Editorial

Persistent Thrombocytosis in Systemic Lupus Erythematosus. Activity, Reactivity, or What?

Hematological manifestations in systemic lupus erythematosus (SLE) are diverse. Some are common, others unusual; some are due to lupus, others are reactive to the inflammatory process, some reflect ongoing disease activity, and others, the presence of particular autoantibodies.

Thrombocytosis is considered when the platelet count is over 400,000/μl. The causes can be broadly categorized as clonal (including essential thrombocythemia and other myeloproliferative disorders), familial, and reactive or secondary (including iron deficiency, malignancies, infectious diseases, inflammation, and postsplenectomy or asplenic states)[1].

Hyposplenism (or asplenia or autosplenectomy) is defined as decreased splenic function resulting from diseases that impair that function, and may or not be associated with a reduction in splenic size. The filtering and immunogenic functions of the spleen are reduced to a varying degree in a number of illnesses, such as sickle cell anemia, autoimmune disorders (e.g., SLE, rheumatoid arthritis), celiac disease, amyloidosis, splenic irradiation, and, of course, splenectomy[2].

The reduction or absence of normal splenic function is accompanied by a slight to moderate increase in white cell and platelet counts. In addition, Howell-Jolly bodies and erythrocyte pits (depressions in the red cell membrane), as well as acanthocytes and target cells are present in the blood smear[2]. Moreover, radiolabeled sulfur colloid is not cleared by the spleen.

In terms of the pathophysiology of the autosplenectomy, several models have been proposed:

1. The classical model in sickle cell disease: in this disease, it has been suggested that functional asplenia is a consequence of altered perfusion imposed by intrasplenic sickling[3,4].
2. Other models in SLE: one model is associated with a defect in splenic phagocytic function. In a classical study, patients with lupus were found to have moderate to profound defects in Fc-specific splenic clearance; further, several patients had an almost total inability to clear IgG-sensitized erythrocytes from their circulation. Defective clearance was found to be significantly correlated both with disease activity and with the presence and levels of circulating immune complexes[5].

However, other patients, especially those with inactive disease, may have other mechanisms explaining hyposplenism.

In a study by Dr. Gabriela Castellino, *et al* published in this issue of *The Journal*, persistent thrombocytosis, an unusual manifestation in patients with SLE, is proposed as a clue to autosplenectomy[6]. Theirs is the first systematic investigation of thrombocytosis in a large population of patients.

In addition to accurately describing the prevalence of persistent thrombocytosis in SLE, their article also exemplifies the diversity of mechanisms underlying hematological manifestations of this disease. Among the small number of patients identified as having persistent thrombocytosis, in one-fifth of them thrombocytosis was not due to disease activity or a reactive process, but to the occurrence of functional autosplenectomy.

Although the prevalence of thrombocytosis reported by Castellino, *et al* is a reliable estimate, the prevalence of asplenia is probably underestimated because the screening procedure employed by the authors (persistent thrombocytosis) has low sensitivity; rheumatologists therefore should consider the estimate reported in the article as the minimum prevalence of asplenia in a lupus patient population.

The authors propose an association of autosplenectomy with antiphospholipid antibodies (aPL) since aPL were detected in all patients with functional autosplenectomy; and one patient met criteria for antiphospholipid syndrome. Given the scarce number of patients with functional

See Thrombocytosis in SLE: a possible clue to autosplenectomy? *page 1497*

autosplenectomy, it would be almost impossible to confirm this association; however, previous reports showing visceral infarctions[7,8] in patients with aPL would support this hypothesis. This concept is interesting since thrombocytopenia is associated with aPL; yet in some patients its correction, which would be considered clinically as an improvement, like one of the cases reported, may not reflect that.

The potential role of aPL in the development of autosplenectomy should be considered in all patients with SLE, but in particular in those with inactive disease, where, as suggested here by Castellino and by investigators elsewhere[9,10], other mechanisms such as splenic microthrombosis and infarctions due to aPL and lupus anticoagulant may explain the hyposplenism.

We agree with the recommendation of Castellino and coworkers, that any patient with SLE presenting persistent thrombocytosis (or any other alteration in the complete blood count) must have a blood smear examined by a hematologist. Even though the blood smear lacks sensitivity for detecting hyposplenism, it can be easily performed in any laboratory[11]. If Howell-Jolly bodies, pitted-erythrocytes > 2%, acanthocytes, and target cells are seen[11], a diagnosis of autosplenectomy should be strongly considered and the immunization against the encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*) must be provided.

Readers should consider some potential limitations of the study. Recent thrombocytosis was not defined by the authors, therefore, one should be circumspect to generalize these findings to patients with prevalent thrombocytosis. Also, they do not describe the time between the measurement of aPL and detection of thrombocytosis. Finally, although autosplenectomy is well demonstrated in the 3 patients reported, the cause of persistent thrombocytosis among the other 14 patients was not determined.

For now, we still do not know the cause of persistent thrombocytosis in most patients with lupus; therefore, when seeing a patient with SLE and persistent thrombocytosis one should wonder: Is it activity, reactivity, or what?

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