HELLP syndrome and its relation with the antiphospholipid syndrome

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Introduction

Anti-phospholipid syndrome (APS) is an autoimmune disorder characterized by recurrent thrombosis and/or obstetric morbidity. These features are linked to the presence in the blood of autoantibodies against negatively charged phospholipids or phospholipid-binding proteins[1-5].

Obstetric complications are major manifestations of APS and have a serious impact on maternal and foetal morbidity. These complications include recurrent abortion (early and late), intrauterine growth restriction, preterm delivery, pre-eclampsia, severe placental insufficiency and probably placental detachment[1,4-6]. Patients with APS may also present with thrombotic microangiopathic disorders, and an increased prevalence of pre-eclampsia/haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome has been described in women who are positive for anticardiolipin antibodies (aCL) and APS[7-10]. The HELLP syndrome is associated with increased risk of materno-foetal complications, still causing high perinatal and maternal mortality rates. Early recognition and rapid therapeutic management of this syndrome are essential for improving materno-foetal prognosis[7]. However, reports of HELLP syndrome complicating APS are scarce and, consequently, information concerning clinical management in these women is quite limited.

In this report we describe three patients with HELLP syndrome complicating secondary APS (in a patient with undifferentiated connective tissue disease and two patients with systemic lupus erythematosus) with heterogeneous clinical presentations and provide an overview of the diagnostic strategies and therapeutic management of such challenging conditions.

We conducted a search of the literature published from 2000 to 2013 using the Medline database and the Cochrane database of systematic reviews. The terms "antiphospholipid syndrome" or "antiphospholipid antibodies" or "lupus anticoagulant", and "HELLP syndrome" were searched for. Reference lists of retrieved articles were also reviewed for additional literature.

Case report 1

A 26-year old woman was admitted to our Centre in June 2009 because of cardio-embolic acute cerebral ischaemia. She was an active smoker (10 cigarettes/day) and overweight (body mass index 25), and had been on oral contraceptives for the preceding 6 months. The patient had never previously experienced thrombotic events or pregnancy morbidity and her family history was negative for thromboembolism. The brain computed tomography (CT) scan was negative, but magnetic resonance imaging (MRI) revealed multiple recent cerebral ischaemic lesions. Two-dimensional and trans-oesophageal echocardiography showed the presence of a mass on the anterior mitral leaflet, with moderate impairment of the valve's function. The levels of plasma antithrombin, fibrinogen, total homocysteine, and anticoagulant proteins C and S were normal, whereas lupus anticoagulant (LA, ratio 2.47) and IgG-aCL (52 GPL/mL, normal levels <20 GPL) were positive. Anti-β2-glycoprotein I antibodies (aβ2GPI) were normal (2 Units, <5 Units). Complement fractions C3 and C4 were reduced and antinuclear antibodies (ANA) were borderline (1:160). Anti double-strand DNA (anti-dsDNA) and anti-extractable nuclear antigen antibodies (ENA) were negative. Cytoplasmic-antineutrophil cytoplasmic antibodies (c-ANCA) were mildly positive (1:20). The presence of arthralgia, Libman-Sacks endocarditis, and positive ANA led to the diagnosis of undifferentiated connective tissue disease. Oral anticoagulant therapy with warfarin, with a target International Normalised Ration of target 2-3, was started. No persistence of mitral thrombosis was shown at echocardiography 6 months later.

In March 2010 the patient discovered that she was pregnant. Oral anticoagulant therapy was replaced by nadroparin (11,400 IU daily subcutaneously). The woman had a spontaneous abortion in the 9th week of pregnancy and subsequently resumed oral anticoagulation. At a laboratory evaluation in September 2010, carried out for bridging to therapeutic nadroparin, LA remained positive (ratio 2.11) and aCL were reduced (16.6, positive levels >20 U). At this stage, due to the persistent positivity for LA and the documented thromboembolic event, the most likely diagnosis was APS secondary to undifferentiated connective tissue disease.

