Antiphospholipid Syndrome Associated with Cytomegalovirus Infection: Case Report and Review


Antiphospholipid antibodies are commonly related to connective tissue disorders, the use of certain drugs, and infection. It is thought that antiphospholipid syndrome (APS) is associated primarily with connective tissue disorders. We describe a healthy young male who had an episode of APS that was associated with cytomegalovirus infection and who developed mesenteric and femoropopliteal thrombosis. We point out the importance of screening for infectious agents in cases of APS; if the agents are identified, APS may be transitory.

Case Report

A healthy 35-year-old male with no history of thrombosis, thrombocytopenia, transient ischemic attacks, or livedo reticularis was in his usual good state of health until the first week of December 1994, when he developed pain in the epigastrium and in the right abdominal quadrants that was associated with the transitory presence of antiphospholipid antibodies and acute cytomegalovirus (CMV) infection.

Available data indicate that ≤50% of episodes of vascular thrombosis can be attributed to factors that clearly promote thrombosis. The hypercoagulable states that present as arterial thrombosis or venous thrombosis in one or more sites can be caused by alterations in protein C or protein S, antithrombin III deficiency, activated protein C resistance, abnormalities in the fibrinolytic system, and the presence of antiphospholipid antibodies [1]. Anticardiolipin antibodies have been reported in association with bacterial, viral, and parasitic infections [2, 3]. We describe a patient who developed vascular thrombosis in two regions; this condition was associated with the transitory presence of anticardiolipin antibodies and acute cytomegalovirus (CMV) infection.

Physical examination revealed a temperature of 37.8°C, a pulse rate of 86, and a blood pressure of 120/70 mm Hg. His abdomen was in his usual good state of health until the first week of December 1994, when he developed pain in the epigastrium and in the right abdominal quadrants that was associated with weakness and anorexia. Three weeks later he developed low-grade fever (temperature, <38°C) and a nonproductive cough in association with progressive worsening of the abdominal pain; he was admitted to the hospital.

Physical examination revealed a temperature of 37.8°C, a pulse rate of 86, and a blood pressure of 120/70 mm Hg. His skin had a slight icteric tint, and bilateral cervical lymphadenopathy was noted. Examination of the abdomen revealed only diffuse tenderness. There were no signs of peritoneal involvement. Findings of the remainder of the physical examination were unremarkable. Twenty-four hours after admission, the patient’s right leg began to swell.

Laboratory studies done on admission showed a WBC count of 7,600/mm³ with 41% lymphocytes; a hematocrit of 43%; and an erythrocyte sedimentation rate of 27 mm/h. Liver function studies revealed elevated levels of aspartate aminotransferase (65 U/L; normal range, 0–37 U/L), alanine aminotransferase (89 U/L; normal range, 0–40 U/L), and bilirubin (4.72 µmol/L).

A contrast-enhanced CT scan of the abdomen demonstrated splenomegaly and thrombosis of the superior mesenteric vein (figure 1). A Doppler ultrasonogram of the right leg showed the presence of femoropopliteal venous thrombosis.

The coagulation work-up included partial thromboplastin time; prothrombin time; serum levels of lupus anticoagulant, protein C and S, and antithrombin III; activated protein C resistance; and an assay for anticardiolipin antibodies. All results were normal except for the presence of antiphospholipid antibodies: the values were IgM, 42.6 MPL (1 MPL is the phospholipid binding activity of 1 µg/mL of an affinity-purified IgM antibody; normal value, <10 MPL); IgG, 25.2 GPL (1 GPL is the phospholipid binding activity of 1 µg/mL of an affinity-purified IgG antibody; normal value, <10 GPL); and a slightly lower than normal value for protein S (0.32 U/mL; normal value, >0.58 U/mL).

Cultures of blood and urine were performed to determine the cause of the febrile syndrome; both were negative. Tests were performed to detect the presence of HIV; hepatitis A virus, hepatitis B virus, and hepatitis C virus; Epstein-Barr virus; and CMV. Findings on chest radiograph were normal. Serology showed the presence of acute infection with CMV: the titer of IgM was 2.446 A450 (absorbance units), and that of IgG was 0.726 A450 during the first week (cutoff values, 0.273 A450 and 0.148 A450, respectively). During the third week, the titer of IgM was 1.387 A450 and that of IgG was
Figure 1. Abdominal CT scan of patient with antiphospholipid syndrome and cytomegalovirus infection shows occlusion of the superior mesenteric vein by a thrombus (arrow).

1.280 A450 (cutoff values, 0.296 and 0.148, respectively). CMV was also isolated from urine.

The patient was treated systematically with heparin, followed by oral acenocumarol. He remained febrile for the first 5 days after admission; the fever then remitted spontaneously.

The patient was discharged in good condition after 10 days of hospitalization. Five months after discharge, titers of IgM and IgG anticardiolipin antibodies had decreased to 1.30 MPL and 12.1 GPL, respectively; therefore, anticoagulant treatment was discontinued. Twelve months after discharge, he remains asymptomatic.

Discussion

Infection caused by CMV is highly prevalent in the general population. Seroprevalence studies have shown that infection ranges between 40% and 100%; the likelihood of infection increases with age [4]. The most common clinical manifestation is a mononucleosislike syndrome, but CMV infection can also present as interstitial pneumonitis, hepatitis, myocarditis, meningitis, thrombocytopenia, hemolytic anemia, retinitis, or asymptomatic subclinical infection in immunocompetent patients.

Serological studies are widely used for diagnosis; an increase in IgG antibody titers confirms the presence of acute infection with CMV. The virus is not normally isolated from the pharynx or from cultures of blood or urine, so its presence indicates infection [5]. Serological abnormalities have been described in patients with CMV mononucleosis or infectious mononucleosis. These abnormalities include the presence of cryoglobulins, cold agglutinins, rheumatoid factor, and anticomplement antibodies [6].

