Hyperferritinemia: A possible marker for diagnosis of systemic lupus erythematosus?

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Abstract: Objectives: Comparing the serum ferritin levels of patients with systemic lupus Erythematosus (SLE) during different phases of activity with rheumatoid arthritis (RA) and osteoarthritis (OA) patients as controls. **Materials & Methods:** Sixty SLE patients (56 females and 4 males) were divided into two groups marked as 1) low/no active (SLEDAI≤10) including 18 patients and 2) active (SLEDAI≥11) composed of 42 patients. Serum ferritin was determined in both SLE and control groups including 20 patients with OA and 20 with active RA (according to DAS28). Data were analyzed using SPSS software version 13.0. **Results:** Of 60 SLE patients, 61.7% had hyperferritinemia. Contrarily, only %5 and 15% of OA an RA patients showed elevated serum ferritin levels, respectively (P<0.001). In differentiating between SLE and RA, hyperferritinemia showed a specificity of 85% and a sensitivity of 61.6% with positive predictive value of 92.5% and negative predictive value of 42.5%. The mean ferritin titer in SLE patients was 2.7 times higher than normal value whereas it was 0.10 and 0.35times in OA and RA, respectively (P<0.001). Ferritin levels were elevated in 27 cases of active SLE and 10 of low/no active SLE but the difference was insignificant. Of SLE patients with nervous system involvement, all (6; 10%) had elevated level of serum ferritin (P<0.04).**Conclusion:** Hyperferritinemia is common in patients with SLE but in case of considerably high titers, the nervous system involvement should be considered. In women with polyarthritis, hyperferritinemia could be considered as a useful marker to differentiate between SLE and RA.
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1. Introduction

Systemic lupus erythematosus (SLE) is a common autoimmune disorder that may affect many organ systems and produces severe conditions. Early diagnosis, evaluating the activity and severity of disease, and proper treatments are essential. Clinical evaluation and paraclinical tests, in particular the detection of some autoantibodies and serologic parameters can help early diagnosis of the disease. C-reactive protein (CRP) test is not a reliable marker for diagnosis and evaluation of disease activity in patients with SLE (Zein, 1997; Bertouch., 1983; Hesselink, 1981). Ferritin, an acute phase reactant is not only a main protein of iron storage, but a regulator of immune system and may play a special role in autoimmune diseases (Recalcati, 2008).

In this study we evaluated the serum ferritin levels in patients with SLE at different stages of activity and further compared the values with those of patients with osteoarthritis (OA) and rheumatoid arthritis (RA) as control groups.

2. Materials and Methods:

This was a cross-sectional study carried out on patients visiting the Rheumatology Clinic at two main medical center of Mashhad University, north east of Iran. Sixty patients with systemic lupus erythematosus (SLE), 20 with rheumatoid arthritis (RA) as those with active non-lupus inflammatory disease and 20 with osteoarthritis (OA) with non inflammatory disease were included in the study based on simple random sampling method. Diagnosis of SLE and RA was accomplished using the American College of Rheumatology (ACR) criteria (Hochberg, 1997; Arnett, 1988). Patients were at different stages of diseases including the new cases, cases with active phase prior to treatment, and also those under treatment either the recurrent cases or at recovery phase. Rheumatoid patients selected from patients with active disease according to disease

activity score 28 (DAS28) (Prevoo, 1995). Following the delivery of proper explanations on objectives and method of the study and obtaining the informed consent forms signed by every members of the study population, the patients were referred to the hospital laboratory for further investigations. The laboratory tests performed were CBC, UA, serum creatinine and BUN, liver function tests (LFT), ESR, CRP, complement component levels (C3 and C4), Anti-dsDNA, serum ferritin (ELISA), Fe, and TIBC levels. Since the serum ferritin, in addition to acting as an acute phase reactant, is considered as an index of body iron stores, patients with iron deficiency anemia were excluded from the study to prevent the interfering effect of such patients on study results. According to the SLE Disease Activity Index (SLEDAI) (Nishiya and Hashimoto, 1997) score, patients with SLE were divided into two low activity (SLEDAI≤10) and high activity (SLEDAI≥11) groups with their serum ferritin levels tested and compared with the results found for the patients with RA and OA. The results were statistically analyzed by SPSS version 16.0. P-values less than 0.05 were considered as significant. This study was approved by the Research and Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran.

3. Results

Of 60 patients with SLE, 56 were females (93.3%) and 4 males (6.7%) with an age range between 13 to 65 years (mean 30 years). Among SLE patients, 18 had low or no active disease (SLEDAI≤10, 30%) and 42 with active disease (SLEDAI≥11, 70%). In control groups, 20 patients were with active RA including 17 females (85%) and 3 males (15%) with a mean age of 45 years, and 20 with OA composed of 13 females (65%) and 7 males (35%) with a mean age of 49 years. Although the distribution of age and sex were different between the study groups, using a regression logistic model, the difference was found to be an insignificant intervenient factor in all analyses.

