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ORIGINAL ARTICLE

Role of CXCL9-CXCR3 AXIS, ANA & DS-DNA ABS in Pathogenicity of SLE in Iraqi Patients

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ABSTRACT

Background: Systematic Lupus erythematosus (SLE) has been described as a chronic inflammatory illness where chemokines play an important role in its pathogenesis. CXCL9 and CXCR3 are chemokines that described their crucial role in immune response in SLE patients.

Aim of the study: To evaluate the serum level of CXCL9- CXCr3 , ANA, ds-DNA Abs in SLE patients without treatment and compare their level with those under treatment (hydroxychloroquin ,predeslone5-20mg ,D3)

Patients collecting and Methods: 180 females with SLE and healthy, with ages ranged between 20-40 years, were involved in this investigation from Medical City (Consultant of Arthritis, Consultant of Dermatology, Lobby of Hematology and Arthritis)/ Baghdad Teaching Hospital and from Al-Imameen Al-Kazimeen Teaching Hospital from August 26 to October 18, 2021. The samples were included 120 females with SLE (60 females as an early diagnosed patients (G2) without treatment, 60 females as patients that received treatment subjects (hydroxychloroquin ,predeslone5-20mg ,D3) (G3) , while the control group included 60 healthy females (G1). Five mL of venous blood were obtained from patients and healthy females for measuring ANA, dsDNA and serum levels of CXCL9 and CXCR3 which were measured using ELISA method.

Results: Our findings demonstrated a significant increases in the serum levels of CXCL9, CXCR3, ANS and dsDNA in SLE patients (with and without treatment) in comparison to control group as well as a significant difference was detected between SLE patients without treatment and patients those receiving treatment.

Conclusion: Based on our findings, CXCL9 and CXCR3 chemokines may have a role in the pathogenesis of SLE as they are increased in SLE patients. In addition, serum CXCL9 levels can be used as an independent biomarker of SLE activity. Interestingly, high levels of ANA and dsDNA are considered as a diagnostic indicator of SLE disease in the patients.

