Catastrophic Antiphospholipid Syndrome in the Second Trimester of Pregnancy

Uriel Elchalal MD[1], Ezra Gabbay MD[2], Michel Nadjari MD[1], David Varon MD[3], Orly Zelig MD[3] and Eldad Ben-Chetrit MD[2]

Departments of [1]Obstetrics and Gynecology, [2]Medicine, and [3]Hematology, Hadassah University Hospital and Hebrew University-Hadassah Medical School, Jerusalem, Israel

Key words: catastrophic aniphosoplipid antibody syndrome, HELLP syndrome, pregnancy complications

IMAJ 2006;8:856–857

The antiphospholipid antibody syndrome is characterized by arterial or venous thrombosis, recurrent fetal loss, moderate thrombocytopenia, and the presence of antiphospholipid antibodies. Classification criteria for catastrophic APS were recently defined, as follows: evidence of involvement of three or more organs, systems, and/or tissues; development of manifestations simultaneously or in less than a week with histopathologic evidence of vascular occlusion; and laboratory confirmation of the presence of antiphospholipid antibodies [1].

Catastrophic APS may also appear in pregnant women, presenting with thrombotic events including liver infarcts and fetal loss, as well as thrombocytopenia. This condition is often labeled as "HELLP-like syndrome." HELLP syndrome (**h**emolysis, **e**levated **l**iver enzymes and **l**ow **p**latelets) is a thrombotic microangiopathic vasculopathy presenting in pregnancy, which has some features similar to catastrophic APS. We present a 37 year old woman with catastrophic APS who developed multiple hepatic infarcts, thrombocytopenia and fetal death in her second trimester of pregnancy, and discuss whether her course represented a "HELLP-like syndrome" or a distinct clinical entity.

Patient Description

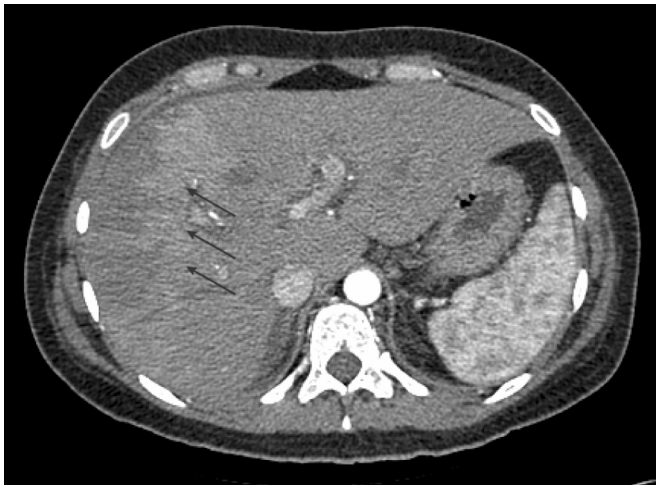
A 37 year old woman presented with malaise, vomiting and right-upper quadrant abdominal pain that began 2 days prior to admission, in the 16th week of her fourth pregnancy. At the time of admission she was treated for known APS with aspirin (100 mg daily), enoxaparin (40 mg twice daily) and folic acid (5 mg daily). Blood pressure and heart rate were normal at presentation; oral temperature was 37.1°C. Mild tenderness in the right upper quadrant of the abdomen was noted. Abdominal sonography revealed mild parenchymal irregularity in the right lobe of the liver. Blood count showed anemia of 11.2 g/dl with no schistocytes on blood smear, leukocytosis (11.4 x 10^3/µl, 71% neutrophils) and thrombocytopenia (74 x 10^3/µl). Liver enzymes (alanine aminotransferase 584 U/L.; normal < 53) and lactate dehydrogenase (872 U/L; normal < 620) were elevated. Electrolytes, creatinine and urea levels were normal. Urinary protein was 100 mg/dl. Diagnostic tests for heparin-induced thrombocytopenia were negative.

The patient had a history of APS and was heterozygous for factor V Leiden. She had a history of deep venous thrombosis and three prior miscarriages that occurred between the 8th and 16th weeks of gestation. Anticardiolipin immunoglobulin G level at the time of admission was 19.4 GPL-U/ml (upper level of normal = 10), IgM levels were within normal range. Fetal sonography revealed intrauterine fetal growth restriction. On the fifth day of hospitalization the patient developed fever reaching 38°C. Amniocentesis showed no evidence of intrauterine infection, however a small amount of amniotic fluid was noted. Intravenous antibiotic therapy was initiated, including ampicillin, gentamycin and clindamycin. On the following day a further rise in liver enzymes was noted and sonography revealed fetal death. Intravenous infusion of oxytocin was therefore given and uterine evacuation of the dead fetus was performed. After the induced abortion of the dead fetus the patient developed dyspnea and the oxygen saturation decreased to 85%. A computed tomography angiography showed no evidence of pulmonary embolus or deep vein thrombosis, but did reveal bilateral pleural effusion and wedge-shaped hypodense lesions near the surface of the right lobe of the liver [Figure].

