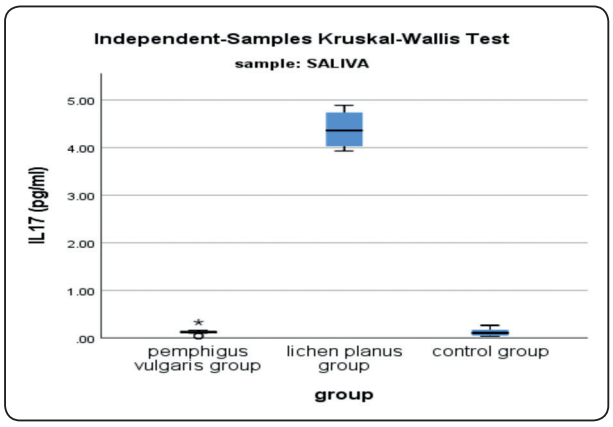
The ELISA assays were implemented according to the manufacturer's references, and 96-well plates pre-coated with IL-17 specific human mono-clonal antibody were used. The pre-coated antibody bound IL-17 present in the test samples. Next to washing of unbound proteins, an enzyme-linked Horse-radish Peroxidase (HRP) poly-clonal antibody specific for IL-17 and substrate solution were added to each micro-plate well. The color change established is comparative to IL-17 amount. The optical density (intensity of the color) was assessed by Spectro-photo-meter at a wave-length of 450 nm then a standard curve was drawn.

STATISTICAL ANALYSIS

Statistical analysis and data management were implemented using Independent-Samples Kruskal-Wallis Test. The Statistical Package for Social Sciences (SPSS) version. 24. Numerical data were concise using means and standard deviations or medians and ranges.

RESULTS

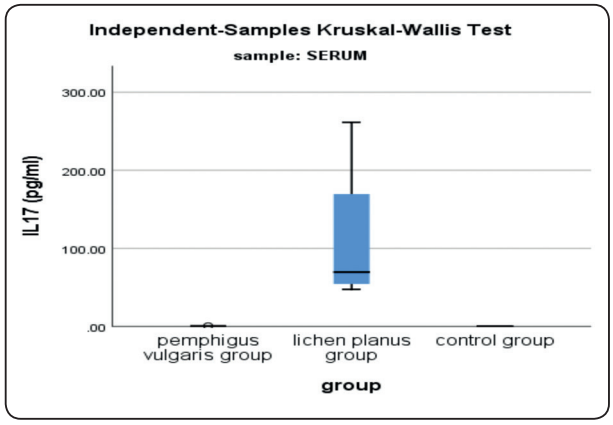
		SALIVA			P value
		pemphigus vulgaris group	lichen planus group	control group	
IL17 (pg/ml)	Mean	.13	4.38	.12	0.010
	SD	.08	.44	.09	
	Median	.12	4.36	.10	
	Minimum	.04	3.93	.04	
	Maximum	.33	4.89	.26	



Saliva	P value
PV group- control group	1.000
PV group- OLP group	.012
control group- OLP group	.030

Post hoc pairwise comparison between each 2 groups

		SERUM			
		pemphigus vulgaris group	lichen planus group	control group	P value
IL17 (pg/ml)	Mean	.40	111.95	.24	<0.001
	SD	.10	100.39	.12	
	Median	.39	69.50	.22	
	Minimum	.30	47.40	.05	
	Maximum	.64	261.40	.51	



Serum	P value
control group- PV group	.013
control group- OLP group	<0.001
PV group- OLP group	.036

Post hoc pairwise comparison between each 2 groups

Saliva and serum levels of IL-17 were determined in both patient and control group. Saliva levels of IL-17 ranged between 0.04 pg/ ml and 0.33 pg/ml in pemphigus vulgaris patients with a mean level of 0.13 ± 0.08 pg/ml. Mean level of salivary IL-17 in OLP group was 4.38 ± 0.44 pg/ml. Control group showed salivary IL-17 level ranging between 0.04 to 0.26 pg/ml with a mean value of 0.12±0.09pg/ml.

Mean IL-17 levels in saliva of OLP group were significantly higher statistically than PV patients and control subjects with p values 0.12 and 0.03 respectively.

Considering serum levels of IL-17, PV patients showed serum IL-17 levels ranging between 0.30 pg/ml and 0.64 pg/ml with mean level of 0.40 ± 0.10 pg/ml. Whereas lichen planus group recorded mean serum IL-17 levels of 111.95 pg/ml ± 100.39 pg/ml; ranging between 47.40 pg/ml to 261.40 pg/ml. Mean IL-17 serum level in control subjects was 0.24 pg/ml ± 0.12 pg/ml.

