http://www.zju.edu.cn/jzus; E-mail: jzus@zju.edu.cn
ISSN 1009-3095 *Journal of Zhejiang University SCIENCE* V.4, No.5, P.616-619, Sep.-Oct., 2003

Antiphospholipid syndrome: a survey of clinical characters in ten cases

CHEN Li-hua(陈李华)†, JIANG Ling-ling(姜玲玲), LI You-ming(厉有名), PENG Qing-bi(彭清璧)

(*Department of Internal Medicine, First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China*)

†E-mail: chenlihua-y@163.com

Received Oct.8, 2002; revision accepted Dec.3, 2002

Abstract: Objective: To gain further understanding of the antiphospholipid syndrome(APS). Methods: Analysing clinical and laboratory data on ten cases of APS. Results: Thrombocytopenia appeared in all cases. Venous thrombi of limbs appeared in five cases and neurological abnormalities in two cases. Renal impairments were found in three cases. One case manifested left renal venous thrombi and the other two cases thrombotic microangiopathy. Budd-Chiari syndrome was found in one case. One of the ten cases was catastrophic APS(CAPS) presented as acute diffuse swelling, cyanosis, pain, ischemia and necrosis in fingers and limbs, recurrent shock, ascites, hepatic and respiratory dysfunction. Anticoagulants and corticosteroids could be effective for dealing with APS. It was critical to treat catastrophic APS with anticoagulants or plasmapheresis as early as possible. Conclusions: APS shows variable manifestations for good prognosis, but catastrophic APS has fatal risk. The main treatment for APS is the use of anticoagulants and immunosuppressives.

Key words: Antiphospholipid syndrome(APS), Antiphospholipid antibodies (APL), Thrombosis
Document code: A **CLC number:** R593.2

INTRODUCTION

APS is the sum total that covers a series of clinical manifestations, caused by antiphospholipid antibodies (APL) associated with habitual abortion or intrauterine fetal death, arterial and venous thrombus, thrombocytopenia and hemolytic anemia. APL, a complement-fixing antibody reacting with extracts from bovine hearts, was detected in 1906 in patients with syphilis. The relevant antigen was later identified as cardiolipin (Pangborn, 1941). In 1983, a more sensitive solid-phase immunoassay for anticardiolipin antibodies(ACL) was developed, and the ACL detected were strongly associated with lupus anticoagulant antibodies(LAC) and thrombosis. The term "APS" was first coined to denote the clinical association between APL and a syndrome of hypercoagulability (Alarcon-Segovia *et al.*, 1989). The most commonly detected subgroups of APL are LAC and ACL. The specificity of ACL for APS increases with titer and is higher for the IgG than the IgM isotope. The APS shows various manifestations associated with multiple organ damage. It is seldom reported in China and prone to be misdiagnosed. We collected ten cases of APS and analysed them.

MATERIAL AND METHOD

All ten cases were female with average age of 37.4 years (18-58 years old). The diagnosis of APS was according to international consensus statement on preliminary classification criteria for definite antiphospholipid syndrome (Wilson *et al.*, 1999) and the diagnosis of systemic lupus erythematosus (SLE) to the standard of the American Rheumatic Association in 1982. APS may be divided into two categories: "Primary" APS occurring in patients without clinical evidence of another autoimmune disease and "secondary" APS occurring in association with another autoimmune disease.

Serum antinuclear antibodies (ANA) were detected by fluorescein-labelled method, normal titre $< 1:20$. Anti-Smith antibodies were determined by immuno blotting technique, normal value was negative. Anti-dsDNA antibodies were

measured by gold-labelled method, normal value was negtive. Anticardolipin (ACL) antibodies (IgG) were measured using an ELISA kit. If the ratio of the OD between the patient sample and the control serum was < 2, the result of ACL was negative. If it was $\geqslant 2$, the result was (+), if $\geqslant 3$, was (++), and so on. Serum ACL (Ig*G*) of all patients were detected on two occasions at least six weeks apart.