Antiphospholipid antibodies, anticardiolipin antibodies, and lupus anticoagulant antibodies are a group of antibodies with apparent affinity for anionic phospholipids. Their presence is associated with APS. The most specific clinical features of APS are venous or arterial thrombosis, recurrent fetal loss, and autoimmune thrombocytopenia. This syndrome is known as primary APS (PAPS) when it is not associated with systemic disease and secondary APS when it occurs in patients with underlying autoimmune disease, usually systemic lupus erythematosus (SLE) [7, 8].

Two types of antiphospholipid antibodies have been described: those that are related to PAPS or secondary APS, and have a pathogenic effect and those that are associated with infections [9] or certain drugs [10] or that are present in the 10%–20% of healthy individuals, especially the elderly [11], who do not develop this syndrome [9]. In this latter group, antiphospholipid antibody is not pathogenic and probably represents an epiphenomenon.

Antiphospholipid antibodies have been associated with various infectious diseases: 75% of patients with syphilis have these antibodies [9]. Antiphospholipid antibodies have also been reported in patients with acute infections due to adenovirus, rubella virus, varicella-zoster virus, mumps virus [12], Mycoplasma pneumoniae [12, 13], Mycobacterium tuberculosis [14], Schistosoma species [14], Borrelia burgdorferi [15], and Plasmodium species [14, 16]. The presence of these antibodies is not usually associated with APS.

Investigators have focused on the relation between viral diseases and the production of antiphospholipid antibodies. These antibodies can be found in a relatively high percentage of patients with infections caused by parvovirus, Epstein-Barr virus, hepatitis A virus, hepatitis B virus, and rubella virus [17]. Thirty-nine percent of 33 patients with infectious mononucleosis were found to have positive titers of IgM anticardiolipin antibodies, and 12% had positive titers of IgG anticardiolipin antibodies; none of the controls had either antibody subtype [18]. The frequency of anticardiolipin antibodies varies between 23% and 75% among HIV-infected individuals [19–24], and the presence of these antibodies is not related to the stage of the disease [23, 25] nor, apparently, to the presence of APS.

It has been shown that pathogenic anticardiolipin antibody, which is associated with APS, requires the plasma protein β2-glycoprotein I (GPI) to bind cardiolipins. On the other hand, anticardiolipin antibodies induced by infections do not require this cofactor to bind cardiolipins and are considered nonpathogenic [26–29]. We studied anticardiolipin antibody with and without the presence of this cofactor in our patient, and we found that anticardiolipin antibody required the presence of GPI to bind cardiolipins.

In contrast to what was demonstrated in the present case, previous studies suggest that antiphospholipid antibodies induced by infection have no pathogenic role. It is possible that
one patient can produce both types of antiphospholipid antibodies. In one study, the lymphocytes of another patient with PAPS were studied in vitro, and the results showed that it was possible to induce two lines of anticardiolipin antibody–producing cells when the lymphocytes were exposed to Epstein-Barr virus; one line produced pathogenic anticardiolipin antibodies, and the other produced nonpathogenic anticardiolipin antibodies [30]. This finding suggests that the difference between pathogenic anticardiolipin antibodies in patients with PAPS or SLE and nonpathogenic anticardiolipin antibodies in patients with infections is not absolute and that an individual exposed to a particular stimulus could produce both kinds of antibodies.

There is evidence that patients with anticardiolipin antibody–associated infections could have the clinical manifestation of APS. During 55 pregnancies among 46 HIV-infected patients, 11 patients with anticardiolipin antibodies showed a significant tendency to have smaller placentas than did those without these antibodies [22]. Furthermore, cases of deep vein thrombosis in patients with tuberculosis are possibly associated with the presence of anticardiolipin antibodies [31]. Moreover, Yamakazi et al. [32] reported the case of a 25-year-old patient with Epstein-Barr virus infection who developed a transient rise in titers of antiphospholipid antibodies that was associated with an episode of deep vein thrombosis of the lower extremity, similar to the case we have described.

It is noteworthy that our patient was previously completely healthy. However, it is highly probable that he may have had a congenital deficit of protein S, which was of no clinical importance because he had no clinical manifestations until this episode of APS occurred. It is possible that this mild deficit could have influenced the development of the hypercoagulable state.

Not only were our patient’s laboratory test results abnormal, but there were also serious clinical manifestations typical of APS, consisting of thrombosis that occurred simultaneously in two independent regions. Furthermore, the anticardiolipin antibodies detected are not those usually induced by infectious agents but are the type that are present in patients with APS. Although thrombotic phenomena can cause fever, the presence of thrombosis itself cannot explain the entire clinical picture for this patient; thus, the clinical and laboratory findings prompted us to search for a possible viral infection.

Finally, infection with CMV in this patient was confirmed. The temporal association between thrombosis and infection suggests a causative association rather than the coincidental occurrence of two separate phenomena. The decrease in titers of anticardiolipin antibodies indicates the transient character of APS; thus, patients with a decrease in these titers may have a more favorable prognosis than patients whose illness is produced by chronic disease (e.g., lupus). We therefore emphasize the importance of considering possible infectious agents in episodes of APS. As there are no precedents in the literature, it was difficult to decide how long to treat the patient with oral anticoagulants.

To our knowledge, this is the first reported case of a patient with acute CMV infection who developed thrombosis due to a transient rise in titers of anticardiolipin antibodies (confirmed by the decrease in titers of these antibodies). Although these antibodies are frequently present during infections, APS with thrombosis is a rare complication.

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References