As shown in figure 1, the serum ferritin level was elevated in 37 patients with SLE (61.7%), 3 patients with RA (15%), and 1 patient with OA (5%) and the differences found to be significant (P<0.001). The difference in serum ferritin level between the patients with SLE and those with RA demonstrated a sensitivity of 61.6%, specificity of 85% and positive and negative predictive values of 92.5% and 42.5%, respectively. Also, the difference in serum ferritin level between the patients with SLE and OA showed a sensitivity of 61.6%, specificity of 95%, and a positive predictive value of 97.3%.

The mean serum ferritin titer in patients with SLE was 2.75 times higher than the mean normal level whereas in those with RA and OA it was 0.35 and 0.10 times the mean normal level and that the difference was found to be significant (P<0.001).
Among the patients with SLE, the serum ferritin level was elevated in 27 patients with active disease and 10 patients with low/no active disease (P=0.52). There was no significant correlation between the serum ferritin level and the occurrence of serositis, arthritis, nephritis, and skin vasculitis in patients with SLE however, 6 patients were demonstrated to have nervous system involvement (10%) and all with increased level of serum ferritin (P=0.04).

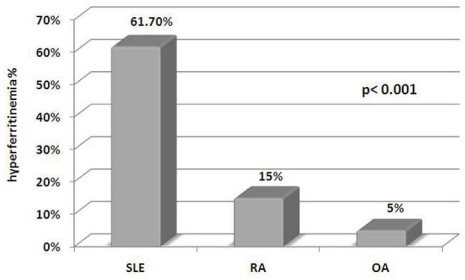

Figure 1: Frequency of hyperferritinemia in patients with SLE, RA, and OA

4. Discussions

The appearance and progression of autoimmune diseases may be influenced by hormonal, metabolic, and immune regulatory effects. Ferritin, an acute phase reactant, is a major iron storage protein within the cells and may increase in response to inflammatory stimulations (Cetinkaya, 2001; Orbach., 2007). Ferritin has a regulatory effect on immune system and may play a special role in autoimmune diseases (Recalcati, 2008; Zandman-Goddard, 2008).

Likewise, CRP is also an acute phase reactant and its serum level is elevated in active phase of many inflammatory and autoimmune diseases however it is not a usual finding in patients with SLE according to conventional methods. Serum CRP may elevate in cases of SLE with polyarthritis, serositis, and infections (Zein, 1997; Hesselink, 1981; Ter Borg, 1990).

Our study showed that 61.7% of patients with SLE had hyperferritinemia whereas only 15% of those with RA and 5% of cases with OA demonstrated elevated levels of this acute phase reactant (P<0.001). Hence, this marker could help to diagnose patients with SLE who have some clinical similarities with RA, particularly in young and middle aged women. The present study also showed a mean increase of 2.7 times the normal serum ferritin titer in patients with SLE which was much higher

than that found for serum ferritin level in patients with RA (P<0.001).

Nishiya and Hashimoto (1997) reported that patients with SLE have considerably higher levels of serum ferritin than those obtained for CRP values compared to RA. They also found a positive correlation between the elevated serum ferritin level and the activity of SLE.

Hesselink et al (1981) in their study on 10 patients with SLE concluded that the serum ferritin and CRP levels could not be constantly considered as indicators of inflammation and activity in all patients with SLE (Hesselink, 1981). In consistent with our study, Lim et al (2001) and Beyan et al (2003) also found that the serum ferritin level significantly increases in patients with SLE compared to patients with RA(Lim, 2001; Beyan, 2003).

We failed to find any significant difference between the increase in serum ferritin level of patients with active and inactive SLE however, in some studies, a correlation has been reported (Cetinkaya, 2001; Lim, 2001). Positive correlations between serum ferritin level and anti-DNA titer (Nishiya and Hashimoto, 1997), serositis and hematologic disorders (Lim, 2001), and nephritis have been demonstrated in patients with SLE.

In the present study, a positive correlation between higher serum ferritin levels and nervous system involvement in patients with SLE was also found.

Conclusions:

Hyperferritinemia is more frequent in active SLE than inactive phase. In patients with polyarthritis, the elevated serum ferritin levels provide a useful marker for differentiation between SLE and RA. Moreover, the nervous system involvement should be considered as a possible complication in patients with SLE who have increased titers of serum ferritin. Since the detection of serum ferritin is both easy and economic, the measurement of this substance is recommended in patients with SLE.

Disclosure:

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