in PBSC relative to PB. The data have implications for HSCT and adoptive immunotherapy.

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To the editor:

Antinuclear antibody (ANA)–positive thrombocytopenia: primary, but with a difference

In the recent Vicenza Consensus Conference,[1] 2 clinical-immunologic entities have been considered when defining the criteria for differentiating "primary" from "secondary" forms of immune thrombocytopenias. However, although the thrombocytopenia associated with the presence of antiphospholipid antibodies is discussed at some length (obviously within the limits of a standardization conference), this is not so for ITP with antinuclear antibodies (ANA), which is even more complex and challenging.

There are 2 eras in the study and in the gradual elucidation of this intriguing clinical and immunologic entity. The first clinical era included the description of distinct histologic patterns in spleens resected from apparently idiopathic ITP patients who then went on to develop systemic lupus erythematosus (SLE).[2,3] At the same time there was a hot debate as to whether splenectomy for ITP could precipitate SLE,[4] a hypothesis that was ultimately disproved.[5] The second era is founded mainly on longitudinal studies of patients with ITP in which low-titered ANAs did not predict for the late development of SLE,[6] but high-titer ANA, irrespective of subtype, did.[7,8] In a recent study Abbadi et al[9] have found that a positive ANA test (no pattern specified) predicted for a poor response to initial steroid therapy in adults with ITP.[9]

There is no doubt that an isolated positive ANA test in low titers does not contradict the diagnosis of primary chronic ITP, even it there already appears to be a different response to corticotherapy. However, the condition may progress, step by step, along with the increasing amount of ANA and, of course, of other antibodies such as anti-ds DNA, anti-Sm and antinuclear ribonucleoprotein antibodies. In a landmark study, Arbuckle et al[10] have found that in 115 of 130 patients with SLE (88%), at least one SLE autoantibody tested was present before the diagnosis (≤ 9.4 years earlier; mean, 3.3 years). In this clinical material ANAs appeared significantly earlier than the other, more "ominous" antibodies. Similarly, in an imprecise number of ANA-positive ITP patients, a progressive spreading of autoimmunity ("a crescendo of autoimmunity"[10]) may take place, from organ-specific to non–organ-specific antibodies.

In conclusion, the potential evolution from ITP to SLE depends on a galaxy of genetic and epigenetic factors that dictate the fate of any single case. However, the demonstration of varying degrees of steroid-refractoriness in the ANA-positive subgroup, together with long clinical and immunologic histories such as those that have been discussed warrant, in my opinion, a special consideration for this entity, which even at the stage of conventional "primariness" carries some degree of difference.

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Response

Immune thrombocytopenic purpura: terminology and definitions

We thank Professor Marmont for his interest in our work and for the opportunity to further discuss some controversial aspects on terminology and definitions in immune thrombocytopenic purpura (ITP).[1]

Primary ITP is a diagnosis of exclusion, characterized by a great heterogeneity in the pathogenesis and clinical outcomes.[2] The International Working Group (IWG) is aware that certain cases of primary ITP may be accompanied by coexisting antibodies such as antiphospholipid or antinuclear antibodies (ANA). However, the IWG classifies as secondary ITP only those cases in which the underlying disorder modifies the natural course or influences the treatment approach. A significant proportion of patients diagnosed with ITP has been found to have ANA. For example, in a prospective study in 186 adult patients,[3] weak positivity (titer from 1:40 to 1:80) or definite positivity (titer higher than 1:80) were found in 18 (10%) and 7 (4%) of cases, respectively. However, the impact of ANA as an adjunctive prognostic marker in isolated thrombocytopenia, otherwise meeting our criteria for primary ITP, is not defined. Although the development of other autoimmune disorders, including systemic lupus erythematosus, has been reported in a minority of cases during prolonged follow-up (around 5%),[4] in a more recent retrospective analysis of 108 adult ITP patients the presence of ANA (titer higher than of 1:80) was found in 36 (33%), but no case of systemic lupus erythematosus was recorded after a mean follow-up of 3.6 years (range, 2.1-7 years).[5] This finding was also confirmed in a prospective evaluation in patients with high ANA titer (1:160 or higher) after a similar follow-up period.[6] Regarding the less favorable response to steroid therapy, the study cited by Marmont[7] refers to a small cohort of patients (41 cases, 10 with ANA). In a larger study,[8] 39 patients with a positive test for ANA showed a response to steroids similar to that of 506 negative cases. Thus, IWG maintains that isolated ANA positivity at diagnosis should not shift toward a secondary form of ITP, unless large-scale prospective studies will provide evidence of a significant clinical impact of this finding.

We hope that Professor Marmont's comments will raise interest in such studies.

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