‘Secondary’ Hughes (Antiphospholipid) Syndrome in Unusual Clinical Settings

Abstract

Objectives and Importance: Hughes (antiphospholipid) syndrome is mainly seen among patients with systemic lupus erythematosus (SLE). This has been called ‘secondary’ in contrast to ‘primary’ where no obvious underlying disease is detectable. The objective of this report is to highlight the fact that Hughes syndrome can, however, also occur in association with other underlying diseases or, as a result of certain therapies. The importance of this report is in emphasizing the fact that secondary Hughes syndrome can occur in several settings other than SLE or SLE-like illness. Clinical Presentation: Here we describe 3 patients with clinical features of arterial or venous thromboses associated with significant levels of antiphospholipid antibodies. Their underlying diseases were, however, neither SLE nor ‘SLE-like’ illness. One of them had been on oral contraceptive pills, the 2nd patient had Behçet’s disease and the 3rd patient had liver carcinoma associated with hepatitis C infection. Thus, these patients could be classified under the category of ‘secondary’ Hughes (antiphospholipid) syndrome. Conclusion: The 1st patient recovered and remained well during a 12-month follow-up after the discontinuation of oral contraceptive pills combined with long-term low-dose aspirin therapy. The last patient remained normal in the 12-month follow-up period on long-term warfarin treatment at a dose adequate to keep the international normalized ratio above 3. The 2nd patient died of uncontrollable hypercoagulability associated with advanced extensive malignancy and related complications. It is, therefore, recommended that the possibility of Hughes syndrome be considered in any clinical situation characterized with hypercoagulable state. If proven, long-term anticoagulation may benefit the patient.
Introduction

In 1983, G.R.V. Hughes [1] from London was the first to draw attention to a clinical syndrome that was later named antiphospholipid syndrome (APS) [2, 3]. The syndrome consisted of three main clinical features and a laboratory marker: (i) hypercoagulability with markedly increased tendency for venous and/or arterial thrombosis; (ii) recurrent fetal wastage (usually >10 weeks of gestation); (iii) subclinical thrombocytopenia; (iv) autoantibodies reactive against anionic phospholipids of the prothrombin activator complex (PAC) in the coagulation cascade (a family of autoantibodies given the generic name of antiphospholipid antibodies, APA [4]). The discovery of this syndrome was historically linked to the discovery in the early 50s of biologically false positive serological test for syphilis (BF-STS) which was followed by the detection of in vitro coagulation abnormalities among patients with systemic lupus erythematosus (SLE) [5–7]. Both of these phenomena were later linked to increased incidence of arterial and/or venous thrombosis [8–10]. These coagulation abnormalities were shown to be related to serum factors that were named lupus anticoagulants (LAC) [9, 11]. Subsequent studies demonstrated that both the BF-STS as well as the coagulation abnormalities were due to serum factors that were autoantibodies reactive against anionic phospholipids in PAC [12]. With this background information, the London group was able to standardize methods for routine estimation of these autoantibodies in clinical practice. They used an easily available anionic phospholipid, namely cardiolipin (the anionic phospholipid that is one of the components of the antigen used in serological test for syphilis) and standardized a radioimmunoassay and an enzyme-linked immunosorbent assay technique that could be used for routine estimations of anticardiolipin (aCL) antibodies [13, 14]. With the availability of this technique, this group studied the syndrome extensively and proposed a set of diagnostic criteria as follows [3, 15]: (a) clinical: venous thrombosis, arterial thrombosis, fetal loss, and thrombocytopenia; and (b) laboratory: IgG aCL in moderate/high levels, IgM aCL in moderate/high levels, and/or positive LAC test.

At least one criterion each from clinical and laboratory categories must be present and the laboratory test for the diagnosis of APS must be found positive on at least 2 occasions more than 3 months apart.

Thus it became possible for the clinicians to diagnose this syndrome in the presence of any of the three clinical features mentioned above, associated with the presence of significant titers of aCL that persisted for 3 months or more. The clause ‘persistent’ was necessary for it was shown that nonpathogenic forms of these autoantibodies could occur transiently in a variety of clinical settings including infections, intake of different drugs etc.