Serum levels of IL-17 in OLP and PV patients were higher compared to control subjects with a statistically significant p value of <0.001 and 0.013 respectively. IL-17 serum levels were significantly higher statistically in OLP than PV patients with a p value of 0.036.

DISCUSSION

In the present study, serum and salivary IL-17 levels were assessed in PV patients with oral lesions and in OLP with erosive lesions, found that IL-17 was over expressed in serum and saliva of PV patients than the control group but with no statistical significance difference .While the results of OLP patients were the highest when compared to either the control group or PV group with statistically significant difference.

In a previous study conducted to evaluate the influence of IL-17 serum levels in PV patients, it demonstrated no significant difference noticed between cases and control groups regarding IL-17 serum levels despite its higher values in PV group ***(Najafi et al, 2017)*** which also matched our results. Also in another study conducted to evaluate cytokines index in PV concluded that the serum levels of IL-2, IL-4, IL-17 and IFN-γ in most patients and controls were undetectable ***(Masjedi et al, 2017)***. In a study by ***Mortazavi et al***. in ***2014***, the mean IL-17 level in PV patients was higher than in controls, although the difference was not significant. This research finding is compatible with our study.

While ***Jixin Xue etal*** in ***2014*** results showed that the numbers of IL-23+ cells and IL-17 + cells were

significantly higher in PV skin lesions compared to normal control skins. Which also supported by the results of previous experimental study by ***Arakawa et al*** published in ***2009***, which presented the possibility of Th-17 (IL-17+cells) to play an important role in the pathogenesis of PV. They quantified Th-17 cells in lesional biopsy specimens from PV patients and found a significantly higher expression of IL-17 +cells compared to control. The conflicting results in these studies may reflect the genetic variations. In conclusion, further investigations with larger numbers of patients with PV will be necessary to elucidate this discrepancy.

Salivary IL-17 level in PV group of our study was higher than that in control group but the difference was statistically insignificant. On the basis of our knowledge there is no study on salivary IL-17 level in PV.

Shaker and Hassan in 2012 studied IL-17 serum levels amongst 20 LP patients, and compared it to its level among 20 healthy subjects. In their study, IL-17 serum levels of LP patients were higher than corresponding healthy subjects levels, which matched our result. These results were also emphasized by the results of a previous study presented by two of the current study authors **(Hussine et al, 2016)** that demonstrated the increased expression of serum, tissue level of IL-17 and IL-17 tissue receptors in atrophic and erosive forms of OLP patients. Suggesting that IL-17 may be considered a crucial pro-inflammatory cytokines in OLP, and also matched with the results of **Pouralibaba *et al, 2013*** study which demonstrated that the high IL-17 serum level in erosive OLP patients compared to the non-erosive type and healthy individuals may account for higher inflammation and atrophy existing in erosive OLP.

In a recent study by ***Shirazian et al in 2017,*** found that the level of IL 17 was significantly higher in serum of OLP patients than controls and in erosive-atrophic OLP than reticular. Which is affirmed by our results but on the other hand he found that the mean rank of salivary IL-17 was 37.33 and 33.59 for OLP and healthy cases respectively .The difference was not significant. That was in contrary to our results which revealed statistical significance difference in the salivary levels of IL-17 in OLP group and both the other two groups of the present study. The difference in these results need further investigations as our results regarding salivary IL-17 levels in OLP patients were in agreement with the results of ***Wang et al*** in ***2015,*** study which concluded that Salivary IL-17 concentrations in erosive OLP group were significantly higher than in those with reticular OLP and in healthy controls. Moreover, positive significant correlations were interpreted between IL-17 salivary concentrations and disease clinical scores.

The purpose of this study was to compare the salivary and serum levels of IL-17 because saliva originates from blood and its collection is an easy, non-invasive method, so it can be a diagnostic fluid that has logistical advantages when compared with serum ***(Hosseini et al, 2015***).

It is clear that IL-17 plays a role in OLP pathogenesis despite its role in PV needs further investigation.

CONCLUSION

According to our results the high serum and salivary IL-17 levels in OLP patients when compared to its level in either healthy control group or PV group advocate that it could be used as a diagnostic marker for OLP and could be used to differentiate it from PV.

RECOMMENDATION

Further investigations to reveal the genuine role of IL-17 in the pathogenesis of PV are recommended.