Because of a new pregnancy, the patient started treatment with enoxaparin 4,000 IU/daily subcutaneously, and aspirin 100 mg/day. At 25

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weeks of gestation, she presented with fever, nausea, vomiting, epigastric pain and arterial hypertension and was admitted to hospital. Haematological assessment revealed a neutrophilic leucocytosis, anaemia, severe thrombocytopenia (14,000/mm^3) and elevated levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin. Proteinuria was also present. Pre-eclampsia complicated by HELLP syndrome was diagnosed. Aspirin was immediately discontinued and nifedipine, methyldopa, prophylactic enoxaparin and intravenous (IV) steroids and fresh frozen plasma (FFP, 10-20 mL/kg/day), were given. Due to the onset of signs of acute cerebral ischaemia, and the rapid clinical and laboratory deterioration of the patient, an emergency Caesarean section was performed 24 hours later. The patient's clinical course was then favourable, with improvement of laboratory and clinical parameters. Warfarin, to reach a target International Normalised Ratio (INR) of 2-3, was restarted as soon as possible after the delivery. Despite a very low weight at birth and the detection of cerebral haemorrhage, her female infant survived after 3 months of intensive neonatal care.

Case report 2

A 27-year old woman was admitted to our Centre in March 2012, because of a history (8 years previously) of deep vein thrombosis (DVT) of the right popliteal vein which occurred when she was on oral contraceptives. The patient received warfarin, with an INR target of 2-3, for approximately 1 year (2004-2005). Her laboratory tests showed persistent positivity for aCL and LA since 1998, associated with autoimmune thrombocytopenia. The absence of other clinical and laboratory abnormalities at that time suggested an apparently primary APS. She was treated with steroids from 1998 to 2001, with normalisation of the platelet count.

In March 2011, a diagnosis of systemic lupus erythematosus (SLE), associated with APS and autoimmune thyroiditis, was made, because of the presence of arthralgia, clinical photosensitivity, reduced complement fractions C3 and C4, ANA (1:640), and positivity for anti-dsDNA (30.35 IU/mL with normal values 0.00-2.00), anti-thyroid peroxidase (anti-TPO) antibody (>4,000 IU/mL with normal values 0-115) and anti-thyroglobulin (ATG) antibodies (>600 IU/mL with normal values 0-34). The aCL (170.7 GPL/ml, normal levels <10 GPL) and LA (ratio 1.96), remained positive. She started treatment with: 200 mg hydroxychloroquine twice daily, 7.5 mg prednisone, 75 mg levothyroxine, and 100 mg aspirin.

During a visit to our Centre, the patient revealed her intention to become pregnant. A prophylactic dose of enoxaparin 4000 IU was, therefore, added to aspirin as soon the pregnancy was confirmed and the patient continued with prednisone (5 mg daily), hydroxychloroquine, and levothyroxine. In the 29th week of gestation, while still on prophylaxis with enoxaparin plus aspirin, the patient was admitted to the Department of Obstetrics because of anaemia, abnormal levels of serum aminotransferases and bilirubin, and thrombocytopenia (30,000/mm^3). The presence of schistocytes on a peripheral blood smear, together with the elevated serum LDH, confirmed haemolysis and the diagnosis of HELLP syndrome. The clinical status of the patient worsened within the following 24 hours, with the development of arterial hypertension and headache revealing the condition of pre-eclampsia. An emergency Caesarean section was performed, combined with therapy with IV steroids, prophylactic enoxaparin and IV FFP (10-20 mL/kg/day). This treatment resulted in a gradual improvement of the patient's clinical status, whereas laboratory markers including LDH, AST, ALT, and platelet count normalised dramatically. The patient's blood pressure was stabilised by administering methyldopa. Her APS is now managed by long-term aspirin treatment, and laboratory tests show persistent positivity for aCL (25.8 GPL/mL) and LA (ratio 1.80).

