Utility of Serum Ferritin Levels in the Differentiation of Anaemia in Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a chronic immune inflammatory disease characterized by a wide range of clinical manifestations. Anaemia in SLE is multi-factorial in origin and found in about 50% of patients. Anaemia of chronic disease (ACD), iron deficiency anaemia (IDA), autoimmune haemolytic anaemia (AHA), anaemia of chronic renal insufficiency, and cyclophosphamide-induced myelotoxicity are the most common causes. Aplastic anaemia, pure red cell aplasia (PRCA), pernicious anaemia, myelofibrosis, sideroblastic anaemia, haemophagocytic syndrome and thrombotic microangiopathy occur less frequently. A thorough history and physical examination is essential for placing the anaemia in its proper context. 1

Iron deficiency anaemia (IDA) is common in patients with SLE as a result of menorrhagia and increased gastrointestinal blood loss, caused by use of NSAIDs, aspirin, and oral anticoagulants. In addition to this, population-based surveys have found anaemia secondary to dietary deficiency of iron is fairly common in Indian population2 and this is also true for Indian patients with SLE.

Measurement of serum ferritin provides a useful indirect estimate of body iron stores, and a level of <15 ng/ml is generally taken as indicating absent iron stores. However, a ferritin levels of <30 ng/ml provides better positive predictive values for iron-deficiency anaemia when studied in several populations.3 Using the receiver operating characteristics (ROC) a study in Indian rheumatoid arthritis patients showed that the serum ferritin <82 ng/ml yielded maximum sensitivity and specificity and is useful in complementing and confirming the clinical impression of IDA.4

On the other hand, serum iron, total iron binding capacity (TIBC), and RBC indices mean corpuscular volume (MCV) mean corpuscular haemoglobin concentration (MCHC) have limited value in diagnosing IDA.

ACD occurs in patients with acute or chronic immune activation. The condition has thus been termed “anaemia of inflammation”. ACD typically occurs despite adequate reticuloendothelial iron stores and will improve with adequate treatment of underlying cause. Therefore the distinction between IDA and ACD is important particularly because of the risk of overlooking iron deficiency given the high prevalence in Indian population. IDA is an easily treatable form of anaemia. A ratio of <1 suggests anaemia of chronic disease, whereas a ratio of >2 suggests absolute iron deficiency coexisting with anaemia of chronic disease.7

SLE is a multi-systemic autoimmune disease that is characterized by an unpredictable disease course, interspersed with periods of remission and flares. Conventional serological markers of SLE such as anti-dsDNA and complement levels are not ideal as they are not sufficiently sensitive and specific for monitoring of disease activity, particularly in certain systems like the central nervous system and the gastrointestinal tract. Even for more

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common manifestations such as lupus nephritis, these conventional markers also lack sensitivity and specificity in gauging residual inflammation and predicting flares of renal disease. Thus, novel biomarkers for SLE activity have to be developed. Ideal biomarkers for SLE should have high specificity for the disease (or specific end-organ involvement) to aid early diagnosis have good correlation with disease activity and be sensitive to change in disease status to allow for serial monitoring, and be able to detect flares early so that treatment strategies can be instituted to minimize organ damage.8

In the present issue of the Journal, Pradhan V et al.9 have addressed this issue and made an attempt to correlate serum ferritin and its association with haematological and renal manifestations in 90 SLE patients. All these 90 patients had modest elevation of serum ferritin levels (270.2 ± 266.0 ng/ml) tested by ELISA method. They have concluded serum ferritin is an excellent marker of SLE which can be used for an evaluation of disease activity particularly in active stage of disease mainly in patients having haematological and renal manifestations. Their results are consistent with the findings of three previous studies published almost ten years back.10-12 A more recent study published in 2015, showed that serum ferritin levels had positive correlation with SLEDAI but also positively associated with proteinuria, serum urea and creatinine.13 The strength of the study by Pradhan V et al.9 lies in its unbiased cross-sectional inclusion of SLE patients. The limitation of this study is lack of characterisation the various anaemia categories in 34 patients with Hb <10 gm/dl.

What lessons can be learned from the study by Pradhan V et al? Is it time for the clinicians to use serum ferritin levels for judging the disease activity in SLE patients? Definite answer to this question depends on the results of the further studies on topic of biomarkers on SLE. A study published in 2016 evaluated the performance of serum protein markers for detecting concurrent clinical activity in patients with SLE. These were identified by proteomic study using a commercially available antibody-coated microarray screen of 274 targets. Among these, four protein biomarkers were studied in a cohort Chinese patients with SLE. These are Axl, ferritin, IGFBP2 and TNFR2. Axl is a member of the Tyro3-Axl-Meer (TAM) family of tyrosine kinase receptors and plays a major role in the immune response by regulating inflammation and helping to clear apoptotic cells. All these were more specific for SLE activity than conventional marker. TNF is an important cytokine involved in the pathogenesis of autoimmunity. TNF binds to two distinct receptors, TNF receptor 1 (TNFR1) and TNF (TNFR2). Insulin-like growth factor binding protein-2 (IGFBP2) is a member of the IGFBPs family that binds to insulin-like growth factors and hence regulates signalling through IGF receptors, Axl and IGFBP2, could differentiate active renal from active non-renal or inactive SLE.8

Further research is needed to determine the sensitivity, specificity and predictive value of serum ferritin levels and its utility in the differentiation of anaemia in Indian SLE patients.

References