Keywords: Systemic lupus erythematosus, CXCL9; CXCR3. ANA, dsDNA

INTRODUCTION

The term lupus is attributed to the 13th century physician who studied it, Rogerius, who described facial lesions reminiscent of a "wolf bite" (Blotzer,1983). The name lupus erythematosus dates back to the early twentieth century, as the word lupus is derived from the Latin and it describes the rash that appears on the face of the patient, which reminds the doctor of the white marks on the face of the wolf and the word red describes it sign of patients (SLiva and Isenberg,2001 ;Talbot,1974). About 70 years ago, it was found that there were phagocytic cells eating cells coated with autoantibodies (Arnett, and Shulman, 1976). Until it was prescribed in other diseases such as (RA), it was thought to be lupus (Dubois, 1953 ; Harvey et al, 1954). Finally, the work of Hughes, Harris, Gharavi, Asherson, and Alarcón-Segovia to name a few opened the door to our understudied of the antiphospholipid antibody as an important aspect of lupus (Harris et al.,. 1988). SLE is a complex multisystem autoimmune disease with significant organ involvement. Clinical symptoms are range from mild to transient to fatal. SLE develops between the ages of teenage and adults, especially between 15-44 years old (Al-Sarray et al., 2020). The incidence of this disease is more in females than males, with a ratio of 9:1 (Bultink et al., 2021). while SLE causes inflammation of the organs. Its pathogenesis includes in the formation of pathogenic autoantibodies directed towards nucleic acids and the proteins that bind to them, indicating a complete loss of self-antigen recognition. (Choi et al., 2012). This disease results from the union of several causes, including genetic and environmental factors (Barbhaiya and Costenbader, 2016). It is also characterized by many clinical phenotypes and production of different antibodies against nuclear contents (Chen et al.,2018). Furthermore, a lot of organs can be contribute to SLE, and typical major organ manifestations such as kidney disease, skin, heart, central nervous system and abnormalities of the highly pervasive blood system in SLE (Bengtsson and Rönnblom, 2017: Beyan et al ., 2007) lupus erythematosus among its features is the activation of B cells and thus activates the autoimmunity resulting from the production of many cytokines and chemokines. Cytokines and chemokines possess a very important role in the etiology of SLE (Lee and Song, 2017). Although accurate current data on SLE incidence and prevalence is somewhat lacking, there are several indications that SLE is less common in Europeans and their descendants than in all other races (Stojan and Petri, 2018). Clinical manifestations of the disease showed geographic or ethnic variation, and are generally less severe in patients of European descent than in Africans, Asians, and various indigenous peoples. Genetic, environmental, social, demographic, and sociocultural factors likely are contribute to the variation in the incidence and clinical expression of SLE (Duarte-García et al., 2021:Barber MRW et al., 2021). In the East Asian countries, it was found that the incidence of the disease was 3 per 100,000 people (Yin et al., 2021). In contrast, in studies involving China, especially Shanghai, the infection rates were shown to increase at a rate of 30-50 per 100,000 people (Leong et al., 2021). At the regional level, the study of Alhassan et al. (2021) revealed that the infection rate in the Kingdom of Saudi Arabia was 3.2-19.3 per 100,000. In Oman, the