The patient received oral prednisone therapy (60 mg/day) and enoxaparin (40 mg twice a day) with mild improvement in liver function. On the tenth day in hospital the platelet count dropped to 32,000, with a renewed increase in liver enzymes (ALT 844 and LDH 1686); renal function remained normal. The patient was given IV hydrocortisone 500 mg daily for 3 days. In addition, she received one course of IV immunoglobulin therapy (36 g). Her platelet count subsequently rose to 85,000 and liver enzyme levels decreased, approaching normal. These trends continued after the patient was transferred from IV hydrocortisone back to oral prednisone. However, proteinuria of up to 4 g/day was noted at this time. Albumin levels were 26 g/L. Total cholesterol levels measured 2 months later were elevated at 7.3 mmol/L. Urine sediment showed no casts. Renal biopsy was not performed. An ultrasound of the kidneys performed about 3 weeks after admission showed enlarged echogenic kidneys, suggesting

APS = antiphospholipid antibody syndrome

Ig = immunoglobulin
ALT = alanine aminotransferase
LDH = lactate dehydrogenase



Computed tomography abdominal scan after the abortion, revealing wedge-shaped hypodendese areas in the right lobe of the liver (arrows)

nephritis. However, the absence of hypertension or urinary casts and the degree of proteinuria suggest that the renal process was predominantly nephrotic. Antinuclear antibody was negative. The patient was discharged receiving prednisone 40 mg daily, enoxaparin 40 mg twice daily, and aspirin, iron and folic acid supplements. Four months later, proteinuria of 0.5 g/day was still evident. Pathologic examination of the fetus revealed asymmetric growth retardation and multiple placental infarcts.

Comment

According to the accepted diagnostic criteria [1], the patient described here had probable catastrophic APS, based on the hepatic infarcts, proteinuria, placental infarcts, and thrombocytopenia, with a rapidly developing clinical course and the presence of antiphosholipid antibodies. Several case reports describe women with a clinical presentation resembling the HELLP syndrome in patients with APS syndrome [2,3]. Most authors chose to call this entity "HELLP-like" syndrome or refractory HELLP, suggesting that the syndrome is a variant of typical HELLP, differing somewhat due to the concomitant presence of APS. However, comparison shows HELLP and "HELLP like" syndromes to be two quite distinct disorders. The HELLP syndrome is a thrombotic microangiopathic vasculopathy presenting in pregnancy, typically in the context of preeclampsia. The syndrome usually resolves after the delivery of the fetus, but may lead to life-threatening complications. Patients are usually in the third trimester of pregnancy but may be far from term. Characteristic complaints are: malaise (90%), epigastric or right upper quadrant pain (65%), nausea or vomiting (50%), and non-specific viral illness-like symptoms.

Microangiopathic hemolytic anemia is the hallmark of HELLP syndrome. Disseminated intravascular coagulation occurs in 21–38% of patients with HELLP syndrome [4]. In the case of the catastrophic APS in pregnancy, the presentation is earlier (before the 27th week of gestation) and includes fever and localized pain in the right upper quadrant. Imaging of the abdomen may show infarction of the liver, rather than diffuse changes seen in the HELLP syndrome [2]. Moreover, recovery tends to be slower, and exacerbations may still appear following discontinuation of pregnancy. The two disorders would also seem to differ with regard to the pathophysiologic mechanisms involved. In catastrophic APS the main process is that of thrombosis and hypercoagulation as well as an immunologic process involving autoimmune antibodies, whereas in classic HELLP the mechanism is a thrombotic microangiopathic vasculopathy leading to hemolysis, microthrombi and diffuse liver injury. This may indicate that the predominant features of the "HELLP-like syndrome" are determined by the presence of APS. Whether the patient's heterozygosity for factor V Leiden contributed to the clinical course is unclear. There is, however, one case report describing a 33 year old woman with known APS and heterozygosity for factor V Leiden who developed thrombo-hemorrhagic complications in the late puerperal period [5]. The clinical course of this patient illustrates that while catastrophic APS in pregnancy shares certain features of the HELLP syndrome, the severe complications and the aggressive treatment required render its distinction from HELLP syndrome critical, and therefore the term "HELLP-like" may be misleading in this condition.

References

1. Asherson RA, Cervera R, de Groot PG et al. Catastrophic Antiphospholipid Antibody Registry Group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. *Lupus*. 2003;12:530–4.
2. Koenig M, Roy M, Baccot S, Cuilleron M, de Fillippis J-P, Cathebras P. Thrombotic microangiopathy with liver, gut, and bone infarction (catastrophic antiphospholipid syndrome) associated with HELLP syndrome. *Clin Rheumatol* 2005;24:166–8 .
3. Li Thuong D-L, Tieule N, Costedoat N, et al. The HELLP syndrome in the antiphospholipid syndrome: retrospective study of 16 cases in 15 women. *Ann Rheumat Dis* 2005;64:273–8.
4. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol* 1993;169:1000–6.
5. Bladt V, Steengaard-Pedersen K, Poulsen LH, Petersen OB, Laursen B, d'Amore F. Late puerperal thrombohemorrhagic complications in a patient with antiphospholipid syndrome. *Eur J Haematol* 2004;73:437–40.

Correspondence: Dr. U. Elchalal, Dept. of Obstetrics and Gynecology, Hadassah University Hospital, P.O. Box 12000, Jerusalem 91120, Israel.
Phone: (972-50) 787-4356
Fax: (972-2) 677-8889
email: elchalal@huji.ac.il

Men always want to be a woman's first love – women like to be a man's last romance

Oscar Wilde (1854-1900), Irish writer and witticist