More recently, rapid strides have been made in the understanding of the autoantibodies associated with this syndrome and the antigens (the chemical structures associated with anionic phospholipids) with which these antibodies react [16–18]. It has now been shown that these belong to a family of autoantibodies reactive against various chemical configurations associated with anionic phospholipids of the PAC in the coagulation cascade. The list of these antigens is ever-increasing and includes: (i) phospholipids, e.g. cardiolipin, phosphatidylserine, phosphatidylcholine, (ii) cofactors, e.g. prothrombin, β2 glycoprotein I, activated protein C, protein S, annexin V, kininogen, kininogen-protein, just to name a few. Because of the ever-increasing list of such antibodies, the generic name ‘antiphospholipid/cofactors’ antibodies has now been proposed for this family of autoantibod-
ies [16, 17]. It has also been proposed that instead of the different names that are being used for this syndrome (e.g. 'anticardiolipin syndrome', 'antiphospholipid syndrome', 'antiphospholipid/anticofactor syndrome'), it could simply be called Hughes syndrome in honor of the person who led the team that described the syndrome for the first time in 1983 [19].

The early description of this syndrome by Hughes and colleagues was in patients with SLE or SLE-like diseases. However, soon it became obvious that many patients show full clinical features of this syndrome in the absence of SLE or any SLE-like diseases. This led these researchers to propose a classification for this syndrome as follows [20, 21]: (1) primary APS not associated with any underlying disease and (2) secondary APS where an underlying disease (or cause) can be easily established (the most common underlying disease being SLE or a SLE-like disease).

A recent report has shown that Hughes syndrome is a common problem in hospitals in Kuwait [22]. Among several additional cases seen since the earlier report, we came across 3 unusual patients with this disease, and who had no associated SLE or a SLE-like disease. Yet, because of the presence of a definite underlying disease or cause, and having significant levels of APA, they could not be classified as primary Hughes syndrome. This report discusses the concept of primary and secondary Hughes syndrome and points out that the 'secondary' category could actually be much broader than those cases associated with SLE or lupus-like illness only.

**Case Reports**

**Case 1**

A 26-year-old Jordanian woman was admitted with a 12-hour history of right-sided hemiplegia. She had 2 previous full-term normal deliveries with no history of abortions or miscarriages. On direct questioning the patient admitted to the use of oral contraceptive pills (OCP) for the last 12 months. There were no other relevant points in the history. On examination the only positive findings were in the nervous system. She showed grade 2/5 motor weakness on the right half of the body with extensor plantar reflex on the same side. The eye fundi were normal. A CT scan of the brain showed a left internal capsular infarct with no features suggestive of increased intracranial tension. The electrocardiogram, 24-hour Holter monitoring and duplex-Doppler studies of the carotid arteries were all normal. Complete blood counts as well as prothrombin time and activated partial prothrombin time (APTT) were within normal range. The serological test for syphilis was negative. The fluorescence antinuclear antibody test was positive at a titer of 1:40. Anti-DNA antibody test was negative. Antithrombin III, protein C and protein S levels were within the normal range. aCL screening and quantitation for IgG and IgM iso-

types were carried out using commercially available enzyme-linked immunosorbent assay kits (Pasteur Institute, France). aCL antibody levels were interpreted as follows: IgG isotype APA < 20 phospholipid units (PLU)/ml was considered negative or 'low level' positive; 20–60 PLU/ml was considered 'moderately high positive'; > 60 PLU/ml was considered 'high positive' [23]. Normal range of IgM APA was 0–11 PLU/ml). Only 'moderate' or 'high' positives were considered to be significant [15]. IgG isotype of aCL antibody was present in a titer of 41 PLU/ml and IgM isotype was present in a titer of 11 PLU/ml. OCP was discontinued.

After the investigation results became available, the patient was provisionally diagnosed as 'secondary' APS secondary to OCP. Treatment with warfarin was initiated at the dose required to keep the international normalization ratio (INR) at 3 or slightly higher. aCL levels were repeated 4 months later. Results showed aCL IgG isotype levels to be 20 PLU/ml, and IgM isotype to be 11 PLU/ml. Warfarin was discontinued and replaced with 325 mg of aspirin daily. aCL levels were again repeated at an 8-month follow-up. The aCL IgG isotype was 11 PLU/ml and the IgM isotype was 9 PLU/ml. The patient was advised against the use of OCP and counseled to use an alternative method of contraception. In the follow-up period of a total of 12 months, the hemiplegia recovered with residual weakness of fine movement in her fingers with no recurrence of the thrombotic episode. She was advised long-term use of low-dose aspirin daily.
Case 2