infection rate was range 5-63 per 100 000 inhabitants (Aladhoubi et al., 2021) .On the Turkish side, in a study of Uzuner et al. (2021), the incidence was 9.73 per 100,000 people. As for Persia, the studies of Esmaeilzadeh et al. (2019) and Gachpazan et al. (2021) showed that the rate of infected cases was 40 per 100,000. Furthermore, Jones et al. (2012) study reported in Iraq that the incidence rates of SLE are in an increasing state over the years preceding the study, as it was 2-8 per 100,000. Cytokines are important mediators of inflammation associated with SLE. CXCL9 is a member of the CXC family of chemokines, and can be stimulated by interferon-γ (IFN-γ) (Balkwill, 2004). The cellular mediator CXCL9 binds to its receptor CXCR3 that can activate CXCR3+ cells, such as effector T cells, regulatory T cells ,CD8+ cytotoxic T cells, and macrophages (Redjimi et al., 2012). As well, CXCL9 is a small cytokine belonging to the CXC chemokine family that is also known as monokine induced by gamma interferon (MIG). CXCL9 is one of the chemokine which plays role to induce chemotaxis (Belperio et al., 2003), it promotes differentiation and multiplication of leukocytes, and cause tissue extravasation. CXCL9/CXCR3 receptor regulates the immune cell migration, differentiation, and activation. Immune reactivity occurs through recruitment of immune cells, such as cytotoxic lymphocytes (CTLs), natural killer (NK) cells, NKT cells, and macrophages. In addition, Th1 polarization activates the immune cells in response to IFN-γ (Dai et al., 2021: Cheng et al., 2021). The role of CXCL9

and its receptor CXCR3 in SLE have chemotactic activity mainly for activating of Th1 cells, macrophage and are involved in the pathogenesis of various Th1-dominant autoimmune diseases (Villarroel et al., 2014: Nakayama et al .,2021). It was shown to be important for cell-mediated inflammation in developing autoimmune disease such as SLE, thus implication these chemokines might have an important role in pathogenesis of SLE (Kameda et al., 2020). Furthermore, (Usami et al., 2019). who indicates the high percentage of it is used as a marker to diagnose SLE,

MATERIAL AND METHODS

This study included 180 females (with SLE and healthy) with ages ranged between 20-40 years, which were collected from Medical City (Consultant of Arthritis, Consultant of Dermatology, Lobby of Hematology and Arthritis)/ Baghdad Teaching Hospital and from Al-Imameen Al-Kazimeen Teaching Hospital from August 26 to October 18, 2021. The samples were included the control group 60 healthy females (G1). 120 females with SLE 60 females as a early diagnosed patients (G2) without treatment, 60 females as patients that received treatment subjects (G3),

All samples were collected and diagnosed by the a consultant in unit in the hospitals according to the protocols followed by them through the official specialist. Data related to age, duration of illness (as initial diagnosis or exposure to treatment), exposure to other diseases were recorded. Antinuclear antibody test (ANA) and Double strand DNA antibody ds(DNA) were assessed, in addition to the fact that the diagnosis was made by clinical examination by the consultant doctors .The venous blood (10 mL) was collected from the control group and patient groups. The blood samples were distributed in test tubes and the serum was separated using centrifuge (3000 rpm for 30 min), and then transferred into 0.5 mL Pendorf tubes that were immediately frozen at -20^0 C until using in the determination of studied parameters.

