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Research Article

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Histological Evaluation of Arthritis in Mice

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Abstract

Arthritis is one the almost commonly prevalent painful diseases which cause limit the movement of joints. This study conducts to investigate histological alterations resulted in rheumatoid arthritis (RA)-induced in mice and estimating the levels of some serum biomarkers including serum IL-6, CRP and RF. Totally, 30 were purchased, acclimated, and divided into two groups; control that injected distilled water, and arthritis that injected adjuvant (CFA). Post the 25th day of experiment, all study mice of both groups were subjected for collection of blood and right ankle joints. Serologically, the findings of IL-6, CRP and RF of arthritis group were elevated significantly when compare to control mice. Histologically, the findings observed in mice of control group were included the proliferation of chondrocytes of articular cartilage with moderate cellular and subchondral marrow space, infiltration few inflammatory cells in dermis, proliferation of chondrocytes in articular cartilage with absence of inflammatory reaction in synovial cavity, moderate infiltration of inflammatory cells in subcutaneous tissue, nearly normal articular cartilage with regular tidemark and absence of sclerosis in marrow spaces, regenerative articular cartilage and regular tidemark line with presence of very narrow distance between articular cartilage and marrow bone, and existence of normal bone trabeculae. In arthritis mice, there were an infiltration of inflammatory cells in subcutaneous tissues and dermis, marked increases in numbers of osteoclasts, sclerosis, regular tidemark and proliferation of chondrocytes, low amonunt of abscesses in subcutaneous tissue, thickness of bone trabeculae, fragments of bone, subchondral sclerosis, moderate distance between bone and articular cartilage. In conclussion, RA causes severe impacts on tissues of affected joints. Studying the mechanism of inhibition during different inflammatory process appear needed.

Keywords: Rheumatoid arthritis, Interleukin-6, C-reactive protein, Rheumatoid factor, Iraq

Introduction

Arthritis or "joint disease" is an acute or chronic inflammation of bone or connective tissues in any joint causing varied degrees of pain [1]. According to recent reports, musculoskeletal illness is a more recurrent reason of disability in many populations, which increased remarkably in last 2 decades at alarming rates [2]. Episodic or chronic pain is the main cause of losing joint function and mobility which leading to impaired quality of life and psychological distress [3]. Inflammatory arthritis can range from autoimmune processes to inflammatory reactions and infections [4,5]. Additionally, arthritis may correlate with other diseases as celiac illness, tuberculosis, myositis and scleroderma [6]. Bacterial arthritis is a rare type of arthritis that affects the general public, but immunosuppression, aging, diabetes, artificial joints, and using of intravenous drugs may predispose to this case [7, 8]. Rheumatoid arthritis (RA) is an inflammatory condition of arthritis which characterized by inflammatory process that lays an important role in joint deformity with infiltration of inflammatory cells to synovial tissue. Joint symptoms result in severe joint pain and inflammation, causing joint dysfunction [9]. In comparison with the normal state, severe fatigue could be seen obviously in individuals who have not been diagnosed with RA [10]. The greater financial burden of RA, loss of control of prognosis, lack of lifelong activities, lack of social interaction, social aspects of life, psychological and medical problems are the main factors related to increasing anxiety in RA patients [11-13]. Also, there are many predetermined risk factors such as genetics and epigenetic mechanisms which develop RA by increasing an expression of inflammatory cytokines [14].

Recently, various reports showed that there is a significant increase in cases RA that might exist several weeks before clinical emergence of symptoms [15-17]. Also, joint inflammations with destruction processes caused by RA is often considered as the symptoms of disease activity, and continued of inflammation may result in permanent damaging to bones, cartilage and connective tissues [18,19]. Hence, investigation of histological changes occurred due to RA-induced in mice was the aim of the current study. Biomarkers including serum interleukin-6 (IL-6), C-reactive

protein (CRP) and rheumatoid factor (RF) were estimated, also.
Materials and Methods

Ethical Approval

Official license to doing this study was awarded by the Scientific Committee of the College of Medicine (University of Al-Qadisiyah).

