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CASE REPORT

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Recurrent life-threatening thromboembolism and catastrophic antiphospholipid syndrome in a patient despite sufficient oral anticoagulation

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Abstract We report on a 32-year old female patient with primary antiphospholipid syndrome (PAPS) and several thromboembolic events despite stable doses of oral anticoagulation, good patient compliance and maintained INR values of > 3. Over the preceding 3 years the patient had presented a wide spectrum of manifestations of APS, including recurrent venous and arterial thromboses, cardiac, gynecological (HELLP syndrome), neurological involvements, livedo reticularis, a mild thrombocytopenia and the most feared manifestation of the catastrophic antiphospholipid syndrome (CAPS). Life-threatening bilateral subdural bleeding occurred while she was anticoagulated. The clinical features appeared to be refractory to oral anticoagulation with phenprocoumon. They were life threatening on each occasion and she developed repetitive episodes of organ damage with cardiac insufficiency (NYHA III), pulmonary hypertension and other residual defects. Even during heparinization recurrent thromboembolism supervened as well as livedo reticularis of the extremities. Lupus anticoagulants (LAC), anticardiolipin (aCL) antibodies and anti-β_2-glycoprotein-1 (β_2GPI) titers were all markedly elevated. This case report shows that recurrent episodes of thrombosis can occur despite seemingly adequate anticoagulation in patients with CAPS.

Keywords Anticoagulation · Antiphospholipid syndrome · Catastrophic antiphospholipid syndrome · Myocardial infarction · Recurrent pulmonary thromboembolism

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Abbreviations aCL: Anticardiolipin · aPL: Antiphospholipid · APS: Antiphospholipid syndrome · ARDS: Adult respiratory distress syndrome · β_2GP1: β_2-glycoprotein-1 · CAPS: Catastrophic APS · HELLP syndrome: Hemolysis, elevated lever enzymes, low platelet count · ICA: Index of circulating antibodies · INR: International normalized ratio · LAC: Lupus anticoagulants · NYHA: New York Heart Association · SLE: Systemic lupus erythematosus

Introduction

The antiphospholipid syndrome (APS) is one of the most common causes of acquired thrombophilia and is characterized by arterial and/or venous thrombosis, recurrent pregnancy losses, and the laboratory evidence of antibodies against phospholipids or phospholipid-binding protein cofactors [1]. APS is considered to be an autoimmune disease with unpredictably occurring episodes of thromboembolism combined with serological demonstration of antiphospholipid antibodies (aPL) [2, 3].

Further manifestations may include thrombocytopenia, valvular heart disease and a variety of neurological and gynecological disorders. The thromboembolic manifestations may be heterogeneous, possibly reflecting the heterogeneity of the aPL themselves. Common laboratory tests include functional coagulation tests for lupus anticoagulants (LAC) and immunological assays for antibodies against cardiolipin (aCL) and β_2-glycoprotein I (β_2GPI). This syndrome may be 'primary' or may be associated with other diseases, particularly systemic lupus erythematosus (SLE). Retrospective studies suggest that patients with APS have an increased risk of recurrent thromboembolism [4, 5, 6], and for this reason it is recommended that they receive oral vitamin K antagonists, such as warfarin, in order to achieve an international normalized ratio (INR) range within a therapeutic level (INR $\rightarrow$ 3). In most clinical situations,

therapeutic doses are sufficient to control this disease and prevent further thromboembolism.

The following case study documents a patient who, despite receiving the recommended oral anticoagulant therapy, developed recurring thromboembolic complications. These clinical features were life threatening on each occasion and appeared to be refractory to oral anticoagulation.

Methods

The diagnosis APS was defined by the international consensus criteria (Sapporo criteria) [1].

The lupus anticoagulants (LAC) were measured in platelet-depleted plasma and positive results were established following the guidelines proposed by the Subcommittee for Standardization of Lupus Anticoagulants (SSC) of the Scientific and Standardization Committee of the ISTH [7]. At our institution, lupus anticoagulants were determined by the kaolin-clotting time [8], the Textarin/Ecarin time [9], a modified dilute Russel viper venome time (DRVVT) [10], and confirmed by the Staclot LA test [8]. The detection and quantitative evaluation of circulating antibodies was calculated according to Rosner [11]: (ICA = KCT (1:1 mixture of patient/normal plasma)-KCT (normal plasma)/$_{\text{aKCT (patient plasma)}}$.