CXCL9 and their receptors CXCR3 were measured in all under studying groups using ELISA technique. ANA, dsDNA analysis was performed using Algeria device, and the results are presented in an IU/mL, as well as determining the degree of functional impairment of the organs and clinical signs of the disease.

Statistical Analysis: All the data were analyzed using SPSS V.28 program; independent t-test and Anova One Way ANOVA (LSD) were used for calculating p value and significant differences between the studied groups as well as using Pearson correlation coefficient was used to find correlations for the studied data. All data were presented as mean±S.E and $p<0.05$ was considered significant difference.

RESULTS

This study included 60 healthy females(G1) , 120 Iraqi female with SLE which divided into two groups, the first included 60 patients with early diagnostic (G2) while the second group included 60 treated patients (G3). understudied group age ranged from 20-40 years , result of age (Mean+S.E) for G1,G2,G3 was (28.7±0.74 , 29.76±0.91 , 31.7±0.85) years as shown in (Table 1)

Table 1: The (Mean±S.E) of age for all understudied groups

Groups	Control	Early diagnostic	Treated
	Mean+S.E		
Age	28.7±0.74	29.76±0.91	31.7±0.85

in table (2),which illustrated the serum level of (CXCL9 & CXCR3) axis the result showed a significant increase in CXCL9 ($P<0.00$) in G2 group (treated patients) in comparison to control (G1) and early diagnosed patients (G3), while no significant was fount between G1 and G2 group. The means were (259.47±9.69), (483.85±33.43) and (264.25±13.18)] pg/mL in control, G1,G2 and G3 group respectively.

Additionally, a significant elevation ($P<0.001$) was found in CXCR3 serum level in G2 group as compared to G3 and control group whereas no significant was detected between G3 and control group. The mean was (1.68±0.13) pg/mL in G2 group, (0.66±0.03)] pg/mL in G3 group and (0.55±0.03) pg/mL in (G1) control group (Table 2).

On the other hand, the serum level of ANA significantly increased ($P<0.001$) in G2 (4.88 ± 0.24) U/mL and G3 groups (1.90 ± 0.16) U/mL in comparison to control group (G1) (0.55 ± 0.03) U/mL (Table 3). Furthermore, a significant decreased ($P<0.001$) was found in ANA levels in G3 comparison to G2 group refereeing to the modulation of ANA levels after treatment.

Table 2: serum level of CXCL9 - CXCR3 in patients & control

Parameter	Group	Mean+ S.E	P value		
			Control	Early diagnostic	Treated
CXCL9	Control (G1)	259.47 ±9.69	-	0.001	0.88NS
	Early diagnostic(G2)	483.85 ±33.43	0.001	-	0.001
	Treated (G3)	264.25 ±13.18	0.88NS	0.001	-
CXCR3	Control (G1)	0.55±0.03	-	0.001	0.34NS
	Early diagnostic(G2)	1.68±0.13	0.001	-	0.001
	Treated (G3)	0.66±0.03	0.34NS	0.001	-

Table 3: serum level of ANA and ds-DNA in patients and control

Parameter	Group	Mean+ S.E	P value		
			Control	Early diagnostic	Treated
ANA	Control (G1)	0.55±0.03	-	0.001	0.001
	Early diagnostic(G2)	4.88±0.24	0.001	-	0.001
	Treated (G3)	1.90±0.16	0.001	0.001	-
Ds-DNA	Control(G1)	21.25± 0.82	-	0.001	0.001
	Early diagnostic(G2)	82.12± 1.57	0.001	-	0.001
	Treated (G3)	64.11± 2.30	0.001	0.001	-

Table 4: Correlation of age and studied parameters.

