Thrombocytosis in Systemic Lupus Erythematosus: A Possible Clue to Autosplenectomy?

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ABSTRACT. ***Objective.*** Thrombocytosis can be due to a myeloproliferative disorder or to a reactive or secondary process; among these are connective tissue disorders, in particular systemic lupus erythematosus (SLE). Besides being an expression of active disease, this unusual finding has also been described in SLE complicated by autosplenectomy. We evaluated the prevalence of thrombocytosis in a series of SLE patients and its relationship to functional asplenia.

Methods. Platelet count was evaluated in 465 consecutive Caucasian patients with SLE (387 women, 78 men, median age 54 yrs). Thrombocytosis was defined as platelet count > 400 × 10^9/l in at least 3 blood samples. All patients with thrombocytosis underwent peripheral blood smears for erythrocyte abnormalities and instrumental spleen evaluation.

Results. Seventeen patients (3.7%) with thrombocytosis were observed. Peripheral blood smear showed Howell-Jolly bodies, spherocytes, and target cells in 3/17 patients (17.6%). In the same 3 patients, ultrasound and computed tomography failed to evidence the spleen, and liver-spleen scans showed absence of splenic uptake (a finding indicative of functional autosplenectomy). One satisfied criteria for antiphospholipid syndrome (APS), and the other 2 patients had positive IgG antiphospholipid antibodies (aPL) at medium titer.

Conclusion. The sudden appearance and persistence of thrombocytosis or even the apparent reversal of thrombocytopenia in patients with SLE should raise suspicion of autosplenectomy, in particular if secondary APS or aPL is present. (First Release June 1 2007; J Rheumatol 2007;34:1497–501)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS
THROMBOCYTOSIS
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ANTIPHOSPHOLIPID ANTIBODIES

Thrombocytosis is typically discovered as an incidental laboratory abnormality when the routine complete blood count is obtained. By far, the most common cause of thrombocytosis is a reactive or secondary process[1]: connective tissue disorders, in particular systemic lupus erythematosus (SLE), are listed among these. Besides being an expression of active disease, this finding has also been described in the setting of SLE complicated by autosplenectomy, suggesting that thrombocytosis may be an indicator of autosplenectomy[2,3]. While true congenital asplenia is a coincidental finding in SLE, acquired functional asplenia is described in 3% to 7% of cases[4-7]. Among the possible pathogenetic explanations are splenic vasculitis and antiphospholipid-related coagulopathy.

We evaluated the prevalence of thrombocytosis in a series of patients with SLE and its relationship to functional asplenia.

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MATERIALS AND METHODS

With informed consent and ethics committee approval, the platelet count was determined in 465 consecutive Caucasian SLE patients (387 women, 78 men; mean age 54 yrs, range 20–89 yrs; median disease duration 6 yrs, range 3 mo to 25 yrs) fulfilling the 1982 American College of Rheumatology criteria for the disease[8].

Serological tests included antinuclear antibodies (ANA; by indirect immunofluorescence method with HEp-2 substrate), anti-DNA antibody (indirect immunofluorescence with *Crithidiae luciliae* substrate and by enzyme immunoassay), antibodies to extractable nuclear antigen (ENA; by ELISA), antiphospholipid antibodies (aPL; standardized ELISA kit), and lupus anticoagulant (LAC; by kaolin clotting time and Russell's viper venom test).

Thrombocytosis was defined as a platelet count > 400 × 10^9/l in at least 3 blood samples taken during 3 consecutive visits 3 months apart from each other. All patients with thrombocytosis underwent a peripheral blood smear and abdominal ultrasonography (US). Peripheral blood smears were stained with May-Grunwald Giemsa.

In addition, a peripheral blood smear was performed in 20 consecutive SLE patients without thrombocytosis (6 with secondary APS) matched for sex, age, and disease duration.

In the presence of erythrocyte abnormalities (Howell-Jolly bodies, spherocytes, increased number of "pitted" erythrocytes) and in the absence of US spleen visualization, a computed tomography (CT) scan and a selective liver-

spleen scan with ^{99m}Tc-radiolabeled sulfur colloid (^{99m}Tc-SC) and/or ^{99m}Tc-radiolabeled heat-damaged autologous red blood cells (^{99m}Tc-HDRBC) were performed.

Splenic size was estimated by real-time US using an Esaote AU5 scanner. Measurements in 3 planes were used to calculate spleen volumes.

CT was performed with a Tomoscan Philips SR 7000 scanner using intravenous contrast. The interval between sections varied between 10 and 30 mm using 1.0 mm collimation.