The aCL-IgG and IgM antibodies were determined by solid-phase, β_2-glycoprotein-dependent standardized enzyme-linked immunosorbent assays (ELISA) [12]. An ELISA method also measured β_2-glycoprotein antibodies.

The level of protein S activity was low at 34% (normal value 74–142%). All other tests for thrombophilia (factor V mutation/activated protein C resistance and factor II mutation) were negative, and the level of protein C was normal at 94% (normal value 72–142%). Assessment of heparin-induced thrombocytopenia was not performed because the patient's platelets were above 90/nl throughout her hospital stay. ANA, AMA, and rheumatoid factor tests were negative. Antithrombin, homocysteine levels and lipid profile were normal. Liver function tests showed mild elevations of AST and ALT (125 and 79 U/dl, respectively) and a total protein of 9.5 mg/dl with normal albumin. Blood protein electrophoresis showed normal values. Hepatitis profile revealed that the patient had antibodies against hepatitis B virus. Serum cryoglobulins were negative.

Case report

The patient, a 35-year-old Turkish woman was previously known to suffer from a glucose-6-phosphate-dehydrogenase deficiency as well as from a previous hepatitis B infection.

At the age of 29 the patient gave birth to a male child in the 28th week of pregnancy after an emergency cesarean section undertaken because of HELLP syndrome.

From 21 June 1999 to 14 July 1999 the patient was admitted to hospital, initially because of nausea and vomiting. Examination on entry to hospital showed livedoid discoloration of the third to the fifth toes on the right foot, as well as hepatosplenomegaly. Angiography of the inferior vena cava showed an hourglass-shaped stenosis with prestenotic dilatation and retrograde filling of the veins of the liver. A diagnosis of a vena caval thrombosis with Budd–Chiari syndrome was made (Fig. 1).

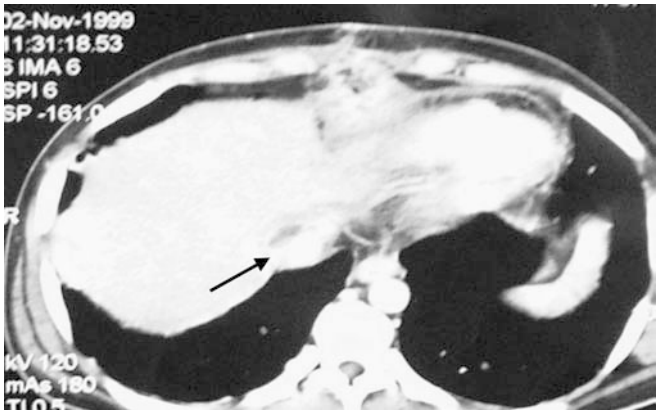

Fig. 1 Thrombosis of the inferior vena cava

First episode of pulmonary embolization

The patient was transferred to the thoracic surgery department of the Frankfurt University Hospital for replacement surgery for the vena cava. ANCA was negative. Phospholipid antibodies and lupus anticoagulants were not determined. On 18 October 1999 a pericardial patch operation was carried out in the presence of subtotal membranous inferior vena cava stenosis.

Two weeks later the patient was readmitted to hospital with tachycardia and dyspnea. A spiral CT scan of the thorax showed the presence on the right side of small peripheral wedge-shaped thickenings, indicating pulmonary emboli. Ultrasound of the leg veins showed no evidence of thromboses. A spiral CT scan of the abdomen, using non-homogeneous contrast medium enhancement, showed hepatomegaly. Thrombosis with a light restriction of 40% appeared attached subphrenically to the wall of the vena cava, and this had probably caused the pulmonary embolism.

Laboratory analysis revealed a PTT of 240 s. Lupus anticoagulants and high-titer anticardiolipin antibodies were positive and she was immediately started on oral anticoagulation with phenprocoumon.