RESULT

Serum anticardiolipin antibodies (Ig*G*) of all cases presented at moderate or high levels (++ −++++) in different time. All cases (except the seventh case) showed venous thrombosis or thrombotic microvascular lesions confirmed by histopathology or imageology. Whereas the seventh case presented as acute swelling, cyanosis and pain in right fingers, and her condition was relieved after anticoagulation therapy. Venous thrombosis in right fingers of this case could be diagnosed clinically. Hence a diagnosis of definite APS in all cases could be set up . The second, fourth, seventh, eighth and tenth cases were secondary APS associated with SLE and the others were primary APS. Five of ten cases showed thrombi in limbs. Three cases had renal impairment. Two cases were complicated with nervous system damage. One case was CAPS with appearance of ischemic changes in extremities and dysfunction in multiple organs. She died half a year after disease onset. One case suffered from Budd-Chiari syndrome. Two cases once suffered complications of pregnancy. Except CAPS, most cases could be relieved after anticoagulation and immunosuppression therapy. Table 1 shows the clinical data and the results in detail.

DICUSSION

APS is caused by APL that includes ACL and LAC. ACL has high specificity and close relationship with clinical manifestations of APS. The basic pathological changes of APS are vascular affection, of which exact mechanism is unclear and may be associated with autoimmune system, prostaglandin, vascular endothelium, platelet, complement, blood coagulative and fibrinolytic system.

Although the clinical manifestations of APS are variable, thrombosis and thrombocytopenia are very common. All ten cases showed thrombocytopenia that may be a result of platelet consumption and damage. The number of platelets changed with the severity of the disease, and decreased obviously as the patient's condition worsed and increased immediately after treatment as the state of illness became better (cases 3 and 4). Therefore, platelet number can serve as an indicator for the severity of the illness. Arterial and venous thrombi are important lesions of APS. Some patients (case 5) showing chronic course, were undiagnosed and not treated effectively for more than ten years. One of the ten cases was CAPS (case 3) and showed acute diffused swelling, cyanosis and pain in her limbs and ischemia and necrosis in her fingers. She also suffered from ascites, recurrent shock, hepatic and respiratory dysfunction. B ultrasonic examination indicated thrombi in deep veins of lower limbs. A skin-biopsy revealed extensive intravascular thrombi and necrosis in cutaneous and subcutaneous tissues. She failed to respond to methylprednisolone and died half a year after disease onset. This was rarely reported in China. Greisman had reported a case characterized by acute, diffused, non-inflammatory vascular obstruction with high titre of ACL(Greisman *et al.*, 1991). The patients with CAPS often showed ischemic changes in extremities and dysfunction in some organs (Harris *et al.*, 1991). The mortality of these patients was 60% (Asherson *et al.*, 1996). Plasmapheresis and anticoagulants were recommended and corticosteroids and other immunosuppressives should be considered (Greisman *et al.*, 1991). Case 3 had been treated with methylprednisolone (600 mg) for seven days, but her condition did not improve. She became better for three months after the use of heparin, but later got worse and died. CAPS, an uncommon variant of the APS, often presents with multiorgan failure. Precipitating factors include surgical procedures, drugs, and discontinuation of anticoagulant therapy. Increasingly, infections are recognized as a major precipitating codition(Triptt *et al.*, 2000).

