

ANTICARDIOLIPIN ANTIBODY-RELATED THROMBOCYTOPENIA: PERSISTENT REMISSION AFTER SPLENECTOMY

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ABSTRACT

The lupus anticoagulant (LAC) and anticardiolipin antibody (ACA) syndromes require particular therapeutic approaches: thrombotic accidents are an indication for oral anticoagulant therapy (OAT), whereas severe thrombocytopenia may require the special treatments used for immunologic thrombocytopenic purpura (ITP). We describe the case of a 21-year-old male who presented with axillary vein thrombosis associated with LAC and ACA at high titers in December 1990. OAT was begun and, due to repeated episodes of thrombocytopenia, high-dose steroid therapy was later added with success. The daily steroid dose was reduced because of patent hypercortisolism, but the platelet count fell to $4 \times 10^9/L$. A bone marrow biopsy was characteristic for ITP. Splenectomy was performed in June 1993, and the platelet count rapidly normalized. Platelet antibodies were always detectable before and after splenectomy. The patient is currently asymptomatic, with platelet counts above $300 \times 10^9/L$ at one and a half years after splenectomy. This case indicates that ACA-associated thrombocytopenia, like ITP and HIV-related thrombocytopenias, can be successfully treated with steroids and splenectomy, even though different pathogenetic mechanisms are responsible for the antibody-induced platelet consumption.

Key words: anticardiolipin antibodies, thrombosis, thrombocytopenia, splenectomy

Thrombocytopenia is one of the most frequent features reported in the lupus anticoagulant (LA) and anticardiolipin antibody (ACA) syndromes.¹⁻⁵ The degree of thrombocytopenia varies from moderate or asymptomatic to severe. The dangerous hemostatic defect in the latter type may require specific treatments such as high-dose intravenous immunoglobulins, danazol or immunosuppressive therapy.^{2,6-8} We describe a case of ACA-related severe thrombocytopenia, observed for more than four years, that was first treated with corticosteroids and then with splenectomy, and followed by a sustained complete remission.

Case report

In January 1991, C.P., a 21-year-old male university student and volleyball player, presented

with a clinical history of recent right axillary vein thrombosis and a negative family history of thrombotic or hemorrhagic episodes.

There were no clinical signs and the hematochemical parameters thrombin and prothrombin time, fibrinogen, plasminogen, PF4, β_2 -thromboglobulin, D-dimers, antithrombin III, protein C and S levels were in the normal range. A prolonged APTT (42 sec, with a reference value < 32 sec) indicated a search for LA: the Kaolin Clotting Time test after Exner⁹ and the Diluted Russell Viper Venom test after Thiagarajan¹⁰ (a ratio of 2.6, with respect to a reference value < 1.2) were strongly positive. This positivity was confirmed through monthly checks till the end of the observation period. The patient immediately began oral anticoagulant therapy (OAT) with warfarin at appropriate dosages to keep the INR value between 2.0 and 3.0.

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In March 1992, IgG anticardiolipin antibodies (ACA) were measured by ELISA (FIRST Cardiolipina IgG reagents, Eurospital Pharma, Trieste, Italy) (reference value: 6.5 ± 2.4 IgG U/mL); values higher than the reference value + 2 SD, i.e. > 11.3 IgG U/mL, were considered positive. From the first measurement (June 7, 1991: 190 IgG U/mL) until today, the ACA values have always been pathologic, ranging from 38 to 260 IgG U/mL.

Levels of plasmatic β_2 -glycoprotein I (β_2 -GPI) were measured in quantitative immunoelectrophoresis after Laurell¹¹ with rabbit polyclonal anti-human β_2 -GPI antiserum (Behring, Scoppito, Italy), at a final concentration of 0.6% (v:v) in agarose gel; the value of a plasma pool from 30 blood donors was considered to be the 100% level of β_2 -GPI. The mean reference value in our laboratory was 98.5 ± 24.1 , with a range from 46-170%. From November 1992 to January 1994, the β_2 -GPI levels in our patient varied from 60 to 140%.

In order to exclude the possibility of concomitant resistance to activated protein C as the cause of the thrombotic tendency,¹² which was not evaluable with coagulative methods because of the OAT in course, we conducted a search through selective amplification for the Arg 506→Gln mutation on the factor V gene. The results were negative.

In July 1991, platelet count began to fall under 50×10^9 /liter, and the patient was given prednisone at an initial dose of 50 mg/day. Progressive reduction of this dosage, indicated by clinical and laboratory evidence of hypercortisolism, induced a relapse of thrombocytopenia that reached a platelet nadir of 4×10^9 /L in February 1992. Platelet transfusions and high-dose intravenous immunoglobulin (IVIg) (400 mg/kg) for five days were necessary for the hemostatic emergency. A bone marrow biopsy at that time showed normal cellularity with an augmented megakaryocyte matrix, especially in the younger stages, as occurs in idiopathic thrombocytopenic purpura (ITP). A subsequent cycle of prednisone therapy (100 mg/day) was carried out, but the lower dosage led to a second relapse, so that after two years of corticosteroid therapy, in July 1993, a splenectomy was per-

formed. The persistent high ACA titer and the thrombotic risk of splenectomy suggested suspending OAT and starting pre- and postoperative prophylaxis with heparin (25,000 U/day s. c.). The spleen was reduced in size and showed a histopathologic pattern of corticosteroid-induced lymphocytic depletion. The post-operative period was uneventful. The patient's previous history of juvenile thrombosis and the persistently high ACA levels suggested reinstating OAT. The platelet count, after a post-splenectomy zenith of 580×10^9 /L, stabilized above 300×10^9 /L more than a year later.