Study Animals

Totally, 30 female BALB/c mice of 26-47 gm weight and <3 months age were purchased from the local markets, and acclimated for 1 week. During study period, mice were exposed to dark/light to 12/12 hours, received tap water and fed pellet,

Experimental Design

Initially, study mice were divided equally and randomly into two groups:

G1: Control group, the study mice were once injected 0.01 ml of distilled water into their right hind metatarsal foot-pad.

G2: Experimental group, the study mice were once injected 0.01 ml of using the complete Freund's adjuvant (CFA), (Sigma-Aldrich, Canada) into their right hind metatarsal foot-pad [20].

Samples

At the 25th day of experimental period, mice were euthanized with chloroform and blood samples were drained directly into free-anticoagulant vacutainer tubes for measurement of serum biomarkers; while, tissue samples of right ankle joints were sectioned carefully and kept covered with 10% neutral buffered saline (NBF) into plastic containers for histological examination.

Serology

Mouse IL-6 (SL0326Mo), CRP (SL0272Mo) and RF (SL0309Mo) ELISA Kits (SunLong Biotech, China) were provided to this study. Following the manufacturer instructions of each kit, the solution of standards/control and sera were prepared, processed, and read at 450 nm by the Microplate reader (BioTek, USA). The concentrations of IL-6 and CRP were identified quantitatively using the Standard Curve; while, the levels of RF were measured qualitatively.

Histopathology

The tissue samples were dehydrated, cleared, infiltrated, embedded, sectioned, loaded on slides, and stained with Hematoxylin and Eosin to be examined at × 100 and × 400 of light microscope (MEIJI, Japan), [21].

Statistical Analysis

The t-test in GraphPad Prism Software was applied to identification significant variation between values of targeted biomarker in both study groups at $P<0.05$ (*) [22]. Values were recorded as Mean ±Standard Errors (M±SE).

Results

Biomarkers

With regard to the serum biomarkers, the findings of arthritis group were elevated significantly (P±0.05) in concerning with levels of IL-6 (65.3 ± 1.236 ng/L), CRP (632.2 ± 14.58 pg/ml) and RF (0.392 ± 0.0165) when compared to those of control group (26.97 ± 0.78 ng/L, 353.3 ± 9.4 pg/ml and 0.172± 0.0068, respectively), (Figures 1-3).

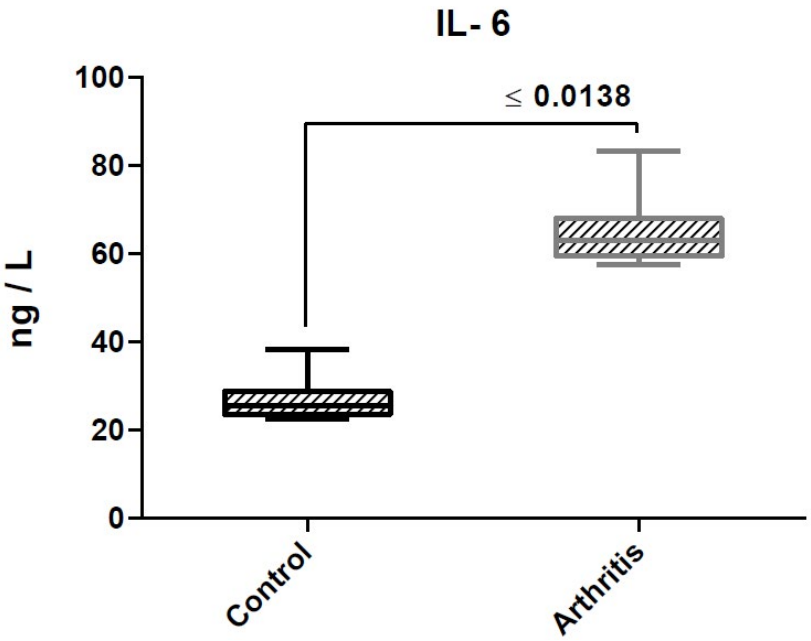


Figure 1: Levels of IL-6 in mice of control and arthritis groups.