Sulfur colloid scan was performed 14 min after intravenous injection of 100 MBq ^{99m}sulfur colloid; the spleen scan was performed 30 min after intravenous injection of 60 MBq (1.5 mCi) of ^{99m}Tc-autologous red blood cells heat damaged during their *in vitro* labeling process. For both scans a series of planar scans of the abdomen were taken by a single-head camera equipped with a high resolution parallel-hole collimator (415W Elscint Haifa) to identify the presence of the spleen and/or any accessory splenic tissue.

RESULTS

Among the 465 Caucasian SLE patients, 17 (3.65%, 95% CI 1.9–5.3%; 16 women, 1 man, mean age 48 yrs, range 19–70 yrs) had recent onset of thrombocytosis. Autoantibody profiles of these patients were: ANA in all 17 patients, anti-DNA in 5, ENA in 7 (5 anti-Ro/SSA, 1 anti-RNP, 1 anti-Sm), and aPL and/or LAC in 6. At the time of platelet determinations all the patients had inactive SLE (European Consensus Lupus Activity Measurement scale score ≤ 1). All 17 patients had peripheral blood smears. Howell-Jolly bodies, spherocytes, and target cells suggestive of asplenia were detected in 3 of these patients (17.6%). In these 3, US showed splenic atrophy (confirmed by CT), while a selective liver-spleen scan with ^{99m}Tc-SC or ^{99m}Tc-HDRBC showed no splenic uptake (indicative of functional autosplenectomy). Other possible causes of thrombocytosis (tuberculosis, cirrhosis, inflammatory bowel disease) and asplenia (sickle cell disease, celiac disease, ulcerative colitis) were ruled out.

The 3 patients with functional autosplenectomy had aPL and/or LAC antibodies (1 patient had positive LAC and medium-titer IgG aPL; 1 patient had positive high-titer IgG aPL; 1 patient had positive medium-titer IgG aPL).

One patient had a history of venous thromboembolism and satisfied the criteria for definite antiphospholipid syndrome (APS)[9]. Notably, the prevalence of either antiphospholipid antibodies or positive LAC in our cohort of 465 SLE patients was 28%.

None of 20 SLE patients without thrombocytosis showed the presence of Howell-Jolly bodies and pitted erythrocytes.

Details of the 3 cases of SLE in whom persistent thrombocytosis led to the discovery of autosplenectomy are described below.

Patient 1. This case has been described in detail[2]; in December 1996 a 34-year-old Caucasian woman with SLE for 2 years presented with a severe disease flare characterized by cutaneous vasculitis requiring high doses of glucocorticoids, plasma exchange, and pulse intravenous cyclophosphamide. Prednisone 10 mg daily and azathioprine 100 mg daily were necessary as maintenance. Aspirin 100 mg daily was added because of the presence of LAC and high-titer IgG aPL. After the first cyclophosphamide pulse, she developed a persistent unexplained thrombocytosis (platelet count ranging from 46 to 910 × 10^9/l). Leukocyte count was within normal range. Peripheral blood smear showed Howell-Jolly bodies, spherocytes, and target cells. Abdominal US and CT scan revealed a markedly atrophic spleen, which failed to take up either ^{99m}Tc-SC or ^{99m}Tc-HDRBC at scintigraphic evaluation (Figure 1). In April 1998 she was admitted to the emergency department with deep vein thrombosis complicated by pulmonary embolism. According to the Sapporo criteria[9] a diagnosis of APS was established and longterm oral anticoagulation was started. She underwent polyvalent pneumococcal vaccination to avoid infectious complications. US examination and ^{99m}Tc-HDRBC scintigraphic evaluation performed in January 2006 confirmed the autosplenectomy. The platelet count was 550 × 10^9/l at that time.

