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A Successful Planned Pregnancy in a Patient with Antiphospholipid Syndrome Positive for Anti-CL-Beta2 GP I Antibody

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Summary. **A woman (gravida-2 para-0) with a history of two intrauterine fetal deaths accompanied with severe preeclampsia, who was positive for anti-cardiolipin-beta2 glycoprotein I antibody, was treated using prednisone and low-dose aspirin during a third pregnancy. This pregnancy continued uneventfully, and the prophylactic therapy was considered to be efficacious.**

Key words—anti-cardiolipin-beta2 glycoprotein I antibody, anti-phospholipid antibodies, anti-phospholipid syndrome, prophylactic therapy.

INTRODUCTION

A new concept concerning generalized thrombosis caused by autoimmune mechanisms has come to be accepted following the recognition of an antiphospholipid syndrome, which was first reported to include venous or arterial thrombosis and recurrent fetal wastage due to the formation of thrombi at the intervillous space[1]. The diversity of neurologic symptoms is reported to be associated with antiphospholipid antibodies[2]. The autoimmune factors reported to be implicated in the genesis of antiphospholipid syndrome are lupus anticoagulant, an acquired circulating serum gamma globulin which prolongs all phospholipid-dependent coagulation tests, and conventionally detected antiphospholipid antibodies. The importance of an antibody against the complex of cardiolipin and beta2 glycoprotein I was noted in addition to the conventionally detected antiphospholipid antibodies.[3,4,5]

The treatment for patients with recurrent fetal wastage positive for anti-cardiolipin-beta2 glycoprotein I antibody, however, has not yet been established, although a combination therapy with corticosteroid hormone and low-dose aspirin has been reported to be efficacious for patients with recurrent fetal wastage who are also positive for lupus anticoagulant or conventionally detected antiphospholipid antibodies.[6,7,8] In this report, the clinical course of a successful planned pregnancy in a typical patient with antiphospholipid syndrome is described, and the efficacy of prophylactic therapy for patients with antiphospholipid syndrome positive for anti-cardiolipin-beta2 glycoprotein I antibody is discussed.

CASE REPORT

In September, 1994, a 30-year-old woman first visited the obstetric outpatient clinic of Yurin Hospital with a pregnancy history of 2 intrauterine fetal deaths (IUFD). Her first pregnancy had resulted in IUFD of a baby boy weighing 600 grams at 24 weeks of gestation complicated by severe preeclampsia in March, 1991. Her second pregnancy also had resulted in IUFD of a baby boy weighing 500g at 24 weeks of gestation complicated by severe preeclampsia in June, 1994. Just after the second pregnancy, she had suffered her first epileptic seizure and was being administered 400mg of sodium valproate daily with her informed consent.

A laboratory examination revealed positive antinuclear antibodies (1:80) with a speckled pattern, prolonged activated partial thromboplastin time

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(APTT) (99.7 sec, control 30.0 sec) and positive antiphospholipid antibodies as evaluated according to our previously reported method[8] (anticardiolipin antibody, +11.9SD; antiphosphatidyl serine antibody, +4.3SD; cut-off value, +3.0SD). She also showed a positive anti-cardiolipin-beta2 glycoprotein I antibody of more than 125 units (cut-off value, 3.5 units) according to the method by Matsuura et al..[3] No thrombocytopenia or "biological false positive test" for syphilis was observed. Her platelet count was 190×10^9/liter. Although she had no history suggestive of systemic lupus erythematosus, the autoimmune abnormalities such as positive antiphospholipid antibodies and prolonged APTT were considered to be the cause of the recurrent reproductive failure, and prophylactic therapy was performed to improve the abnormal autoimmune condition with her informed consent. At first the Japanese modified Chinese herbal medicine Sairei-to (chan ling-tan), which is reported to possess a corticosteroid-like action[9], was administered to this patient beginning in November, 1994. She became pregnant for the third time in August, 1995. Prednisone with an initial dose of 30 mg per day and low-dose aspirin (81mg per day) were also administered beginning in August. The dose of prednisone was reduced to 10 mg per day at the 31st week of gestation. The prolonged APTT normalized at the 16th week of gestation, and the titer of anti-cardiolipin-beta2 glycoprotein I antibody gradually decreased to less than 10 units at the 26th week of gestation. The levels of anti-cardiolipin antibody and anti-phosphatidyl serine antibody also decreased to the normal range during the prenatal course. The pregnancy continued beyond the critical period of the 24th week of gestation. Ultrasonographically estimated fetal growth appeared with in the normal range, and examination of the fetal condition using a cardiotocogram and pulse doppler velocimetry technique revealed a healthy fetus. No symptoms of preeclampsia were observed during the prenatal period, which was accompanied by normal APTT and lower antiphospholipid antibody titer. She vaginally delivered a mature male infant weighing 2762g without any anomalies at the 37th week of gestation. She suffered no epileptic seizures during the prenatal course except one during the first trimester, after which the dose of sodium valproate had been gradually increased to 800mg per day on the basis of the examination of serum valproate concentration. Five mg of prednisone, low-dose aspirin, and 600mg of sodium valproate per day were continued after delivery, though the Chinese herbal medicine was discontinued. The adverse effects considered to be generated by the prophylactic therapy were not observed at any time during the prenatal course (Fig. 1).