Case report 3

A 33-year old woman was admitted to our Centre in October 2008 because of swelling and pain in her left leg, and chronic arthralgia. One year earlier, her first pregnancy was complicated by early pre-eclampsia and HELLP syndrome in the 22nd week of gestation, treated with IV steroids, FFP and urgent Caesarean section, with a poor outcome for the foetus. Doppler ultrasonography of the left leg revealed DVT of the popliteal vein and anticoagulant therapy with therapeutic doses of a low molecular weight heparin was given, followed by oral treatment with warfarin (INR target 2-3) scheduled for 6 months. Routine laboratory analyses, including fibrinogen, basal prothrombin time and activated partial thromboplastin time, were within the normal ranges, except for an increased erythrocyte sedimentation rate (38 mm/h). The levels of antithrombin, total homocysteine, and anticoagulant proteins C and S were normal. Mild elevations of IgM-aCL and IgG-aCL (22 MPL and 21.6 GPL, respectively) were found, and confirmed 12 weeks later. Complement fractions C3 and C4 were reduced and ANA were positive (1:640), as were anti-dsDNA (114 IU/mL, normal values <10), and ENA. At this point the patient was diagnosed with APS secondary to SLE, and was treated with prednisone (30 mg/day, then progressively reduced to 12.5 mg). In October 2009 she became pregnant, and started prophylaxis with daily aspirin 100 mg and enoxaparin 4,000 IU subcutaneously. She continued the prednisone during her pregnancy, and

a Caesarean section was carried out at 38 weeks without complications while she was on an intermediate dose of enoxaparin (100 IU/kg) (aspirin had been withdrawn at 30 weeks). Presently, the patient receives aspirin (75 mg/day), prednisone (5 mg/day) and 200 mg of hydroxychloroquine twice daily. Laboratory tests show persistent aCL, LA, and ANA, anti-dsDNA and ENA positivity.

Discussion

The autoimmune thrombophilic condition APS is associated with vascular thrombosis and pregnancy complications. When diagnosed in patients with underlying autoimmune diseases (usually SLE), APS is termed "secondary", while APS in apparently healthy people is termed "primary APS". Laboratory tests used for diagnosing APS include immunoassays (aCL and anti-β2GPI antibodies) and coagulation tests (LA)[1-5]. The APS can be diagnosed in women in whom positive LA or moderate- to high-titre antibodies to IgG or IgM aCl (40 GPL or MPL or 99th percentile) or IgG or IgM anti-β2GPI (99th percentile) are detected on two occasions at least 12 weeks apart and who experience at least one unexplained foetal death (later than 10 weeks of gestation), three or more unexplained consecutive miscarriages (before 10 weeks of gestation), or one or more premature births of a morphologically normal neonate before the 34th week of gestation because of eclampsia, severe pre-eclampsia, or placental insufficiency. In addition, APS patients may present with HELLP syndrome as well as other thrombotic microangiopathic disorders[7-15]. The rate of APS in patients with HELLP syndrome was 10.5% in a prospective study by Le Thi Thoung *et al*.[12] (Table I). HELLP syndrome is a multisystem disease of yet unknown origin associated with pregnancy, and is considered as a severe variant of pre-eclampsia. Disseminated intravascular coagulation may complicate the most severe cases[9,16,17]. HELLP occurs in 0.2-0.8% of pregnancies and in 70-80% of cases it coexists with pre-eclampsia[16]. In the majority of patients, clinical and laboratory abnormalities are found in the third trimester of pregnancy, however HELLP syndrome may also occur in the first week of the puerperium. Laboratory abnormalities associated with HELLP syndrome include anaemia, elevated levels of LDH, bilirubin and aminotransferases, low platelet counts and the characteristic presence of red cell fragments (schistocytes) on a blood smear[6,15,16]. There are two main diagnostic definitions of the HELLP syndrome. The widely used "Tennessee classification" requires the presence of: (i) microangiopathic haemolytic anaemia with an abnormal blood smear, low serum haptoglobin and elevated LDH levels (>600 U/L), (ii) elevation of AST above 70 IU/L, or bilirubin more than 1.2 mg/dL, and (iii) a platelet count below 100,000/mm^3 [18]. The incomplete syndrome with only two of these three criteria ("ELLP") may be clinically less severe. The "Mississippi Triple-Class System" defines the severity of the disorder according to the nadir of the platelet count[7]. The onset of HELLP syndrome prior to 34 weeks of gestation ("early-onset types") may be more often associated with severe disease[16]. APS may be associated with early onset, and thus, severe forms of HELLP[19-24]. Published data on HELLP syndrome complicating APS are still scarce in the literature[9,12-15] (Table I). In this report three patients with early onset HELLP syndrome are described, all with a diagnosis of "secondary APS". In the first two cases, the diagnosis of APS preceded the pregnancy complicated by the HELLP syndrome, while in the third case, the latter was the first clinical manifestation, followed by the development of DVT of the left popliteal vein and by the detection of other laboratory and clinical signs leading to the diagnosis of SLE and secondary APS. The common pathogenic mechanisms underlying HELLP syndrome and APS include haemolytic anaemia, placental infarcts, and possibly thrombocytopenia. In pregnancy, antiphospholipid antibodies, especially anti-β2GPI, may trigger thrombosis in the placental vessels (activation of endothelial cells and monocytes), leading to insufficient blood flow in and impaired nutritive function of the placenta, but they also may act by inhibition of the trophoblast invasion associated with decidual killer cells[8,9,25]. The uncontrolled activation of the complement pathway is another important cause of pregnancy complications[8].