Patient 2. An 18-year-old Caucasian male was diagnosed with SLE and autoimmune hepatitis at age 8 years. Clinical onset of disease was characterized by a scaly, erythematous rash over his face and arms, malaise, pleural and pericardial effusions, positive ANA and anti-dsDNA, positive IgG aPL (medium titer), thrombocytopenia (47 × 10^9/l), and elevated transaminase levels (AST 402 U/l, ALT 227 U/l), with negative hepatitis B and C markers. A liver biopsy showed interface hepatitis and a lymphocytic infiltrate of the portal zones. He was treated successfully with glucocorticoids and aspirin (100 mg/day). In 1995, steroid-sparing therapy with azathioprine was withdrawn after a few months due to worsening transaminase levels. At the age of 10 years, he had a recurrence of pericarditis and thrombocytopenia (45 × 10^9/l). It reversed after a short course of high-dose glucocorticoids. Subsequently, clinical remission of SLE and normal transaminase levels were maintained by prednisone 5–10 mg daily and cyclosporin A 150–200 mg daily. He remained asymptomatic until July 2002 when, due to a persistent increase of transaminase levels and sudden appearance of thrombocytosis (621 × 10^9/l) with normal leukocyte count, he was readmitted to hospital. The presence of aCL was confirmed and a peripheral blood smear showed Howell-Jolly bodies, spherocytes, and target cells. Abdominal US and CT scan revealed a marked increase of the hepatic volume and a small spleen (3.8 × 2 × 1.5 cm). A liver-spleen scan revealed a markedly atrophic spleen, which failed to take up either ^{99m}Tc-SC or ^{99m}Tc-HDRBC (Figure 2). A diagnosis of autosplenectomy was made and pneumococcal polyvalent vaccine was administered. He started mycophenolate mofetil (1 g daily) and low-dose prednisone (7.5 mg daily), with an improvement of his liver enzyme levels. In January 2006 the platelet count was still elevated (656 × 10^9/l); US examination and ^{99m}Tc-HDRBC scintigraphic evaluation confirmed the persistence of autosplenectomy.

Patient 3. A 40-year-old Caucasian woman was admitted to hospital in January 2001 because of sudden appearance of cervical and axillary lymphadenopathy, stiffness, and swelling of