Parameter		CXCL9	CXCR3	ANA	Ds-DNA
Age	Pearson Correlation	-0.071	-0.005	0.056	0.086
	Sig. (2-tailed)	0.34	0.95	0.45	0.25

Table 5: Correlation among the studied parameters

Parameter		ANA	Ds-DNA	CXCL9	CXCR3
ANA	Pearson Correlation	1			
	Sig. (2-tailed)				
Ds-DNA	Pearson Correlation	0.755**	1		
	Sig. (2-tailed)	<0.001			
CXCL9	Pearson Correlation	0.562**	0.394**	1	
	Sig. (2-tailed)	<0.001	<0.001		
CXCR3	Pearson Correlation	0.631**	0.519**	0.518**	1
	Sig. (2-tailed)	<0.001	<0.001	<0.001	

Correlation: The statistical analysis of the collected data found that there is no significant correlation between age and the studied parameters in understudying groups (Table 4). While a significant correlation ($P<0.001$) has been found among all understudied

groups parameters and recorded a positive correlation, as shown in (Table5)

Moreover, the serum level of Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) was significantly elevated (P<0.001) in the both patients groups (G2 and G3) as compared to control group (G1) (Table 3). In contrast, ANA level was significantly decreased (P<0.001) in treated patients (G3) in comparison to early diagnosed patients (G2). The means were (21.25 ± 0.82), (82.12±1.57), (64.11 ± 2.30)] IU/mL in G1, G2 and G3 groups respectively.

DISCUSSION

Our findings revealed that serum CXCL9 and CXCR3 levels in early diagnosed and treated SLE patients were considerably higher than in control, and also significantly difference among SLE patients especially after the treatment. These results were consistent with Usami et al. (2019) who referred to the increasing of CXCL9 serum levels in SLE patients; also it was in agreement with other study which found a higher significant difference in CXCL9 expression between patients and control in some autoimmune disease (Graver et al ., 2021). Moreover, Han et al. (2019) observed that CXCR3 in SLE patients is a sensitive indicator to assess SLE disease activity, and CXCR3 might contribute to B cell and generation of autoantibodies in patients. Additionally, the results of this study also indicated that the treatment group and the control group have close CXCR3 ratio, and this is evidence that the treatment group had reduced CXCR3 levels. While, our findings is not agree with result recorded by Yang et al (2021) who referred that level of CXCR3 was decreased in lupus peripheral blood.

Moreover, Watanabe et al. (2008) and Henneken et al (2005) reported an elevation in the ratio of CXCR3+ B cells in SLE patients as well as an elevation in CXCL9 serum levels. Our results revealed also there is no significant relationships between CXCL9 and CXCL10 regarding age or disease duration.

The serum level of ANA results in the current study is consistent with those found by ELAMIR et al. (2019) which recorded a highly significant differences between patients and control where the percentage of ANA in the control group was (0.53 ± 0.23) U/mL and was (1.95 ± 5.51)U/mL in the patients group. Wichainun et al, (2013) also illustrated the prevalence of positive ANA is 90-100% in SLE patients; moreover our results were similar to the results performed by Frodlund et al. (2020). Who recorded increase ANA level in patients with SLE.

Interestingly, the findings in relationship to ds-DNA serum level is in agreement with previous study that recorded dsDNA level in control was (22.03 ± 17.2) while it was (133.2 ± 100.5)IU/mL in SLE patients referring to the elevation in anti-dsDNA (Gheita et al., .2018). In addition, ds‑DNA may decrease after the improvement of the disease through using the treatment, so anti-DNA antibodies can provide a basis for the treatment monitoring (Waris and Alam, 2004). Moreover, the high percentage of ds-DNA was found in most of the cases with autoimmune diseases including SLE (Song XY et al ., 2017)

CONCLUSION

Based on our results, it is concluded that CXCL9 and CXCR3 chemokines may have a role in the pathogenesis of SLE as they are increased in SLE patients. In addition, serum CXCL9 levels can be used as an independent biomarker of SLE activity. Furthermore, high levels of ANA and dsDNA are considered as a diagnostic indicator of SLE disease in people.