A 51-year-old Ethiopian man was referred to the medical service because of a suspected pulmonary embolism on the 2nd postoperative day. He had a past history of blood transfusion during a urinary bladder surgery 30 years ago. Since then he has had several hospitalizations because of urinary tract infections. A year ago he was found to have chronic liver disease with a hepatitis C carrier state with portal hypertension with bleeding from esophageal varices. He was also found to have mild renal impairment and diabetes mellitus. Six months later he underwent cystolithotomy for bladder stones. Two days postoperatively, he developed pulmonary embolism. Venography showed right-sided deep vein thrombosis, patent iliac veins, inferior vena cava obstruction at the level of lumbar 2–3 disk extending up to the right atrium (fig. 1). Transthoracic and transesophageal echocardiography showed the presence of a large thrombus filling the right atrium with loose fragments in its cavity (fig. 2). A CT scan of chest, abdomen and pelvis confirmed the extension of venous thrombus into the inferior vena cava and right atrium. Hepatic veins were patent but the portal veins were thrombosed. The liver showed a big hypodense area affecting the right lobe. The patient also had splenomegaly and ascites. Alfa fetoprotein was markedly elevated (>320 U/L, normal range <10 U/L). These clinical features were suggestive of hepatoma in the background of postnecrotic cirrhosis (due to hepatitis C) associated with a hypercoagulable state with wide-
spread venous thromboses. Because of the presence of catastrophic widespread thrombosis, this patient was simultaneously investigated for the cause of the marked hypercoagulable state. The levels of the IgG isotype of aCL antibodies were found to be markedly elevated (65 PLU/ml). This was considered to be diagnostic of APS. The patient was heparinized to keep his APTT 1.5-fold above normal control. However, he developed hematuria. On the 10th day of hospitalization the patient developed severe hematemesis. A gastroscopy showed large bleeding fundal varices and a nonbleeding duodenal ulcer. The patient was treated with sclerotherapy and somatostatin. However, he passed into prehepatic coma. On day 15, he developed a massive pulmonary embolism and died.

**Case 3**

A 35-year-old Egyptian man was admitted with a 10-day history of painful swelling on the left lower limb with indurated erythematous skin changes and nodules on the shin. On direct questioning he gave a history of recurrent painful orogenital ulcers and pathergy (development of a 'pus-filled abscess' after any superficial skin injury) since childhood. There were no other significant points in history. On examination he was febrile and in distress due to painful swelling of the left lower limb. He was febrile with a temperature of 38 °C and the rest of his vital signs were normal. He had multiple superficial, well-defined ulcers in the mouth involving the tongue, inside the cheeks and the lower lip. Similar but fewer ulcers were also seen on his scrotum. Scars from old healed ulcers were also present. The left lower limb was diffusely swollen both below and above the knee. The skin was stretched and felt indurated with a brawny edematous appearance. Three to four diffuse, dark brownish-red nodules were present on the same side shin. Their size varied from 1 to 3 cm. The rest of the physical examination including the cardiovascular, respiratory, neurological, musculoskeletal systems and the abdomen was normal. Laboratory investigations showed a white blood cell count of 15.1 x 10^9/l, with granulocytes of 77% and lymphocytes of 12%. Hemoglobin was 113 g/l, platelets were 409 x 10^9/l, erythrocyte sedimentation rate was 88 mm for the 1st hour. Routine and microscopic urine tests were normal. Serum biochemistry including the liver enzymes, renal parameters, serum electrolytes, and blood lipids were also normal. Total serum protein varied from 65 to 73 g/l with albumin ranging from 38 to 39 g/l and globulin from 35 to 36 g/l. A left ascending venogram showed an extensive thrombosis in the deep veins of the left leg extending up to the popliteal veins, the deep femoral veins and into the pelvic veins. The level of aCL antibody of IgG isotype was 33.6 PLU/ml and the IgM isotype was 3.2 PLU/ml.

The patient was diagnosed as having deep vein thrombosis secondary to Behçet’s disease associated with Hughes syndrome with secondary erythema nodosum-type I panniculitis related to Behçet’s disease. The patient was treated with full heparinization and died.

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Fig. 2. Transesophageal echocardiography showing the presence of a large thrombus filling the right atrium (a) with loose fragments in its cavity (b).
(32,000 units over 24 h) with a round-the-clock infusion pump. He was simultaneously given 10 mg of warfarin daily in the first 3 days followed by adjusting the dose of warfarin to keep the INR at 3 or just above it. Heparin was stopped as soon as the INR reached 3 (in 6 days). Treatment with 60 mg of prednisolone in a single dose daily in the morning and colchicine 0.5 mg twice per day was initiated simultaneously. The patient showed quick healing of the mouth and scrotal ulcers. The tender nodules on the shin subsided within a few days. The massive indurated edema on the left lower extremity subsided in about 10 days. At the time of this report the patient had completed 1-year follow-up and had remained in normal health. Repeat aCL antibody levels done 3 months after the earlier report was IgG isotype 26.8 PLU/ml and IgM isotype 3.5 PLU/ml (borderline high IgG isotype of aCL).