The antiplatelet antibodies, investigated with flow cytometry using FITC-conjugated polyclonal anti-IgG serum on donor or autologous platelets, often detectable in the first phase of thrombocytopenia, were present even after splenectomy (see Figure 1).

At present, the patient is doing well on OAT without thrombotic or hemorrhagic manifestations, and with platelet counts in the normal range. The entire clinical observation period is illustrated in Figure 1.

Discussion

ACA and LA autoantibodies include a wide group of anti-phospholipid antibodies directed against different epitopes.¹³ The relationships between β_2 -GPI, recognized as a co-factor for the binding of ACA with negatively charged phospholipids, and ACA and LA are controversial.^{14,15} In our patient β_2 -GPI levels were always in the normal range.

A congenital hereditary deficiency of anti-thrombotic factors was excluded through an accurate family history, the levels of ATIII, proteins C and S and plasminogen, and the search for a factor V Arg 506→Gln mutation after Dahlbäck.¹²

At present the pathogenesis of ACA-related thrombocytopenia is still under debate; anticardiolipin antibodies, in particular the IgG variety, may induce platelet activation and consumption or bind directly to platelet antigens.¹⁶ In this patient, platelet antibodies were detectable before and after splenectomy; it may be hypothesized that an important role for platelet

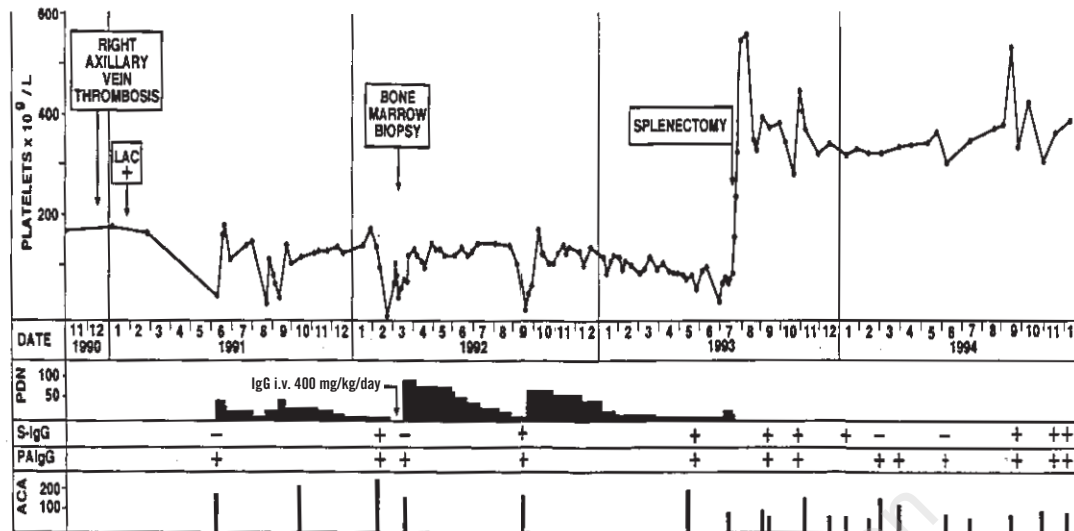


Figure 1. Summary of the clinical-therapeutic course of patient C.P. PdN = prednisone mg/day; S-IgG = serum antiplatelet antibodies; PAIgG = platelet-associated IgG; ACA = anticardiolipin IgG antibodies U/mL. The patient has been on oral anticoagulant therapy since January 1991. For details, see the text.

damage is supported by the very high titers of ACA, which persisted even with prednisone and IVIg therapy, despite temporary improvements in the platelet counts. Splenectomy, unlikely what occurs in many cases of ITP, did not modify the positivity of the anti-platelet serology. Splenectomy may implicate a thrombogenic risk in the presence of ACA but in our case, considering the degree of thrombocytopenia and the failure of corticosteroids, surgery was a last resort, and heparin prophylaxis (25,000 U/day s.c.) was effective in preventing thrombotic complications. Although the therapeutic problem of severe and persistent ACA-related thrombocytopenia was approached with splenectomy, the decision to resume antithrombotic therapy is an open question. In this case, OAT was started after the initial episode of venous thrombosis, and the persistently high titers of ACA indicated it should be continued. We have little knowledge regarding the future course of immunopathologic and clinical behavior, or long-term therapy in such cases.^{3,26} Therefore we chose to continue OAT but we do not know how many years of this treatment will be required to offer the patient a reasonable chance of being thrombosis free in the future.

To our knowledge, this is the first description

of ACA-related thrombocytopenia submitted to splenectomy. The antiplatelet serology, bone marrow pattern, efficacy of corticosteroid therapy and splenectomy, and ACA positivity indicate many similarities with other forms of immune thrombocytopenia. In typical idiopathic or immunologic thrombocytopenic purpura (ITP), the pathogenesis of thrombocytopenia is known to involve the action of platelet autoantibodies directed against different platelet antigens. Other cases of ITP can be recognized as a partial manifestation of a complex autoimmune disorder in which SLE, ACA, LA, antiplatelet and PAIgG antibodies may be present.^{4,16,17} Furthermore, LA or ACA may be observed for a long time after splenectomy in cases of ITP in complete remission. The beneficial effect of corticosteroids and splenectomy in ITP underlines its similarity with ACA-related thrombocytopenia.

Antiplatelet antibodies and ACA are also an important pathogenetic mechanism in HIV-related thrombocytopenia, where IVIg and corticosteroid therapy can induce a short-term improvement and a sustained remission follows splenectomy in 66-100% of cases, with no adverse effect on the progression of the HIV infection.¹⁸

In conclusion, this observation points out that even if different immunopathogenetic mechanisms underlie these thrombocytopenic conditions, they all share a therapeutic indication for splenectomy.

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