Catastrophic APS: second episode of pulmonary embolization and myocardial infarction

Twenty months later (from 9 August 2001 to 10 September 2001) she was admitted to intensive care because of the development of a catastrophic APS [13]. Three weeks prior to admission, during a vacation in Turkey, she had presented to hospital because of severe dyspnea, tachypnea, tachycardia and fever. Her INR on admission was 3.63. LAC and aCL antibodies were markedly elevated (Table 1).

She had signs of acute left-ventricular myocardial infarction (elevated values of CK and CK-MB), and chest X-ray now showed bilateral pulmonary infiltrates. Sepsis and ARDS were suspected and intravenous antibiotics were commenced, which partially improved her condition (she became afebrile). Cultures from blood, urine and tracheal fluid were negative. Because of her serious respiratory condition, she was transferred by plane to the intensive care unit of the Frankfurt University Hospital for further treatment.

Table 1 INR, LAC and anticardiolipin antibodies (9 August 2001)

	Patient	Normal range
INR	3.63	< 1 (%)
PTT	> 120	31–42 s
KCT	positive	
ICA	42.8	0–15
IgG-aCL	42.5	0.9–11.7 (GPL-U/ml)
IgM-aCL	9.9	0.3–4.8 (MPL-U/ml)
β_2-GP-1	positive	

A bronchoscopy showed signs of purulent bronchitis, and a CT scan of the lung showed bilateral infiltrates sparing the periphery which were interpreted as ARDS, as well as a questionable embolus in the right pulmonary artery. There were no signs of coronary artery disease by coronary angiography, and the myocardial infarction was interpreted as caused by coronary embolism. Treatment with unfractionated intravenous heparin (aimed to elevate thrombin time to 40–60 s) was started. Acetylsalicylic acid was not given because of thrombocytopenia (93/nl) and the glucose-6-phosphate-dehydrogenase deficiency. Although fully anticoagulated with heparin with normal antithrombin levels (95% upon admission), she developed arterial thromboembolic ischemia to the right arm and a toe of the right foot, as well as livedo reticularis (Fig. 2).

The clinical situation was interpreted as a catastrophic antiphospholipid syndrome (CAPS), possibly triggered by purulent bronchitis or pneumonia.

Plasmapheresis (PP) (4-h duration, with 3 l of fresh-frozen plasma) was started and continued for 9 days. This led to a dramatic decrease in aCL-IgM and anti-β_2-GP-1 titers, as well as to substantial clinical improvement.

During the course of additional multimodal treatments (intravenous immunoglobulins, steroid therapy) her condition gradually improved; she recovered from shock and became afebrile. A CT scan of the chest revealed marked regression of the bilateral pulmonary infiltrates. Bone-marrow histology was normal. Five weeks later she was discharged from the hospital with residual signs of skin necrosis, and regular follow-up as well as continued anticoagulation was strongly advised. Remarkably, aCL-IgG and ICA and, to a lesser extent, anti-β_2-GP-1 titers had again increased when the patient was seen in the outpatient service (day 25 after plasmapheresis initiation). However, there was no clinical evidence of disease.

Subsequent outpatient observation produced unchanged echocardiogram results, i.e. medium-grade limitation of function of the left ventricle (EF 34–40%) with akinesia of the apex of the heart and the apical septum, as well as anterolateral hypokinesia. The mitral and aortic valves were well separated. There were no indications of right ventricular strain. The right hand showed loss of sensitivity and there was weakness in the median nerve distribution. Electromyography studies were, however, normal.

The patient in fact had burned her fingers and her hand on several occasions, and also complained of pains in the lower right arm. In spite of many attempts at treatment this residual state remained after the CAPS.

Third episode of pulmonary embolization

With an INR of 6.15 there was once again an emergency readmission to hospital from 2 March 2002 to 15 March 2002, with acute dyspnea and right-sided chest pain. Again, a suspected acute pulmonary embolism was diagnosed. LAC and aCL antibodies were markedly elevated.