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REFERENCES

1. Adami S, Cavani A, Rossi F, Girolomoni G. (2014). The role of interleukin-17A in psoriatic disease. BioDrugs; 28: 487-97.
2. Arakawa M., T. Dainichi, S. Yasumoto, and T. Hashimoto (2009). Lesional Th17 cells in pemphigus vulgaris and pemphigus foliaceus. Journal of Dermatological Science, vol. 53, no. 3, pp.228–231.
3. Bascones-Martinez A, Munoz-Corcuera M, Bascones-Ilundain C, Esparza-Gómez G (2010) Oral Manifestations of Pemphigus Vulgaris: Clinical Presentation, Differential Diagnosis and Management, J Clin Exp Dermatol Res 1:112.
4. Black M, Mignogna MD, Scully C (2005). Number II. Pemphigus vulgaris, Oral Dis 11: 119-130.
5. Brant JM, Vasconcelos AC, Rodrigues LV (2008). Role of apop-tosis in erosive and reticular oral lichen planus exhibiting variable epithelial thickness. Braz Dent J; 19:179-85.
6. DeRossi SS, Ciarrocca KN (2005). Lichen planus, lichenoid drug reactions, and lichenoid mucosits. Dent Clin N Am; 49:77-89.
7. Farh D, Dupin N (2010). Pathophysiology, etiologic factors, and clinical management of oral lichen planus, part I: facts and controversies. Clinics in Dermatology; 28:100–8.
8. Gaffen SL (2009). Structure and signalling in the IL-17 receptor family. Nat Rev Immunol; 9: 556-67.
9. Gaffen SL (2011). Recent advances in the IL-17 cytokine family. Curr Opin Immunol; 23: 613-9.
10. Girolomoni G, Mrowietz U, Paul C (2012). Psoriasis: rationale for targeting interleukin-17. Br J Dermatol; 167: 717-24.
11. Gleaves T R, Cather J C and Menter A (2005). Oral erosions and cutaneous bullae. Proc (Bayl Univ Med Cent); 18(1): 71–73.
12. Greenberg M S and Glick M (2003). Ulcerative, Vesicular and Bullous lesions, In: Burket's Oral Medicine Diagnosis and treatment, 10th ed. BC Decker, Inc, United States, Pp. 50- 84.
13. Hosseini F Agha, Dizgah I Mirzaii, Mahboobi N, Shirazian S,Harirchi I. (2015). Serum and Saliva MMP-3 in Patients with OLP and Oral SCC. J Contemp Dent Pract. 1; 16(2):107-11.
14. Hussine A Amal, Maged Amira, Wagih Rasha and Rashed Liala (2016). Evaluation of the possible role of IL-17 and its tissue receptors IL-17R in the pathogenesis of oral lichen planus" Al-Azhar Journal of Dental Science, vol.19-No.1.
15. Jixin Xue,Wenting Su, Zhiwei Chen, Youhui Ke, Xiaojing Du, and Qiaochu Zhou (2014). Overexpression of Interleukin-23 and Interleukin-17 in the Lesion of Pemphigus Vulgaris: A Preliminary study Hindawi Publishing Corporation, Mediators of Inflammation. Volume, Article ID 463928, 5 pages http://dx.doi.org/10.1155/2014/463928
16. Lamey PJ, Rees TD, Binnie WH, Wright JM, Rankin DV, Simpson NB (1992). Oral presentation of pemphigus vulgaris and its response to systemic steroid therapy, Oral Surg Oral Med Oral Pathol; 74: 54–7.
17. Lodi G, Carrozzo M, Harris K, Piattelli A, Teo CG, Gandolfo S, et al. (2000). Hepatitis C virus-associated oral lichen planus: no influence from hepatitis G virus co-infection. J Oral Pathol Med 2000; 29:39-42.
18. Lønnberg AS, Zachariae C, Skov L (2014). Targeting of interleukin-17 in the treatment of psoriasis. Clin Cosmet Investig Dermatol; 7: 251-9.
19. Martin DA, Towne JE, Kricorian G, et al (2013). The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. J Invest Dermatol; 133: 17-26.
20. Masjedi M, Esmaeil N, Saffaei A, Pourazizi M, Haghjooy S and Asilian A (2017). Cytokine Indexes in Pemphigus Vulgaris: Perception of It's Immunpathogenesis and Hopes for Non-Steroidal Treatment. IJPR 16 (3): 1223-1229.
21. Moravvej H, Hoseini H, Barikbin B, Malekzadeh R, MeshkatRazavi G (2007). Association of Helicobacter pylori with lichen planus. Indian J Dermatology; 52:138-140.
22. Mortazavi H, Esmaili N, Khezri S, Khamesipour A, Vasheghani Farahani I, Daneshpazhooh M and Rezaei N (2014). The effect of conventional immunosuppressive therapy on cytokine serum levels in pemphigus vulgaris patients. Iran J. Allergy Asthma Immunol. 13: 174-83.
23. Murphy G (2003). Blistering (bullous) disease. In: Robbins basic pathology, 7th ed. Eds: Robbins S L, Kumar V and Cotran R S, Pp795-98.
24. Najafi Shamsolmoulouk, Zohreh Bijad, BitaRohani, Narges Gholizadeh, GholamaliJafari (2017). "The role of serum levels of interleukin 17 in patients with pemphigus. Journal of Dentomaxillofacial Radiology, Pathology and Surgery Vol 5, No4.