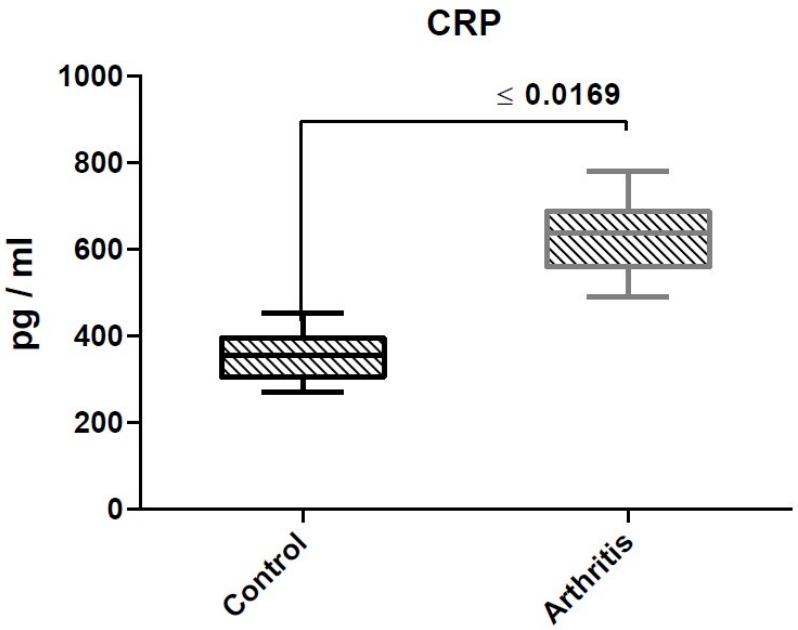


Figure 2: Levels of CRP in mice of control and arthritis groups.