REFERENCES

1. Blotzer, J. W. 1983. Systemic Lupus Erythematosus 1: Historical Aspects. Marlyand State Med J 32:439.
2. Sliva, C.; Isenberg, M. (2001). Aetiology and pathology of SLE. Hospital Pharmacist, 7,
3. 133-42.
4. Talbot, J. H. 1974. Historical Background of discoid and systemic lupus erythematosus. In Lupus Erythematosus. Introduction xxxi SLEPR 2/11/04 8:24 PM Page xxxi E.L. Dubois, editor. University of California Press, Los Angeles
5. Arnett, F. C. and Shulman, L. E. 1976. Studies in familial systemic lupus erythematosus. Medicine 55:313.
6. Dubois, E. L. 1953. The effect of the LE cell test on the clinical picture of systemic lupus erythematosus. Ann Int Med 38:6
7. Harvey, A. M., Shulman, L. E., and Tumulty, P. A. 1954. Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. Medicine 33:291.
8. Harris, E. N., Gharavi, A. E., Wasley, G. D., and Hughes, G. R. V. 1988. Use of an enzyme linked immunosorbent assay and of inhibition studies to distinguish between antibodies to cardiolipin from patients with syphilis or autoimmune disorders. J Inf Dis 157:23–31.
9. Al-Sarray, Z. A., Al-Rayahi, I. A., Al-Hafidh, A. H., & Dwayyikh, A. T. (2020). Serum Protein Electrophoresis in Iraqi Systemic lupus Erythematous Patient. Al-Nisour Journal for Medical Sciences, 2(1).
10. Bultink, I. E., de Vries, F., van Vollenhoven, R. F., & Lalmohamed, A. (2021). Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus vs matched controls. Rheumatology, 60(1), 207-216.
11. Barbhaiya, M., & Costenbader, K. H. (2016). Environmental exposures and the development of systemic lupus erythematosus. Current opinion in rheumatology, 28(5), 497.
12. Chen, L. Y., Shi, Z. R., Tan, G. Z., Han, Y. F., Tang, Z. Q., & Wang, L. (2018). Systemic lupus erythematosus with and without a family history: a meta-analysis. Lupus, 27(5), 716-721.
13. Bengtsson, A. A., & Rönnblom, L. (2017). Systemic lupus erythematosus: still a challenge for physicians. Journal of internal medicine, 281(1), 52-64.
14. Beyan, E., Beyan, C., & Turan, M. (2007). Hematological presentation in systemic lupus erythematosus and its relationship with disease activity. Hematology, 12(3), 257-261.
15. Lee, Y. H., & Song, G. G. (2017). Association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and mean platelet volume with systemic lupus erythematosus disease activity: a meta-analysis. Journal of Rheumatic Diseases, 24(5), 279-286.
16. Balkwill, F. (2004). Cancer and the chemokine network. Nature Reviews Cancer, 4(7), 540-550
17. Redjimi, N., Raffin, C., Raimbaud, I., Pignon, P., Matsuzaki, J., Odunsi, K., ... & Ayyoub, M. (2012). CXCR3+ T regulatory cells selectively accumulate in human ovarian carcinomas to limit type I immunity. Cancer research, 72(17), 4351-4360.
18. Stojan, G., & Petri, M. (2018). Epidemiology of systemic lupus erythematosus: an update. Current opinion in rheumatology, 30(2), 144.
19. Duarte-García, A., Hocaoglu, M., Osei-Onomah, S. A., Dabit, J. Y., Giblon, R. E., Helmick, C. G., & Crowson, C. S. (2021). Population-based incidence and time to classification of systemic lupus erythematosus by three different classification criteria: a Lupus Midwest Network (LUMEN) study. Rheumatology.
20. Barber MRW, Drenkard C, Falasinnu T, Hoi A, Mak A, Kow NY, Svenungsson E, Peterson J, Clarke AE, Ramsey-Goldman R. Nat Rev Rheumatol. 2021 Sep; 17(9):515-532. Epub 2021 Aug 3.
21. Yin, X., Kim, K., Suetsugu, H., Bang, S. Y., Wen, L., Koido, M., ... & Bae, S. C. (2021). Meta-analysis of 208370 East Asians identifies 113 susceptibility loci for systemic lupus erythematosus. Annals of the rheumatic diseases, 80(5), 632-640.
22. Leong, P. Y., Huang, J. Y., Chiou, J. Y., Bai, Y. C., & Wei, J. C. C. (2021). The prevalence and incidence of systemic lupus erythematosus in Taiwan: a nationwide population-based study. Scientific reports, 11(1), 1-8.
23. Alhassan, N., Almetri, T., Abualsoud, S., Malhis, A., Al-Qahtani, K., Alwazna, A., ... & Al Ghanim, N. (2021). Causes of Hospitalization for Systemic Lupus Erythematosus in Saudi Arabia Compared With the Global Setting: A Retrospective Single-center Observational Study. Cureus, 13(10).
24. Uzuner, S., Durcan, G., Sahin, S., Bahali, K., Barut, K., Kilicoglu, A. G., ... & Kasapcopur, O. (2021). Caregiver burden and related factors in caregivers of patients with childhood-onset systemic lupus erythematosus. Clinical Rheumatology, 40(12), 5025-5032.
25. Esmaeilzadeh, E., Khodamoradi, Z., & Nazarinia, M. A. (2019). One-decade study of distinct features, morbidity and mortality of systemic lupus erythematosus (an update on systemic lupus erythematosus in the Fars Province of Iran). Lupus, 28(11), 1360-1367.
26. Gachpazan, M., Akhlaghipour, I., Rahimi, H. R., Saburi, E., Mojarrad, M., Abbaszadegan, M. R., & Moghbeli, M. (2021). Genetic and molecular biology of systemic lupus erythematosus among Iranian patients: an overview. Autoimmunity Highlights, 12(1), 1-13.