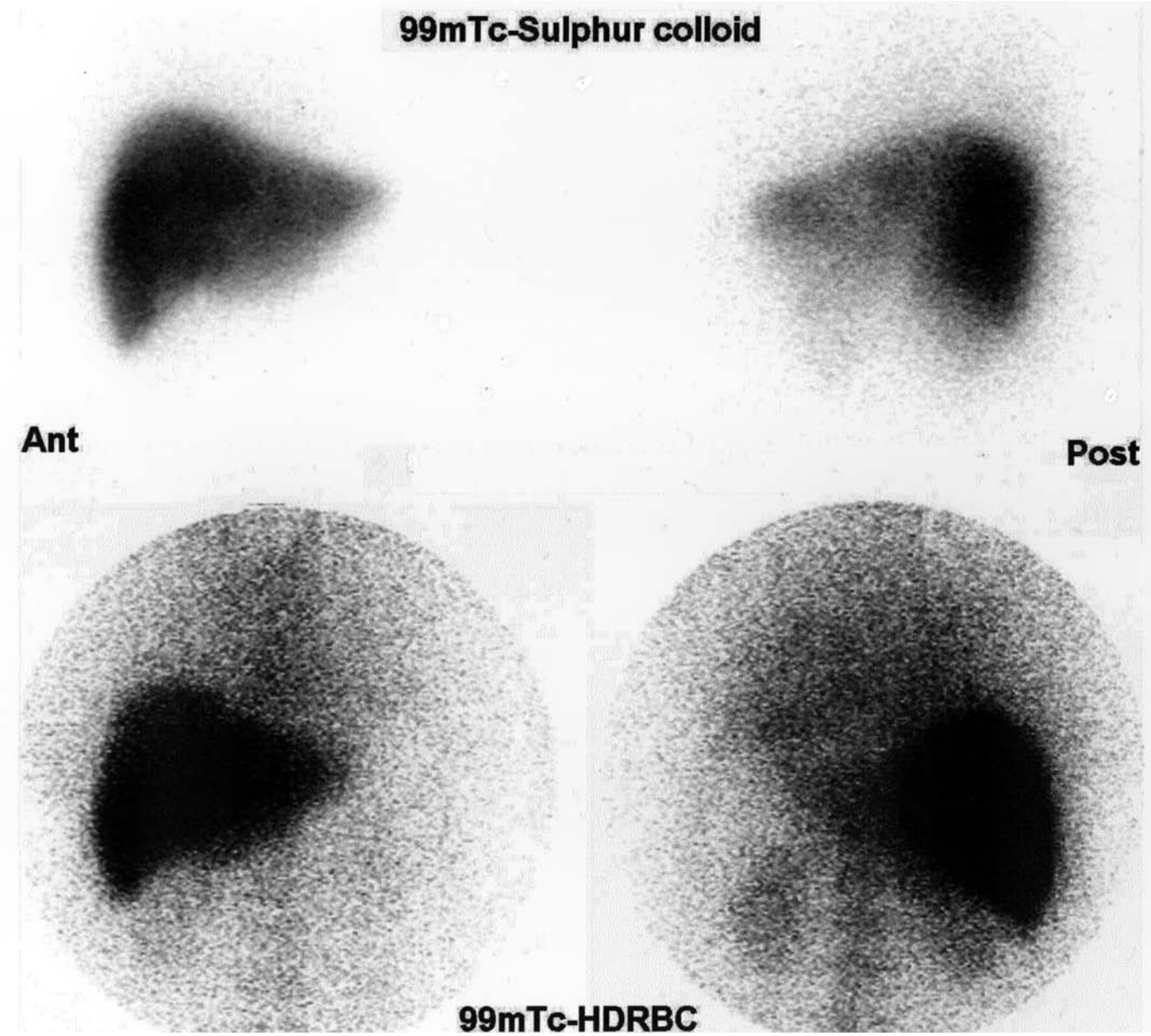

Figure 1. ^{99m}Tc-sulfur colloid (upper row) and ^{99m}Tc-HDRBC in Patient 1: no visualization of spleen with both methods (anterior and posterior views).

joints in fingers, elbows and wrists, low-grade fever, dry mouth, and dysphagia. Laboratory findings revealed elevated erythrocyte sedimentation rate (40 mm/h) and C-reactive protein (4.4 g/l, normal < 0.6 mg/dl), ANA, anti-dsDNA, IgG aCL (medium titer), and elevated platelets (710 × 10^9/l) with normal leukocytes. Subsequent investigation excluded an infectious disorder. Histological examination of a cervical lymph node showed a benign pattern of reactive follicular hyperplasia. An abdominal US showed retroperitoneal and hepatic lymphadenopathy and a dishomogeneous echogenicity of the spleen. Salivary gland US showed a chronic sialoadenitis with lymphadenopathy. A diagnosis of SLE was made and therapy with methylprednisolone (16 mg daily) and low-dose aspirin (100 mg/day) was started, with disappearance of the fever and lymphadenopathy. The thrombocytosis (811 × 10^9/l) persisted. One year later she was readmitted to hospital due to the appearance of mouth ulcers, fatigue, Raynaud's phenomenon, and photosensitivity. ANA, anti-DNA, anti-Ro-SSA, IgG aPL, and thrombocytosis (750 × 10^9/l) were detected. US failed to visualize the spleen, which was seen to be markedly atrophic (6.5 × 3 × 1.5 cm) on CT scan. Absence of splenic uptake was noted by ^{99m}Tc-SC and ^{99m}TC-HDRBC evaluation (Figure 2). A diagnosis of acquired autosplenectomy was established and pneumococcal polyvalent vaccine was given. She continued therapy with glucocorticoid (methylprednisolone 4 mg daily), aspirin 100 mg/day, and