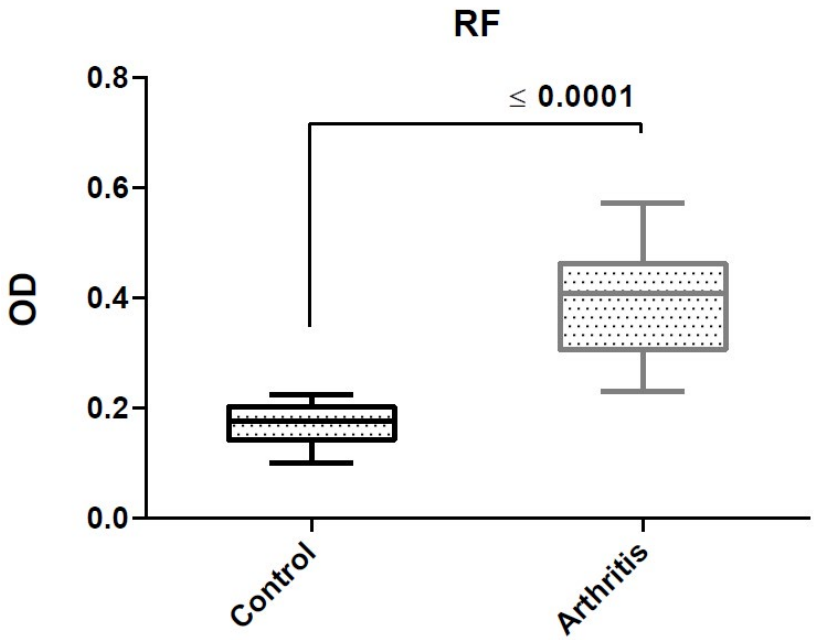
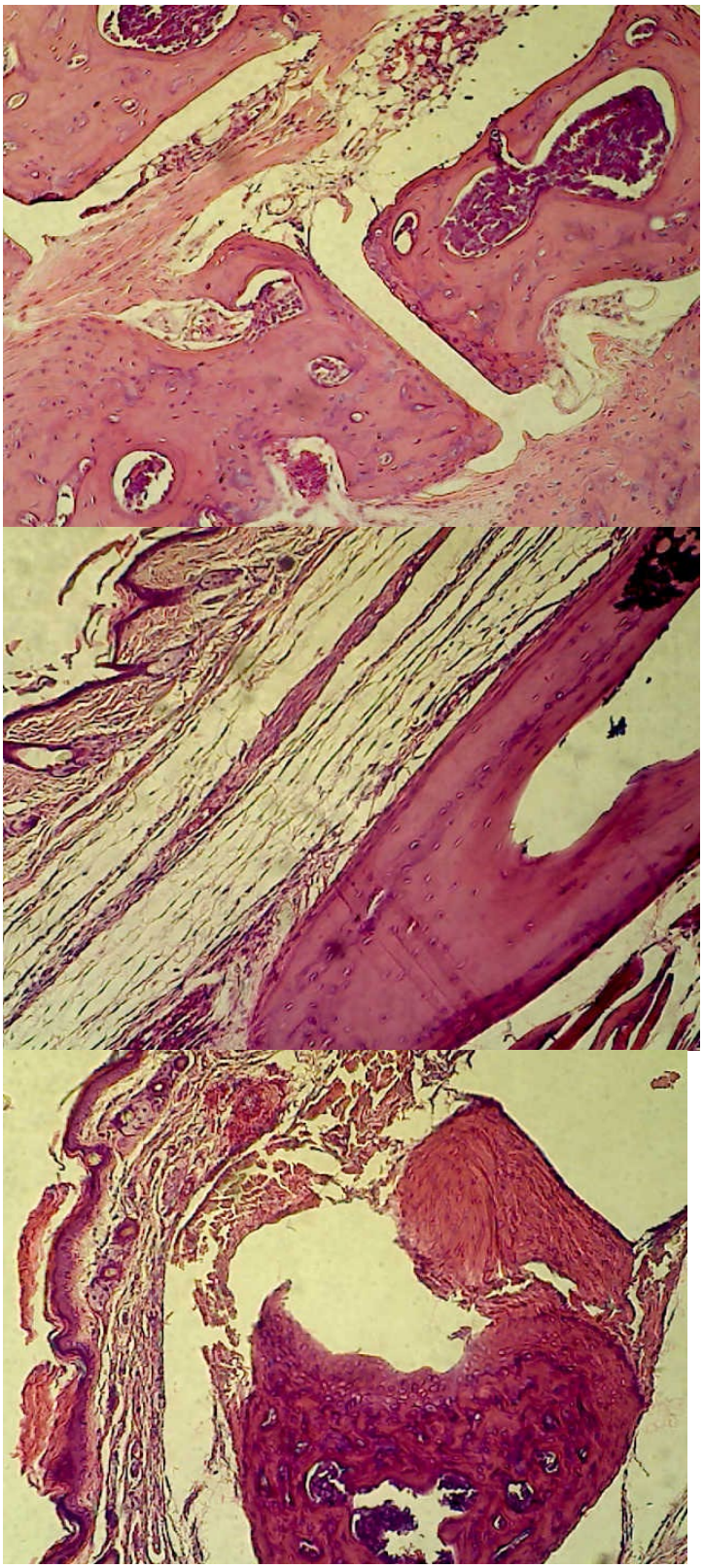


Figure 3: Level of RF in mice of control and arthritis groups.

Histology

The findings observed in mice of control group were included the proliferation of chondrocytes of articular cartilage with moderate cellular and subchondral marrow space, infiltration few inflammatory cells in dermis, proliferation of chondrocytes in articular cartilage with absence of inflammatory reaction in synovial cavity, moderate infiltration of inflammatory cells in subcutaneous tissue, nearly normal articular cartilage with regular tidemark and absence of sclerosis in marrow spaces, regenerative articular cartilage and regular tidemark line with presence of very narrow distance between articular cartilage and marrow bone, and existence of normal bone trabeculae (Figure 4).