Table 1 Clinical data on ten cases of APS

No	Sex	Age	Clinical manifestation	Blood routine	Other examinations	Immuno-test	Treatment and result
1	F	56	Swelling and ulcer on legs	WBC 3×10^9/L HGB 31g/L PLT 19×10^9/L	Ultrasonic: Thrombi in two femoral veins	ANA 1:80 ACL + + − + +	Out of follow up
2	F	33	Swelling and ulcer on righ leg, headache, tic, repeated consciousness loss	WBC 5×10^9/L HGB 110g/L PLT 60×10^9/L	Angiography: Thrombi in deep vein of lower limbs MRI: multiple cerebral infarction	ANA 1:160 SM + ACL + + + + − +	Corticosteroids, small dosage of aspirin. Follow up for three years. Alive
3	F	42	Swelling, cyanosis and pain in limbs, ischema and necrosis in fingers, repeated shock, ascitis, hepatic and pulmonary dysfunction, fetal deaths of intrauterine two times	WBC 10×10^9 L HGB 51g/L PLT 8×10^9/L	Ultrasonic: Thrombi in deep veins of lower limbs, Skin Biopsy: Diffused thrombi and necrosis in cutaneous and subcutaneous tissue	ANA 1:80 ACL + + − + +	Corticosteroids and heparin. Remission for three months, but died finally
4	F	22	Arthralgia, dystropy, left hemiplegia, aphasia	WBC 4×10^9/L HGB 68g/L PLT 13×10^9/L	CT: Multiple ischemic cerebral infarction	ANA 1:640 DsDNA + ACL + − + +	Corticosteroids, small dosage of aspirin Recovered
5	F	35	Swelling in right limbs, spontaneous abortion three times, livido reticularis on skin	WBC 5×10^9/L HGB 100g/L PLT 39×10^9/L	Ultrasonic: Thrombosis in deep veins of right limbs	ANA 1:80 DsDNA + ACL + + − +	Corticosteriods, small dosage of aspirin Recovered.
6	F	58	Abdominal distention, hepatalgia, hypodynami, norexia, hapatomegaly, splenomegaly, ascitis	WBC 4×10^9/L HGB 80g/L PLT 40×10^9/L	Ultrasonic: Congestive hapatomegaly and splenomegaly, ascitis, thrombus at the cross of hepatic vein and inferior vena cava	ANA 1:40 ACL + + + − + +	Heparin for eight weeks. Alive
7	F	18	Erythema on face, livido reticularis on upper limb and trunk, swelling, pain and cyanosis in finger	WBC 5×10^9/L HGB 110g/L PLT 70×10^9/L	Thrombus in right index finger vein (clinical diagnosis)	ANA 1:80 DsDNA + ACL + + + − +	Corticosteriods and heparin. Recovered
8	F	20	Recurrent arthralgia, fever, hematuria, skin eruption	WBC 3×10^9/L HGB 73g/L PLT 10×10^9/L	Ultrasonic: Thrombus in left renal vein	ANA 1:1000 DsDNA + SM + ACL + + + − +	Corticosteriods and heparin. Recovered
9	F	50	Arthralgia, hematuria, fever, proteinuria, acute renal failure	WBC 6×10^9/L HGB 90g/L PLT 30×10^9/L	Biopsy: Thrombotic microvascular lesion in renal parenchyma	ANA 1:100 ACL + + + + − + +	corticosteriods and heparin Recovered
10	F	40	Arthralgia, skin erythra, livido reticularis, acute renal failue, proteinuria, hematuria	WBC 9×10^9/L HGB 80g/L PLT 55×10^9/L	Biopsy: Thrombotic microvascular lesion in renal parenchyma	ANA 1:80 DsDNA + SM + ACL + + − +	Hemotodialysis, corticosteriods and heparin Recovered

Neurological abnormalities, such as cerebral ischemia syndrome, are often seen in APS and may be the result of diffused impairment or small thrombi caused by a cross reaction between APL and cephalin in cerebral tissues (Jiang *et al*., 1995). One of the cases manifested epilepsia gravior, and another revealed behavior abnormality, aphasia and hemiplegia. Cerebral ischemic infarction was confirmed respectively by CT or MRI in both cases. Corticosteroids and a small dosage of aspirin were beneficial. APS reportedly might be related with psychopathy. Therefore APS should be considered as a possible cause of undefined psychopathy.

Budd-Chiari syndrome is caused by the obstruction of hepatic vein. Pomeroy *et al*. (1984) first reported a case of Budd-Chiari syndrome with LAC positive and thought that Budd-Chiari syndrome was related to the hypercoagulable state. Some scholars believed that APS was one of the main causes of Budd-Chiari syndrome. There was only one case reported in China (He

et al., 1996). Case 6 had hepatic vein thrombus which was verified by color Doppler flow imaging. Her final diagnosis was APS because she was tested ACL positive. She had been treated with diuretics and albumins, but her condition deteriorated, probably because of the increased plasma colloid osmotic pressure and blood viscosity caused by the treatment. After changing to heparin, the patient's condition became better and the ascites disappeared immediately. Therefore anticoagulant and thrombolytic treatment should be first line treatment in these patients.

