Slow evolution to systemic lupus erythematosus of isolated autoimmune thrombocytopenia

Sirs,

Antinuclear antibody (ANA) positive individuals with isolated autoimmune thrombocytopenia do not seem to evolve to SLE, even after a long follow up (1,2). In a recent retrospective evaluation of clinical files, Moutsopoulos *et al*. (1) showed that hematological abnormalities such as thrombocytopenia in ANA positive individuals are not associated with an evolution to SLE after a follow up of 2-5 years. In the same study arthralgia, easy fatigue and myalgias in ANA positive individuals also did not evolve to any specific autoimmune disease during the follow up period. On the contrary, the development of SLE increases with the presence of arthritis, fever, butterfly rash, discoid rash, Raynaud's phenomenon and anti-Ro/SSA antibodies in ANA positive individuals (1). Here we describe 2 patients with autoimmune thrombocytopenia, both ANA positive at onset, who developed SLE after 7 and 10 years respectively, a very long lapse of time between the onset of cytopenia and the complete expression of the autoimmune disease.

A 12-year-old female presented with a symptomatic (diffuse petechiae) thrombocytopenia (4000/mm^3). Anti-platelet antibodies, ANA (1:640) (determined by indirect immunofluorescence on monolayers of Hep-2) and anti-neutrophil antibodies were present, while anti-DNA antibodies were absent. No other ACR diagnostic criteria were present until she was 19 years old. She was initially successfully treated with steroids, followed by a low-dose steroid maintenance regimen (deflazacort 6 mg/day) with a platelet count constantly above 50,000/mm^3. Relapses occurred at all suspension attempts. At age 16, because of a new episode we decided to try a single high-dose intravenous administration of immunoglobulins, but after 8 months she relapsed again. Very high oral doses of steroids were administered only 4 days a month for six months, in accordance with a recent report (3), but after a transient response she relapsed soon after withdrawal. When she was 19, hypocomplementemia was detected (C3 79 mg/dL, C4 5 mg/dL); 8 months later a maculo-papular photosensitive rash appeared on her forehead, subsequently taking on a malar appearance, associated with diffuse severe arthralgia with fever. For the first time the LE test resulted positive. Eventually, 7 years after the onset of thrombocytopenia, a definite diagnosis of SLE was formalized according to the ACR criteria (4). Prednisone (1mg/kg per day) was started with a rapid resolution of symptoms and normalization of the platelet count.

Our second patient was a 9-year-old female who presented with purpuric thrombocytopenia which responded well to steroids. In the following 6 months isolated thrombocytopenia persisted (40,000 - 60,000/mm^3), while complementemia was always normal (C3 96 mg/dL, C4 16 mg/dL) and associated with the presence of ANA (1:160, 1:1280). No other ACR diagnostic criteria were present until she was 19 years old. For 2 years she was treated with low-dose steroids, remaining asymptomatic for another 4 years, but ANA were always present (1:320), with platelets > 50,000/mm^3 and normal complementemia (C3 96 mg/dL, C4 12 mg/dL). Afterwards, when she was 19 years old, Raynaud's phenomenon, arterial hypertension, alopecia, fever, musculoskeletal pain and leukopenia (WBC 2290/mm^3) occurred, while complementemia began to decrease (C3 63 mg/dL, C4 10 mg/dL).

Ten years after the onset of cytopenia, SLE was diagnosed. A renal biopsy, performed because of proteinuria and persisting arterial hypertension while she was on diuretic and beta-blocker treatment, showed a class III lupic nephritis; ACE-inhibitor therapy and prednisone at 1/8 mg/kg/day were started with a good response.

It is well known that ANA occur in nearly 4-5% of the general population (5). This could be an isolated finding without any pathological meaning. In other cases, ANA positivity is associated with other laboratory alterations and/or symptoms indicative of connective tissue diseases but not fulfilling classification criteria for any autoimmune disease.

It is very difficult to predict an evolution to SLE, either in ANA-positive individuals or in ANA-positive individuals with an isolated symptom. Isolated ANA or ANA associated with unspecific musculoskeletal abnormalities do not seem to increase the risk of developing a connective tissue disease (6); in contrast, if the ANA serum dilution is 1:80 or higher and combined with specific symptoms, there is a markedly increased risk of evolving to SLE (1). Among these specific complaints, thrombocytopenia does not seem to play as dominant a role as fever, arthritis, malar rash, discoid rash, photosensitivity and alopecia, which have all been statistically correlated with SLE (1).

Olivera *et al.* also recently described 4 cases of immune thrombocytopenic purpura diagnosed from 7 months to 5 years (average 3 years) before juvenile SLE became evident (7). In our 2 patients isolated thrombocytopenia was associated from its onset with high ANA; progression to SLE was, however, extremely slow. The low-dose steroid regimen administered to both our patients for many years, as well as all the other types of treatment attempted, did not prevent the clinical evolution to SLE, but we cannot exclude a slower progression of the disease. We would recommend a careful and constant follow-up of those patients who present both isolated thrombocytopenia and ANA.

L. LEPORE, *MD*
C.M. SALVATORE, *MD*
T. PAHOR, *MD*
V. KIREN, *MD*
A. VENTURA, *MD*

Clinica Pediatrica, IRCCS Burlo Garofolo, Trieste, Italy
Please address correspondence and reprint requests to: Dr. Loredana Lepore, Clinica Pediatrica, IRCCS-Burlo Garofolo, Via dell'Istria 65/1, Trieste 34137, Italy.
E-mail: leporel@burlo.trieste.it

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