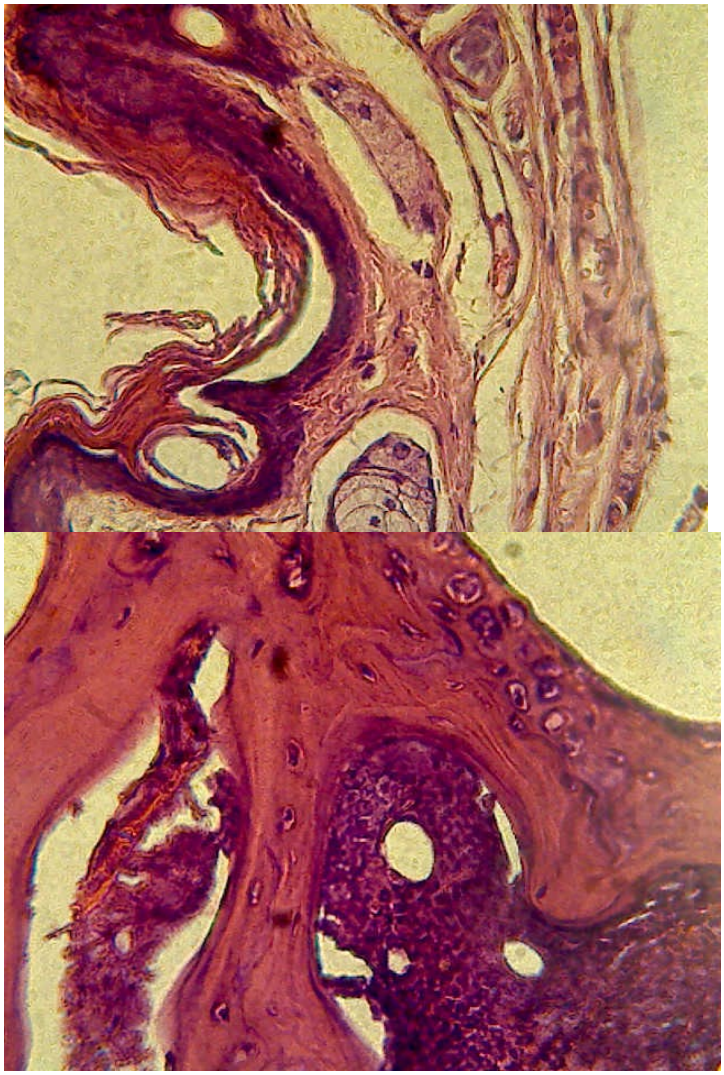
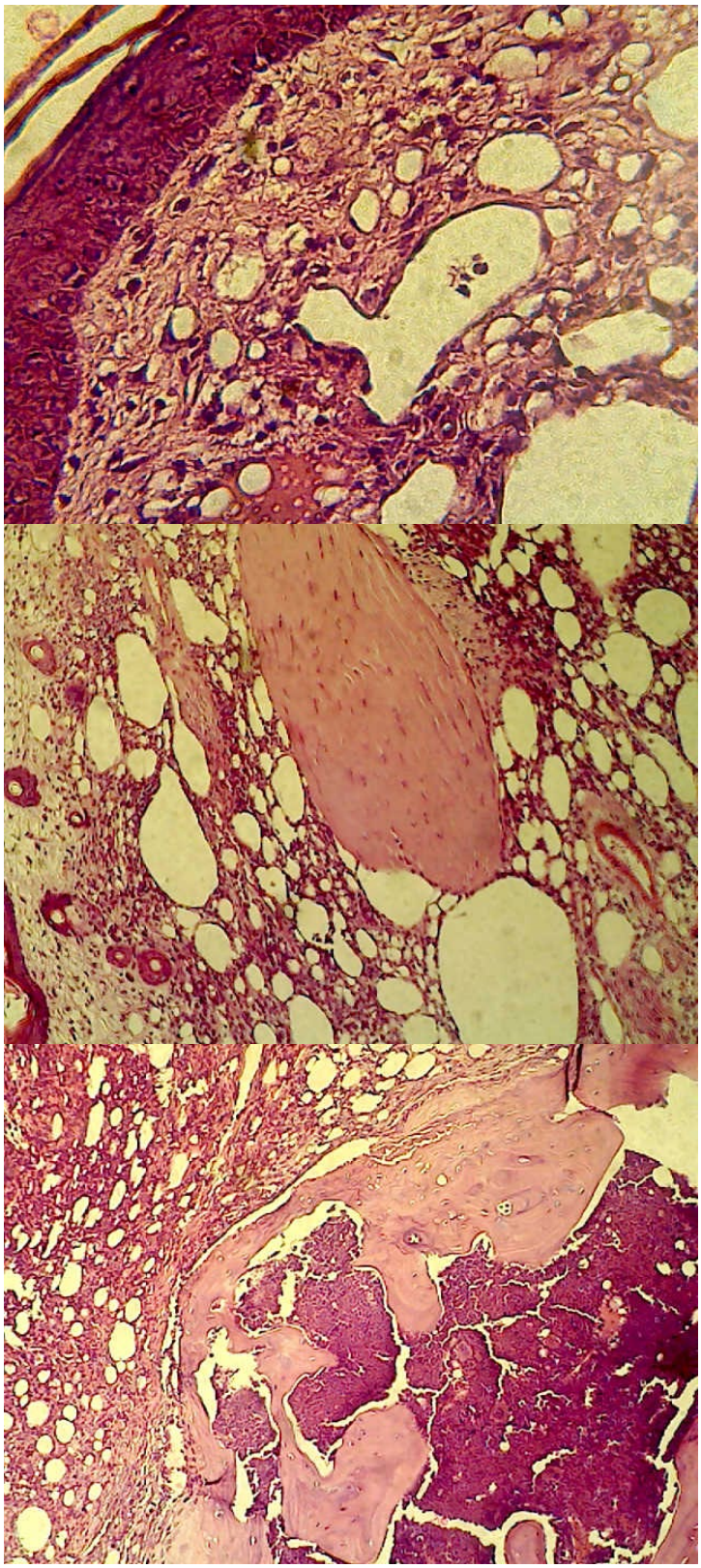