A scintigram/ventilation–perfusion scan showed a subsegmental pulmonary embolism in the lower left in the lingula area, which was confirmed by a CT scan of the thorax. CT scan of the abdomen further showed hepatic venous obstruction with generally thin portal vein and non-homogeneous parenchyma. The vena cava showed perfusion but this was non-homogeneous, especially at the level of the liver. An echocardiogram showed noticeably increased mean pulmonary artery pressure (mPAP 33 mmHg). Levels of D-dimers and Troponin T were initially higher, but then decreased in the course of the treatment. After discontinuing treatment with oral anticoagulants, heparinization with unfractioned heparin was introduced while monitoring the thrombin time (thrombin time: 30–40 s) Methylprednisolone 100 mg daily was also administered. Subsequently, oral anticoagulant treatment was recommenced. This was in addition to the administration of clopidogrel. After 2 weeks the patient recovered and could be discharged.

Fourth episode of pulmonary embolization

Running an INR of 4, the patient was again readmitted to hospital on 27 July 2002 with coughing, dyspnea and pronounced weakness, as well as chest pain. LAC and aCL antibodies were markedly elevated. Although an increased troponin test was found, the CK level was not elevated, and thus more invasive investigations were not undertaken. Newly appearing subsegmental areas of decreased perfusion, typical of emboli, in the right central fold of the scintigram of pulmonary ventilation–perfusion scans strengthened the suspicions of a further acute pulmonary embolism. An echocardiogram showed the left-ventricular function of 25% to be decreasing, while the left atrium was distended (49 mm). The ventricular septum was dyskinetic. In a duplex ultrasound scan the internal jugular vein was seen to be obstructed and partly recanalized. There was also an obstruction in the left external iliac vein.

After discontinuing anticoagulation with phenprocoumon and dosing with unfractioned heparin after thrombin time observation, the patient suffered increasing loss of consciousness accompanied by aphasia 11 days after entering hospital. A CT scan showed bilateral subdural bleeding with compression of the lateral ventricles and displacement of the central line (Fig. 3).

During transportation for neurosurgical treatment, an increasing pupillary difference with dilated pupils was noticed. On arrival the pupils were dilated and round bilaterally. A left frontal craniotomy was immediately carried out, with relief drainage, and a right frontal drill-hole trepanation with drainage tubes was inserted. During the course of treatment, brainstem reflexes remained constant. CT images that were prepared because of persistent headache showed a left parietal cyst formation, which subsequently dissolved. The oral anticoagulation was changed to warfarin.

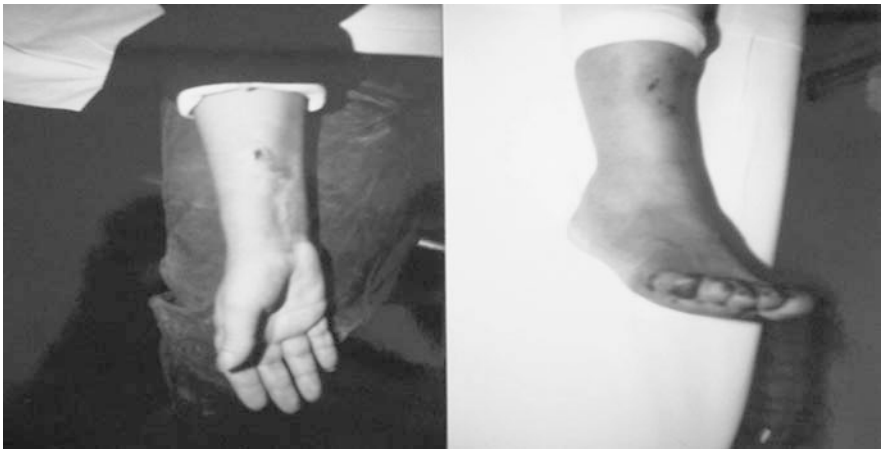

Fig. 2 Thrombotic ulcerations of the right arm and right foot

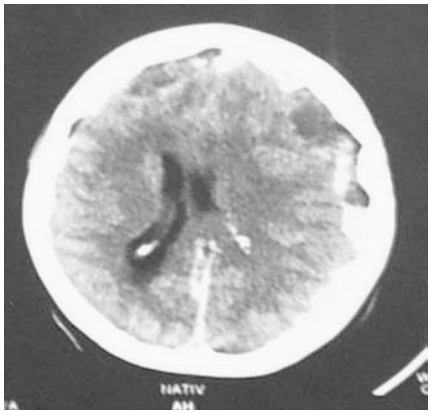

Fig. 3 Bilateral subdural bleeding with compression of the lateral ventricles and displacement of the central line