Early detection and accurate diagnosis are essential for the management of HELLP syndrome. There are descriptions of the use of aspirin and prophylactic low molecular weight heparin in the management of APS patients during pregnancy[26], while the optimal treatment of HELLP syndrome associated with APS is still controversial, and a treatment protocol has yet

Table I - Case series and literature review of HELLP syndrome complicating APS*.

Authors (ref.)	Study	N. of patients
Pauzner R, *et al*. 2003[20]	Case series	4
Le Thi Thuong D, *et al*. 2005[12]	Retrospective analysis of 442 cases of HELLP syndrome over a 15 year-period	15
Appenzeller S, *et al*. 2011[9]	Review of English literature 1994-2010	50

*Excluding single case reports.

to be established with large multicentre studies[8,9]. As also shown in our patients, in most cases, the clinical symptoms and signs of the disease resolve after the delivery of the placenta. However, although HELLP syndrome may be self-limiting, more complex treatment modalities, such as plasma exchange, transfusion of FFP, along with the administration of anticoagulants, IV immunoglobulins, steroids, and/or cyclophosphamide may be necessary in selected patients with severe HELLP and pre-eclampsia[7-11,16,17]. Plasma exchange in these situations exerts beneficial immunomodulatory effects, including the removal of pathogenic autoantibodies and pro-inflammatory cytokines, while IV immunoglobulins may suppress the effects of aCL antibodies[27]. The use of steroids improves platelet counts but is not clearly associated with beneficial effects on maternal or perinatal/infant death[28]. Transfusion of packed red blood cells and platelets may be required before and soon after the delivery.

In conclusion, HELLP occurred in our patients irrespectively of adequate antithrombotic prophylaxis and steroid treatment. Only the third patient had a subsequent pregnancy after the first complicated course. Although chance cannot be ruled out, in this case a meticulous clinical and laboratory follow-up was associated with favourable maternal and foetal outcomes. We believe that such an intensive follow-up is particularly needed in women with APS, in whom frequent clinical and laboratory monitoring, together with careful education of the patient, may be useful for the early recognition of signs of HELLP syndrome and, probably more important, of the frequently associated and preceding state of pre-eclampsia. Intensive laboratory and clinical follow-up is also necessary in the puerperium in women with HELLP syndrome[17]. Patients with persistent positive aCL, such as those reported here, have an increased risk of developing pre-eclampsia and HELLP syndrome, irrespectively of antibody titre[29]. In contrast, testing for aCL should be considered in women with early-onset, severe pre-eclampsia, eclampsia, or HELLP syndrome, especially when additional clinical features of APS are present. Current evidence does not justify the inclusion of pre-eclampsia as a major criterion for APS, but pre-eclampsia has been proposed to be reasonably included, as a secondary or minor criterion, for the diagnosis when a patient has other clinical features of APS[24]. In the lack of clearly effective strategies for preventing and treating such severe complications of pregnancy, we believe that identifying women at risk remains crucial for adequate counselling and planning timely and proper multidisciplinary approaches. Certainly, the treatment should be individualised for each patient and decided by a multidisciplinary team of specialists (i.e. rheumatologists, gynaecologists and internists/ haemostasis experts).

Keywords: anti-phospholipid syndrome, HELLP syndrome, thrombotic microangiopathy, pregnancy complications.

The Authors declare no conflicts of interest.

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