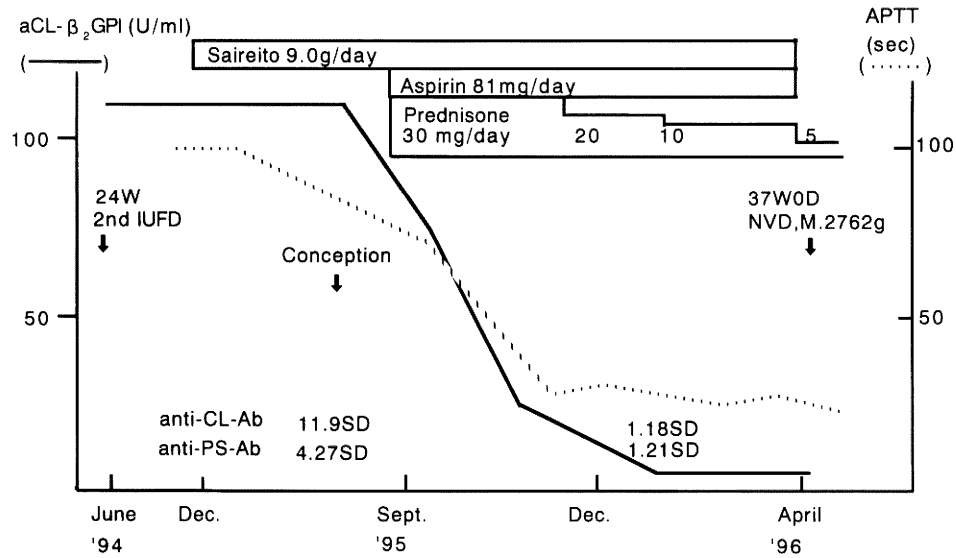

Fig. 1. Clinical course before and during the third pregnancy of this case. The improvement of anti-cardiolipin-beta2 glycoprotein I antibody (*unbroken line*) and prolonged APTT (*broken line*) was observed during the prenatal course. Abbreviations as follow: aCL-β2GPI, anti-cardiolipin-beta2 glycoprotein I antibody; APTT, activated partial thromboplastin time; IUFD, intrauterine fetal deaths; NVD, normal vaginal delivery; anti-CL-Ab; anticardiolipin antibody; anti-PS-Ab, antiphosphatidyl serine antibody.

DISCUSSION

Autoimmune abnormality has been demonstrated in the population with recurrent fetal wastage,[6,7,8,10,11] while it has been widely recognized that reproductive failure such as recurrent spontaneous abortion, intrauterine fetal death, and intrauterine fetal growth retardation are accompanied, during pregnancy, with clinical autoimmune diseases such as systemic lupus erythematosus.[12] On the basis of such findings, reproductive autoimmune failure syndrome (RAFS) was first described in 1987 by Gleicher et al..[13] They suggested that recurrent fetal wastage, endometriosis, and unexplained infertility were included in the RAFS. More recently, autoimmune mechanisms have also been reported to be implicated in the genesis of preeclampsia.[14,15] The antiphospholipid antibodies are considered to be the factor most closely related to the genesis of RAFS. More recently, the antibody against the complex of cardiolipin and beta2 glycoprotein I, which selectively binds to liposomes composed of negatively charged phospholipids, has been reported to have a close association with the occurrence of thrombotic episodes in patients with antiphospholipid syndrome.[3,4,5]

In our patient, positive antiphospholipid antibodies (conventionally detected anti-cardiolipin antibody and anti-phosphatidyl serine antibody) and prolonged APTT (99.7 sec), which were considered to suggest the existence of lupus anticoagulant, were noted before her third pregnancy. Moreover, a very high titer of anti-cardiolipin-beta2 glycoprotein I antibody was observed. The symptoms of recurrent fetal wastage, severe preeclampsia, and epileptic seizures observed in this patient were considered to have been induced by the presence of such autoimmune factors.

There are several reports including ours concerning the effectiveness of prophylactic therapy for patients with recurrent fetal wastages positive for antiphospholipid antibodies using prednisone and low-dose aspirin.[6,7,8] Although we recently reported the efficacy of the Japanese modified Chinese herbal medicine for patients with recurrent abortion who are positive for antiphospholipid antibodies,[9] the medicine did not seem to be efficacious in this case because no improvement of the autoimmune state was found following its administration. There are also reports concerning the efficacy of anticoagulant therapy such as heparin therapy without immunosuppressive agents for patients with antiphospholipid syndrome, as it has been proposed that the generation of thrombi in the intervillous space is the main cause of the recurrent fetal wastage in the antiphospholipid syndrome.[16] It has also been pointed out, however, that the direct toxic action of antiphospholipid antibodies against trophoblastic cells is one of the crucial causes of recurrent fetal wastage in patients positive for antiphospholipid antibodies.[17] According to the hypothesis of such a direct toxic action of antiphospholipid antibodies, the immunosuppressive agents such as prednisone would be considered necessary and efficacious for patients.

There have been few reports concerning the prophylactic therapy for patients with recurrent fetal wastage positive for anti-cardiolipin-beta2 glycoprotein I antibody. The clinical course in this patient clearly implicated the autoimmune abnormality manifesting itself as positive antiphospholipid antibodies, especially anti-cardiolipin-beta2 glycoprotein I antibody, in the genesis of recurrent fetal wastage, preeclampsia, and epileptic seizures. It also demonstrated the efficacy of employing immunosuppressive and anticoagulant therapy to promote a successful planned pregnancy in patients with antiphospholipid syndrome positive for anti-cardiolipin-beta2 glycoprotein I antibody.

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