**Discussion**

As mentioned earlier, when seen in the absence of underlying features of SLE or SLE-like diseases, Hughes syndrome is labeled as primary [20, 21]. On the other hand, when associated with SLE or SLE-like disease, the condition has been designated secondary Hughes syndrome [20, 21]. Hughes syndrome is purported to be the commonest cause of acquired hypercoagulable state [24]. All the 3 patients presented in this report had a hypercoagulable state with venous thromboses, a major clinical feature of this syndrome. In addition, all 3 of them had significant levels of aCL that could be shown to be persistent in at least 2 of them. In the 3rd case, the persistence of aCL could not be demonstrated because of the death of the patient. Thus all 3 patients satisfied the diagnostic criteria for Hughes syndrome [3, 15], barring the nonavailability of aCL at 3 months' interval in the 2nd patient because of his early death. These patients did not have associated SLE or an SLE-like disease. Therefore, by the above definition the clinical features of these patients should be classified as primary Hughes syndrome. Yet, all 3 of them had a definite underlying cause for their hypercoagulable state, namely, OCP in the 1st patient, malignancy associated with hepatitis C in the 2nd and Behçet’s disease in the 3rd. Therefore, because of the presence of an obvious underlying cause in each of these patients it would have been incorrect to classify them as primary Hughes syndrome.

Hughes syndrome has been reported in a variety of other conditions including other connective tissue diseases, autoimmune diseases like Crohn’s disease, several vasculitic disorders including leukocytoclastic vasculitis, giant cell arteritis/polymyalgia rheumatica, in malignancies of the hemopoietic system and immune system, renal cell carcinoma, lung carcinoma, thymoma, and secondary to drugs including procainamide, phenothiazines, ethosuximide, chlorothiazide, etc. [reviewed in ref. 21, 24, 25]. Thus, there are reports of patients with thrombotic events while taking OCP [26, 27]. These patients developed more serious thrombotic complications during pregnancy. However, association of this disease with liver carcinoma with underlying hepatitis C infection has not been reported. Similarly, to the best of our knowledge, Hughes syndrome has also not been reported with Behçet’s disease. Although it is generally true that APA in these disorders do not confer an equivalent risk for this syndrome [25], there are an increasing number of reports of the appearance of clinical features of Hughes syndrome in these patients [reviewed in ref. 21, 24]. Therefore, the proposal of Asherson and Cervera [21] of a much broader concept of ‘secondary’ Hughes syndrome would appear to be most appropriate. With increasing number of reports on patients with this disease associated with conditions other than SLE or SLE-like illness (including patients in this report), their proposal should gain wider acceptance.
Despite rapid advances in the understanding of immunology and molecular biology of this syndrome, the exact mechanism of the hypercoagulable state, recurrent abortions, and thrombocytopenia still remains somewhat unclear. However, the common sense approach of using anticoagulation for a hypercoagulable state appears to have given a definite direction for the management of thrombotic manifestations of this syndrome. Thus, at present the consensus for the appropriate management of these manifestations is to give them long-term anticoagulation with warfarin (or other coumarin drugs) to keep the INR above 3 [28, 29]. The treatment is usually initiated acutely with heparin (through infusion pump at a dose sufficient to keep the APTT 1.5–2 times above the patient’s preheparin APTT). This is usually achieved with a heparin dose of approximately 1,000 units/h. (Note: About 40% of APS patients with LAC would have prolonged baseline APTT where this method of monitoring of heparin dose cannot be used. In such situations actual measurements of blood heparin levels is the only method available for such monitoring.) Whether addition of aspirin (or other antiplatelet aggregants) would further improve the results (or increase the risk of bleeding) has not yet been adequately studied. It has also been confirmed that the use of immunosuppressive drugs and/or corticosteroids has no role in the treatment of Hughes syndrome [30]. The present consensus on the management of recurrent fetal wastage is to give low-dose aspirin (75–150 mg/day) before pregnancy. The patient is switched over to subcutaneous heparin of 5,000 units twice daily till the time of delivery (maximum dose 5,000 units subcutaneously 4 times per day; if a higher dose is required, infusion pump is recommended). After delivery, the patient is switched back to long-term low-dose aspirin therapy [24, 31]. Thrombocytopenia is usually subclinical, not requiring any specific treatment. However, in the presence of clinical manifestations of thrombocytopenia (and in most cases of hemolytic anemia), the standard line of therapy still remains corticosteroids. However, it is interesting to note that anticoagulation has been shown to achieve a response in corticosteroid-resistant thrombocytopenia in APS [32, 33]. The mechanism of thrombocytopenia in Hughes syndrome could be related to peripheral utilization in an ongoing thrombotic process of APS.

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