Figure 4: Histology of right ankle joint of control mice stained with H&E, ×100 & ×400.

In arthritis mice, there were an infiltration of inflammatory cells in subcutaneous tissues and dermis, marked increases in numbers of osteoclasts, sclerosis, regular tidemark and proliferation of chondrocytes, low amonunt of abscesses in subcutaneous tissue, thickness of bone trabeculae, fragments of bone, subchondral sclerosis, moderate distance between bone and articular cartilage (Figure 5).



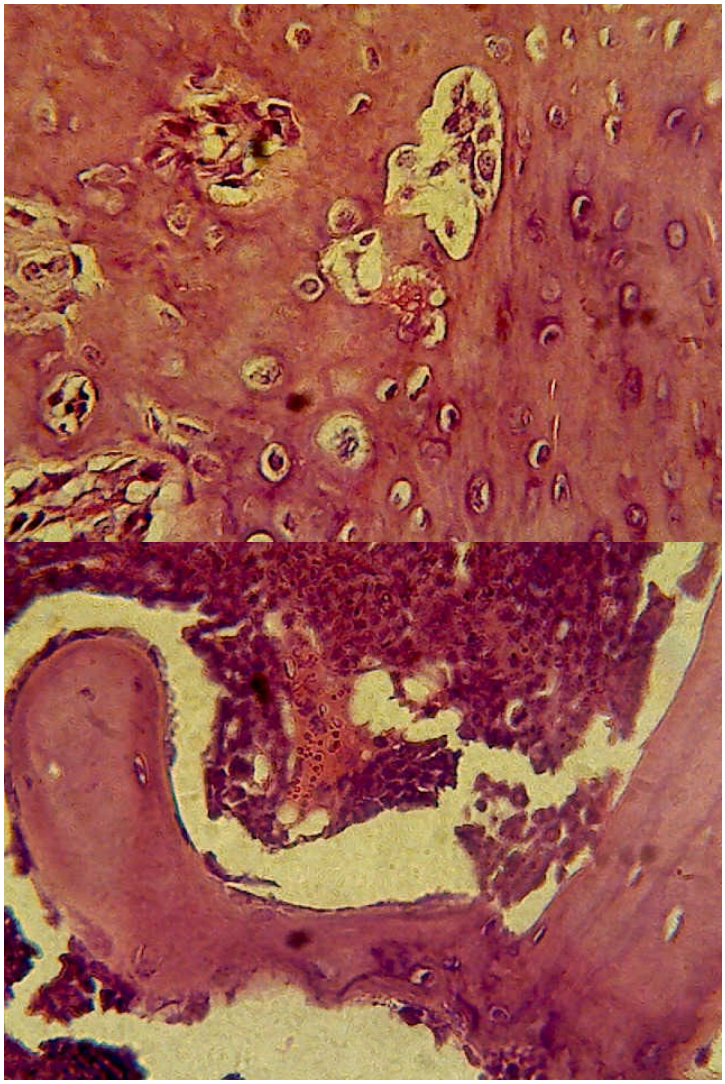


Figure 5: Histology of right ankle joint of arthritis mice stained with H&E, □100 & □400.

Discussion

RA is autoimmune illness that manifested clinically as chronic systemic inflammatory process to resulting in progressive damages in affected joint(s) and finally to lifelong disability due to complicated interplay between different cytokines that triggering proliferation of synovial cells [23-26]. Remarkable elevation in levels of IL-6, CRP and RF is in line with the results of several researchers [27-30]. Reeh et al. [31] mentioned that IL-6 shares the gp130 signaling receptor subunit, is highly expressed during RA with having a clear-cut anti-inflammatory effect in particular on fibroblast and macrophage. In addition, this marker appeared to having various activities on different cells which promoted or suppressed inflammatory processes in RA [32], ameliorating inflammation [33], chondroprotection [34] and development of spontaneous arthritis [35]. Takeuchi et al. [36] recorded that therapeutic intervention against IL-6 can repair the bone through reducing of joint and bone destructive process in association with osteoblasts and osteocytes.

Although, IL-6 can be functioned by driving the production of CRP post the inflammatory events and can act as key marker in different systemic inflammations its association with comorbidities and its overarching role in RA were not comprehensively identified [37]. However, CRP can participate actively in host defense mechanisms towards inflammatory responses and infectious agents through its binding to Fc□R and promoting for producing pro-inflammatory cytokines that lead to exaggeration the inflammatory loops [38-40]. In contrast to our findings, a number of observational and retrospective reports showed that several diseased individuals were having normal concentrations of CRP despite severe activity of RA [41-43]. These findings suggested that the higher levels of CRP may reflect only to one of RA signs [44]. Moreover, many factors could affect the baseline level of CRP during infection such as stress, dietary quality, female hormone levels and body fat [45,46].