It was reported that 25% of APS had renal impairment (Amigo *et al.*, 1992), whose pathogenesis, treatment and prognosis differed from those of chronic glomerulonephritis and lupus nephritis. The histopathologic features of lupus nephritis are immunocomplex deposition in glomerular basement membrane where inflammation can often be seen. They are often treated by corticosteroids and immunosuppressive agents and the prognosis is poor. In contrast, histopathologic features of our APS patients are thrombi in renal artery and vein and thrombotic microvascular lesions in the renal parenchyma with neither inflammation nor immunocomplex deposition in the glomerular basement membrane. Anticoagulant and plasmapheresis are effective and the prognosis is good. Two of our cases (case 9 and 10) showed renal dysfunction and one (case 8) had renal impairment. Left renal venous thrombus in case 8 was verified by color Doppler flow imaging, and renal biopsy of case 9 and case 10 revealed numerous microthrombi in arterioles and glomerular capillaries of renal parenchyma that was manifested as thrombotic microangiopathy. After treatment with corticosteroids and anticoagulants, renal function became normal and the patients recovered soon. Therefore, we must consider APS as a possible cause of undefined renal impairments and investigate them appropriately to make the correct diagnosis in time.

The titre of ACL is related to the activity of APS, and APL correlate with APS in SLE patients (Jiang *et al.*, 1995). The cases presented here were too limited to be analyzed statistically. Eight of the ten cases had anemia which could be the result of hemolytic anemia. Two cases had spontaneous abortion or intrauterine fetal death, which are thought to be associated with APS. All the cases showed different titres of ANA. How the ANA titre correlates with APS is worth being studied further in a larger patient population.

References

Alarcon-Segovia, D., Deleze, M., Oria, C.V., Sanchez-Guerrero, J., Gomez-Pacheco, L., Cabiedes, J., Fernandez, L. and Ponce-de-Leon, S., 1989. Antiphospholipid antibodies and the antiphospholipid syndrome in systemic lupus erythematosus: a prospective analysis of 500 consecutive patients. *Medicine (Baltimore)*, **68**: 353 – 365.

Amigo, M.C., Garcia-Torres, T. and Robles, M., Bochicchio, T. and Reyes, P.A., 1992. Renal involvement in primary antiphospholipid syndrome. *J Rheumatol*, **19**: 1181 – 1185.

Asherson, R.A. and Piette, J.C., 1996. The catastrophic antiphospholipid syndrome: acute multi-organ failure associated with antiphospholipid antibodies: a review of 31 patients. *Lupus*, **5**: 414 – 417.

Greisman, S.G., Thayaparan, R.S., Godwin, T.A. and Lockshin, M.D., 1991. Occlusive vasculopathy in systemic lupus erythematosus (association with anticardiolipin antibody). *Arch Intern Med*, **151**: 389 – 392.

Harris, E.N., Phil, M. and Bos, D.M.K., 1991. An acute disseminated coagulopathy-vasculopathy associated with the antiphospholipid syndrome (editorial). *Arch Intern Med*, **151**: 231 – 233.

He, J., Wang, J.B. and Tang, F.L., 1996. One case of Budd-Chiari syndrome caused by antiphospholipid antibody. *Chinese journal of internal medicine*, **35**: 31.

Jiang, M., Zhu, L.P. and Lin, X.Y., 1995. Rheumatology. Science Publishing Company, Beijing, p.1547 – 1561.

Pangborn, M.C., 1941. A new serologically active phospholipid from beef heart. *Pro Soc Exp Biol Med*, **48**: 484 – 486.

Pomeroy, C., Knodell, R.G., Swaim, W.R., Arneson, P. and Mahowald, M.L., 1984. Budd-Chiari syndrome in patient with the lupus anticoagulant. *Gastroenterology*, **86**: 158 – 161.

Triptt, D.A. and Asherson, R.A., 2000. Pathophysiology of the catastrophic antiphospholipid syndrome (CAPS). *Am. J. Hematol.*, **65**: 154 – 159.

Wilson, W.A., Gharavi, A.E., Koike, T., Lockshin, M.D., Branch, D.W., Piette, J.C., Brey, R., Derksen, R., Harris, E.N., Hughes, G.R., Triplett, D.A. and Khamashta, M.A., 1999. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. *Arthritis Rheum*, **42**: 1309 – 1311.