27. Jones, K. A., Smith, B., Granado, N. S., Boyko, E. J., Gackstetter, G. D., Ryan, M. A., ... & Millennium Cohort Study Team. (2012). Newly reported lupus and rheumatoid arthritis in relation to deployment within proximity to a documented open-air burn pit in Iraq. Journal of occupational and environmental medicine, 54(6), 698-707.
28. Belperio, J. A., Keane, M. P., Burdick, M. D., Lynch, J. P., Zisman, D. A., Xue, Y. Y., ... & Strieter, R. M. (2003). Role of CXCL9/CXCR3 chemokine biology during pathogenesis of acute lung allograft rejection. The Journal of Immunology, 171(9), 4844-4852.
29. Dai, H., Rachakonda, S. P., Penack, O., Blau, I. W., Blau, O., Radujkovic, A., ... & Luft, T. (2021). Polymorphisms in CXCR3 ligands predict early CXCL9 recovery and severe chronic GVHD. Blood cancer journal, 11(2), 1-12.
30. Cheng, C. C., Chang, Y. F., Ho, A. S., Sie, Z. L., Chang, J. S., Peng, C. L., & Chang, C. C. (2021). Irradiation Mediates IFNα and CXCL9 Expression in Non-Small Cell Lung Cancer to Stimulate CD8+ T Cells Activity and Migration toward Tumors. Biomedicines, 9(10), 1349.
31. Nakayama, T., Yoshimura, M., Higashioka, K., Miyawaki, K., Ota, Y., Ayano, M., ... & Niiro, H. (2021). Type 1 helper T cells generate CXCL9/10-producing T-bet+ effector B cells potentially involved in the pathogenesis of rheumatoid arthritis. Cellular Immunology, 360, 104263.
32. Kameda, M., Otsuka, M., Chiba, H., Kuronuma, K., Hasegawa, T., Takahashi, H., & Takahashi, H. (2020). CXCL9, CXCL10, and CXCL11; biomarkers of pulmonary inflammation associated with autoimmunity in patients with collagen vascular diseases–associated interstitial lung disease and interstitial pneumonia with autoimmune features. PloS one, 15(11), e0241719.
33. Choi, J., Kim, S. T., & Craft, J. (2012). The pathogenesis of systemic lupus erythematosus—an update. Current opinion in immunology, 24(6), 651-657.
34. Villarroel L, Massardo L, Martínez ME, et al. Survival of Chilean patients with systemic lupus erythematosus. Semin Arthritis Rheum. 2014; 24(1): 1-11.
35. Usami, M., Shimizu, M., Mizuta, M., Inoue, N., Irabu, H., Sakumura, N., ... & Yachie, A. (2019). Extensive serum biomarker analysis in patients with macrophage activation syndrome associated with systemic lupus erythematosus. Clinical Immunology, 208, 108255.
36. Graver, J. C., Abdulahad, W., van der Geest, K. S., Heeringa, P., Boots, A. M., Brouwer, E., & Sandovici, M. (2021). Association of the CXCL9-CXCR3 and CXCL13-CXCR5 axes with B-cell trafficking in giant cell arteritis and polymyalgia rheumatica. Journal of autoimmunity, 123, 102684.
37. Han, L., Yang, X., Yu, Y., Wan, W., Lv, L., & Zou, H. (2019). Associations of circulating CXCR3–PD-1+ CD4+ T cells with disease activity of systemic lupus erythematosus. Modern Rheumatology, 29(3), 461-469.
38. Yang, M., Cao, P., Zhao, Z., Wang, Z., Jia, C., Guo, Y., ... & Lu, Q. (2021). An Enhanced Expression Level of CXCR3 on Tfh-Like Cells From Lupus Skin Lesions Rather Than Lupus Peripheral Blood. Clinical Immunology, 226, 108717.
39. Henneken M, Dörner T, Burmester GR, et al. Differential expression of chemokine receptors on peripheral blood B cells from patients with rheumatoid arthritis and systemic lupus erythematosus. Arthritis Res Ther. 2005; 7(5):R1001-13.
40. ELAMIR, A. M., FARID, A. A., AMIN, E. S., HASSAN, H. A., MAGED, M. M., & AREF, A. A. (2019). Anti-nuclear antibody (ANA) patterns in egyptian systemic lupus erythematosus. Journal of the Egyptian Society of Parasitology, 49(2), 451-454.
41. Wichainun, R., Kasitanon, N., Wangkaew, S., Hongsongkiat, S., Sukitawut, W., & Louthrenoo, W. (2013). Sensitivity and specificity of ANA and anti-dsDNA in the diagnosis of systemic lupus erythematosus: a comparison using control sera obtained from healthy individuals and patients with multiple medical problems. Asian Pacific journal of allergy and immunology, 31(4), 292.
42. Frodlund, M., Wetterö, J., Dahle, C., Dahlström, Ö., Skogh, T., Rönnelid, J., & Sjöwall, C. (2020). Longitudinal anti-nuclear antibody (ANA) seroconversion in systemic lupus erythematosus: a prospective study of Swedish cases with recent-onset disease. Clinical & Experimental Immunology, 199(3), 245-254.
43. Gheita, T. A., Abaza, N. M., Hammam, N., Mohamed, A. A. A., El-Gazzar, I. I., & Eissa, A. H. (2018). Anti-dsDNA titre in female systemic lupus erythematosus patients: relation to disease manifestations, damage and antiphospholipid antibodies. Lupus, 27(7), 1081-1087.
44. Waris G and Alam K: Immunogenicity of superoxide radical modified-DNA: Studies on induced antibodies and SLE anti-DNA autoantibodies. Life Sci 75: 2633-2642, 2004.
45. Song XY, Huang H, Liu YZ, Zhao YY, Li S and Xu ZJ: Coexistence of sarcoidosis and primary Sjögren syndrome: A clinical analysis and literature review. Zhonghua Nei Ke Za Zhi 56: 375-377, 2017 (In Chinese).