Clopidogrel was discontinued. During the course of further treatments the patient recovered almost completely. She still suffers from disturbances of fine motor function and sensory disorders in the right half of the body.

Discussion

A variety of cardiac, neurologic and gynecologic manifestations are associated with the presence of aPL. A particularly serious and often fatal clinical form with a high mortality rate of approximately 50% despite treatment has been termed the 'catastrophic' antiphospholipid syndrome (CAPS) (Asherson's syndrome) [14, 15, 16, 17]. These patients present with fulminant thrombotic complications affecting predominantly small vessels in the majority of cases. However, large vessel occlusions, e.g. deep vein thromboses affecting the lower limbs mainly, with complicating pulmonary emboli and cerebral arterial occlusions, do also occur in a minority of patients.

Despite the increasing understanding of the mechanism and clinical manifestations of APS, thrombotic complications are unpredictable and 'triggering factors' are not identifiable in the majority of cases, although risk factors are now increasingly being identified. These include warfarin withdrawal, inadequate warfarinization, and the administration of certain drugs, particularly oral contraceptives etc. Retrospective studies suggest that patients with APS have an increased risk of recurrent thromboembolism [4, 5, 6]. Patients with high positive aCL antibodies may have more frequent thrombo-occlusive events after cerebral ischemia [18]. It is therefore recommended that such patients receive oral vitamin K antagonists, such as warfarin, in order to achieve an international normalized ratio (INR) within the recommended therapeutic range. A beneficial role for anticoagulants in decreasing the rate of recurrent thrombosis has been shown in several retrospective studies [19, 20, 21]. Oral anticoagulation therapy with warfarin is monitored by the prothrombin time and the international normalized ratio (INR). In general, therapy with oral anticoagulants targeted at an INR of 2.5 is very effective as it reduces the risk of recurrent thromboembolism by 90–95% [22]. This approach also holds for patients with the hereditary thrombophilias [23]. In patients with lupus anticoagulants who have sustained a thromboembolic event the recommended INR for oral anticoagulation is controversial. It has been recommended by some that high-intensity anticoagulation with INRs of 3.0 or greater for patients with APS should be administered to prevent further thromboembolic complications [21].

A comparison of periods with no treatment, aspirin, and several intensities of oral anticoagulation has shown that only high-intensity anticoagulation was associated with a significant reduction of the recurrence rate. With an INR of >3, no recurrences were noted by Rosove et al. [19], whereas others found 0.015 events per patient-year during the mean evaluation period of 6 and 5 years [21].

In contrast, Ginsberg et al. saw no recurrent thromboses during conventional-intensity warfarin therapy (INR 2.0–3.0) [24].

Data from a recently completed prospective study over a 2-year follow-up period (WARSS/APASS) has suggested that there is no difference between warfarin (INR between 1.4 and 2.8 at a suggested target of 2.2) and aspirin (325 mg/day) in preventing recurrent APS manifestations and major bleeding complications [25]. This is in comparison to a higher rate of recurrence in patients with APS and without any treatment. On the contrary, data from the Stroke Prevention in Reversible Ischemia Trial (SPIRIT) indicate that high-intensity anticoagulation (INR 3.0–4.5) may lead to a significant excess of major bleeding complications [26].

The role of ASA in preventing recurrent pregnancy losses in APS has been well demonstrated [27, 28]. There have been recent reports that emphasize the prophylactic role of ASA [29, 30], although ASA is not administered universally for the primary prevention of thrombosis in aPL-positive individuals.