Concerning RF, different studies of RA etiology have focused on the role of immune complexes and RF associated with vasculitis and

synovitis [47-49]. However, many authors seen that the presence of RF at higher titers correlates with increasing the risk of developing RA or even a more aggressive forms of disease and functional impairment [50,51]. Pertsinidou et al. [52] concluded that RF is highly associated with age at RA onset; but in accordance with sex, it appears that IgA RF and IgG RF are increased significantly in male RA while IgM RF is related to female RA.

In this study, the tissue sections of arthritis mice showed that there were significant alterations and severe infiltration of inflammatory cells. Various studies identified T cell responses and the role of chemokines in severity of RA. Many researchers underscore the importance of humoral immunity in this tissue [53-55]. In patients with arthritis, radiofrequency absorption can be seen as a sign of serious disease in which B cell activity is significantly impaired [56,57]. Recent clinical trials using B cell depletion ensure the idea that humoral immunity produced by RF could play a significant role development of RA [58-60]. Inhibition or stimulation of inflammatory mediators, pro-inflammatory cytokines and immune cells may be involved in RA pathogenesis [61,62]. Hence, alteration of inflammation or immune response represent a frequent mechanism for true incidence of RA symptoms as seen in clinical trials and experimental studies of animal-models [63,64]. Severity of histological signs of AR has been assessed by many authors who recorded that infiltration of inflammatory cells indicates cartilage deterioration [58].

Conclusion

RA causes severe impacts on tissues of affected joints, and immunogenicity might represent as one possible cause of non-responsiveness to treatment process. However, identification of new biomarkers with a real clinical utility remains a major topics on interest in RA. Studying the mechanism of inhibition during different inflammatory process appear needed.

Conflict of Interest

No.

Funding

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