25. Pouralibaba Firoz, Zohre Babaloo, Farzaneh Pakdel, Marziye Aghazadeh (2013). Serum Level of Interleukin-17 in Patients with Erosive and Non-erosive Oral Lichen Planus. J Dent Res Dent Clin Dent Prospect ;7(2):91-94 | doi: 10.5681/joddd.2013.016.

26. Raychaudhuri SK and Raychaudhuri SP (2010). Scid mouse model of psoriasis: a unique tool for drug development of autoreactive T-cell and th-17 cell-mediated autoimmune diseases. Indian J. Dermatol. (2010) 55: 157-60.

27. Regezi JA, Scuibba J, Jordan CR (2008). Oral Pathology Clinical Pathologic Correlations, 5th ed. Philadelphia: Saunders Co:90-5.

28. Rizzo C, Fotino M, Zhang Y, Chow S, Spizuoco A, and Sinha A (2005) Direct characterization of human T cells in pemphigus vulgaris reveals elevated autoantigen-specific Th2 activity in association with active disease,Clinical and Experimental Dermatology, 30 (5): 535-540.

29. Ruocco E, Baroni A, Wolf R, Ruocco V (2005) Life-threatening bullous dermatoses: Pemphigus vulgaris. Clin Dermatol; 23: 223-226.

30. Satyam A, Khandpur S, Sharma V K, and Sharma A (2009). Involvement of TH1/TH2 cytokines in the pathogenesis of autoimmune skin disease pemphigus vulgaris,Immunological Investigations; 38(6): 498-509.

31. Scully C and Challacombe S J (2002). Pemphigus vulgaris: Update on etiopathogenesis, oral manifestations and management. Crit Rev Oral Biol Med 13(5):397-408.

32. Shabgah AG, Fattahi E, Shahneh FZ (2014). Interleukin-17 in human inflammatory diseases. Postep Derm Alergol; 31:256-61.

33. Shaker O, Hassan AS (2012). Possible role of interleukin-17 in the pathogenesis of lichen planus. Br J Dermatol; 166:1367-8.

34. Shaker O, Hassan AS (2012). Possible role of interleukin-17 in the pathogenesis of lichen planus. Br J Dermatol; 166(6):1367–8.

35. Shamim T, Varghese VI, Shameena PM, Sudha S (2008). Pemphigus vulgaris in oral cavity: clinical analysis of 71 cases. Med Oral Patol Oral Cir Bucal; 13:E622-E626.

36. Shirazian Shiva, Farzaneh Aghahosseini, Eisa Salehi, Mehdi Vatanpour,Seyede Niloofar Banijamali and Sara Pourshahidi (2017). "Comparison of interleukin 17 and 22 in saliva of oral lichen planus patients with healthy people" Biosci. Biotech. Res. Comm. 10(3): 587-591 (2017)

37. Stockinger B and Veldhoen M (2007). Differentiation and function of Th17 T cells. Curr. Opin. Immunol. 19: 281-6.

38. Sugerman PB, Savage NW, Walsh LJ, Zhao ZZ, Zhou XJ, Khan A, et al (2002). The pathogenesis of oral lichen planus. Crit Rev Oral Biol Med; 13:350-65.

39. Toto P, Feliciani C, Amerio P, Suzuki H, Wang B, Shivji G, Woodley D and Sauder D (2000). Immune modulation in pemphigus vulgaris: Role of CD28 and IL-10. J.Immunol; 164: 522-9,.

40. Veldman C, Stauber A, Wassmuth R, Uter W, Schuler G and Hertl M (2003). Dichotomy of autoreactive Th1 and Th2 cell responses to desmoglein 3 in patients with pemphigus vulgaris (PV) and healthy carriers of PV-associated HLA class II alleles. J.Immunol; 170 (1): 635-42.

41. Wang K, Miao T, Lu W, He J, Cui B, Li J, Li Y, Xiao L (2015). Analysis of oral microbial community and Th17-associated cytokines in saliva of patients with oral lichen planus. Microbiol Immunol.; 59(3):105-13. doi: 10.1111/1348-0421.12232.

42. Yang J, Sundrud MS, Skepner J, Yamagata T (2014). Targeting Th17 cells in autoimmune diseases. Trends Pharmacol Sci; 35: 493-500.