Recently consensus statements have been published concerning prophylaxis and treatment guidelines of the antiphospholipid syndrome [31, 32, 33, 34, 35, 36, 37].

In patients with catastrophic APS the most common form of treatment is a combination of anticoagulation, corticosteroids and plasmapheresis [14].

Over a 3-year period, our patient presented a wide spectrum of manifestations of APS, including recurrent venous and arterial thromboses, cardiac, gynecological (HELPP syndrome), neurological involvement, livedo reticularis, a mild thrombocytopenia, and the most feared manifestation of CAPS. Life-threatening bilateral subdural bleeding occurred under anticoagulation. The patient fulfilled the definition of CAPS according to Asherson, with involvement of at least three organs and multiple small vessel occlusions (heart, lung, skin and foot) [14] and according to the recently proposed classification criteria of CAPS [37]. As CAPS has been associated with preceding infections [14, 38] the

Table 2 INR at hospital admission

	INR (%)
09.08.01	3.63
02.03.02	6.15
27.07.02	4.00

pulmonary infection leading to an adult respiratory distress syndrome (ARDS) may have triggered its development. Plasmapheresis led to clinical improvement as well as a dramatic decrease of anti-β_2-GP-1 titers that has been correlated with successful treatment of CAPS [39] After the patient's condition gradually improved owing to the multiple modalities of treatments administered, the aCL-IgG-titer and ICA and, to a lesser extent, anti-β_2-GP-1 titers had again increased when she was seen in the outpatient clinic (day 25 after plasmapheresis initiation). There was no clinical evidence of any recurrent complications.

The patient developed multiorgan damage with cardiac insufficiency (NYHA III), pulmonary hypertension, and residual defects following recurrent thromboembolic complications. Most of these manifestations appeared under anticoagulation with phenprocoumon and an INR >3 (Table 2).

The manifestations of CAPS, including myocardial infarction caused by arterial thromboembolism, had also occurred in spite of phenprocoumon treatment with an INR of 3.63, a level that is usually deemed sufficient to prevent thrombosis [22]. However, circulating antibodies have been described which may interfere with correct measurement of the INR [40]. In patients with APS also, a prolonged prothrombin time may be found as a result of an antibody-mediated decrease in factor II levels [41]. Even closely monitored anticoagulation using intravenous heparin in an ICU setting was unable to prevent ongoing embolism, and the patient suffered from arterial embolism to her right foot while being treated with i.v. heparin with a controlled thrombin time of 60 s (normal range <20 s).

Recurrent thrombosis has been observed in patients with CAPS and individual patients may need repeated plasmapheresis for several years [42]. However, recurrences of CAPS are extremely rare.

The low protein S level of the patient may have enhanced her susceptibility for thromboembolism, and antibodies against both β_2-GP-1 and protein S have been described [43]. Alternatively, the antiphospholipid antibodies may have interfered with protein S measurement. A family protein S deficiency is unlikely, because her family tests were normal.

The inhibition of platelet aggregation with clopidrogrel given in addition to the oral anticoagulation was also unable to prevent the ongoing thrombotic process, as recurrent pulmonary emboli and life-threatening cerebral bleeding occurred while she was undergoing this therapy.

The major fear of clinicians in advising high-intensity anticoagulation is that bleeding complications will exceed its beneficial effects, and this fear is well founded. The frequent presence of thrombocytopenia or disturbed platelet function in patients with APS may in fact render these patients more vulnerable to this complication. Several retrospective studies have reported major bleeding complications in these patients [19, 20, 21]. The risk for severe hemorrhagic complications, notably subdural hematoma, in young APS patients with high-intensity oral anticoagulation is certainly increased [44].

The APS is characterized by the presence of different autoantibodies and is a systemic disease with various immunological abnormalities [45]. Future therapeutic interventions will no doubt concentrate on this aspect, and immunomodulation as well as new treatments for recurrent thrombosis for patients such as ours will undoubtedly become important subjects for future research. Because of the rarity of the catastrophic syndrome many newer therapies, e.g. recombinant protein C, have not as yet been documented as being effective in this life-threatening condition.

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