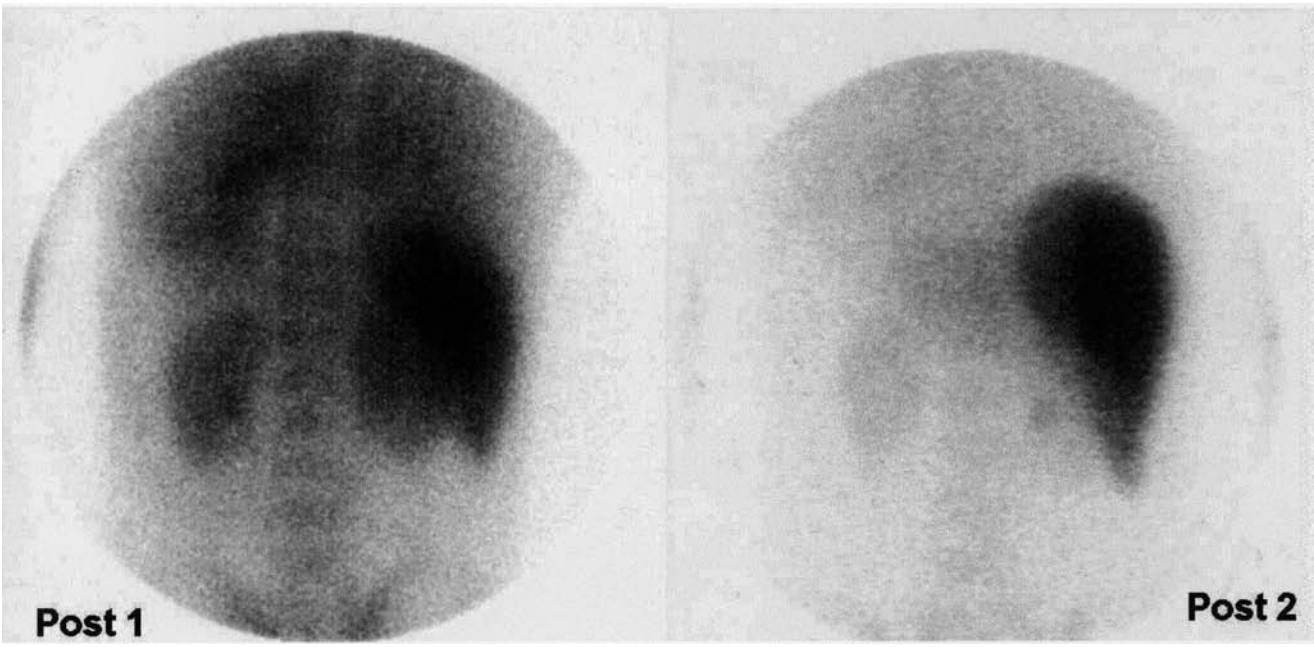

Figure 2. ^{99m}Tc-HDRBC (posterior views) in Patients 2 and 3: both patients show liver activity that is the compensatory effect of impaired splenic function in removing damaged red blood cells.

hydroxychloroquine 200 mg daily. Despite the high platelet count (557 × 10^{9}/l) still present in January 2006, the patient was well. US and ^{99m}Tc-HDRBC scintigraphic evaluation remained compatible with autosplenectomy.

DISCUSSION

Thrombocytosis could be the result of a reactive process (secondary thrombocytosis) or a myeloproliferative disorder. By far, the commonest cause of thrombocytosis is a reactive process such as tissue damage due to major surgery, infections, cancer, acute blood loss, hemolytic anemia, iron deficiency, drug reactions, and chronic inflammation[1].

Thrombocytosis due to SLE, however, is uncommon (3.65% in our series). Thrombocytopenia is more characteristic, particularly when aPL are present.

After the observation that thrombocytosis in a patient with SLE was a clue to autosplenectomy[2], we evaluated the prevalence of this complication in our entire series of 465 patients with SLE.

While splenomegaly is a frequent finding in SLE patients (9% to 46% of cases)[10], functional asplenia is infrequent, 3% to 7%[4-7], and in our series, 0.6%. The percentage of patients with functional asplenia in our series is less than in other reports, yet it represents a large homogeneous SLE population in which all patients with thrombocytosis were investigated for this complication.

To date 18 cases of acquired functional asplenia in SLE (including the first of our 3 patients) have been fully described[2]. Splenic vasculitis with silent infarction or blockage of the splenic reticuloendothelial system by high levels of circulating immune complexes is among the suggested mechanisms. However, the association of some cases with aPL, or even fully developed APS, suggested that multiple thrombotic events within the splenic microvasculature due to the aPL-related coagulopathy could be the cause of autosplenectomy in SLE[11,12]. Supporting this hypothesis is the presence of aPL or APS in the 3 patients we describe. Three other cases in our series had thrombocytosis and aPL, but not asplenia.

To our knowledge only one case of functional asplenia associated with APS has been reported previously. Unfortunately, in many of the reports reviewed the possibility of APS was not addressed[2].

Since thrombocytosis is unusual in SLE, this simple finding may be suggestive of autosplenectomy (among the other possibilities) and may warrant an investigation for aPL[13]. Indeed, in the 3 patients we have described, this was the key that prompted us to investigate for autosplenectomy.

In this regard, the second patient is the most striking. His history was characterized by persistent thrombocytopenia, while during the subsequent 3 years he showed above-normal platelet counts persistently, despite the presence of 3 conditions (SLE, positive aPL, and autoimmune hepatitis) usually characterized by thrombocytopenia.

Patients with SLE are at risk for bacterial infections[14,15], and it is well recognized that functional asplenia increases this risk because of impaired host defences against encapsulated bacteria. Cases of sepsis in patients with asplenia not immunized with pneumococcal vaccine have been described[16]. Therefore, functional asplenia always warrants pneumococcal vaccination[17-19].

Based on our results, the prevalence of functional asplenia is 17.6% in SLE patients with thrombocytosis and 0.6% in all SLE patients. The sudden appearance of persistent thrombo-

cytosis or even the spontaneous reversal of thrombocytopenia should raise the possibility of autosplenectomy.

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