Catastrophic Antiphospholipid Syndrome (Asherson's Syndrome) Associated with Cytokeratin 7-Positive Endometrial Cancer

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Antiphospholipid syndrome is a prothrombotic state characterized by recurrent arterial and venous thrombotic events and fetal loss due to circulating antiphospholipid antibodies including antibodies to cardiolipin or beta-2 glycoprotein, as well as lupus anticoagulant [1]. Asherson defined the particularly serious variant of APS and termed it catastrophic APS [2,3]. CAPS is characterized by the rapid development of fulminant thrombotic complications in at least three internal organs, predominantly in small vessels [2,3]. Precipitating factors may include infections, autoimmunity, trauma, the cessation of anticoagulant therapy, and other factors [2]. We and others previously reported that CAPS may also occur in patients with underlying malignancies [4].

Patient Description

We present the case of a 62 year old woman. Her medical history included aspirin-induced hepatitis. In June 2004, grade II, cytokeratin 7-positive endometrial cancer was diagnosed. The patient underwent preoperative irradiation followed by abdominal hysterectomy, bilateral adnexectomy and postoperative irradiation.

In October 2005 she was admitted to another hospital after a 2 week history of back pain, severe cough, fatigue and weight loss without fever. The clinical signs and the elevated D-dimer (4.23 mg FEU/L (normal < 0.5 mg FEU/L) suggested pulmonary embolism and low molecular weight heparin was therefore introduced. Gastroscopy revealed esophageal varices only. Laboratory tests indicated increased erythrocyte sedimentation rate (83 mm/hour), anemia (red blood cells 3.8 million/µl, hemoglobin 100 g/L, hematocrit 30.3). Platelet count, renal and liver function tests were normal. Chest X-ray showed heart enlargement with peribronchially decreased transparency, suggesting pulmonary embolism and congestive heart failure. Despite the administration of diuretics, the pulmonary status did not improve. Brain computed tomography excluded cerebral metastasis.

The patient then developed abdominal pain and was admitted to the 2nd Department of Surgery, University of Debrecen Medical Center, where congestive heart failure and hepatorenal insufficiency were indicated by hyperbilirubinemia (32 µmol/L), increased serum creatinine (205 µmol/), lactate dehydrogenase (6157 U/L), aspartate aminotransferase (295 U/L), alanine aminotransferase (424 U/L), gamma-glutamyltransferase (118 U/L), alkaline phosphatase (389 U/L) and C-reactive protein (74 mg/L) accompanied by thrombocytopenia (15,000/µl), anemia (hemoglobin 109 g/L) and leukocytosis (12,000/µl).

Echocardiography revealed a 2–4 cm thick pericardiac effusion and 600 ml blood-stained pericardial fluid was aspirated. At the same time, the mediastinal pleura was opened and altogether 2000 ml pleural fluid was removed. The pericardiac and pleural fluid cultures tested negative.

The patient still had no fever and her liver function gradually improved, but serum urea and creatinine levels increased. This was accompanied by more prevalent leukocytosis and elevated serum procalcitonin level, while CRP did not change. The patient was admitted to our intensive care unit. She also had jaundice, cyanosis of the fingers, generalized edema, sub-ileus, oligo-anuria. There was no blood in the stool. The patient was somnolent but was able to answer questions. Laboratory tests again indicated anemia (hemoglobin 94 g/L, hematocrit 0.28), thrombocytopenia (57,000/µl), leukocytosis (20,000/µl), hyperbilirubinemia (32 µmol/L), abnormal liver (alkaline phosphatase 233 U/L, GGT 36 U/L, AST 158 U/L, ALT 456 U/L, LDH 1147 U/L) and renal function (urea 43 mmol/L, creatinine 339 µmol/L). Abnormal values of hemostasis were noted (international normalized ratio 2.29 then 9, activated partial thromboplastin time 64 sec then > 200 sec, thrombin time 25 sec). These values along with the observed oral and respiratory bleeding indicated diffuse intravascular coagulation. Bedside vascular ultrasound demonstrated extensive thrombosis in the internal jugular and inferior cava veins. Chest and abdominal CT scans indicated pleural effusion, infiltrate in the right lung, ascites, as well as stasis and thrombosis in the chest and abdominal large veins including vena cava inferior.

The differential diagnosis included heparin-induced thrombocytopenic thrombosis, paraneoplastic thrombosis

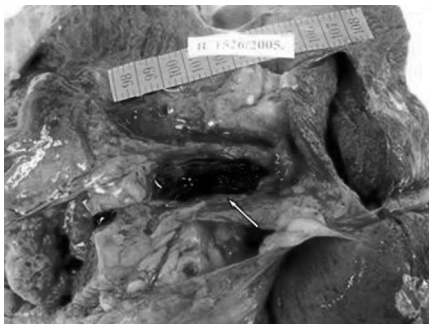
APS = antiphospholipid syndrome
CAPS = catastrophic APS

CRP = C-reactive protein
GGT = gamma-glutamyltransferase
AST = aspartate aminotransferase
ALT = alanine amainotransferase
LDH = lactate dehydrogenase

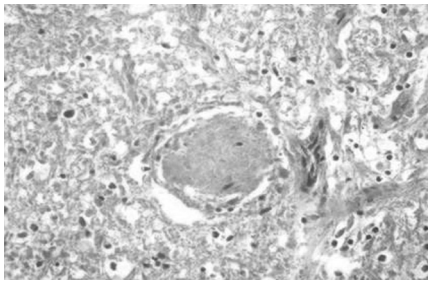
or venous stasis caused by pericardiac tamponade. However, the patient tested positive for APA (immunoglobulin G, anticardiolipin antibody 236 U/ml, normal < 10 U/ml, IgM anticardiolipin, IgG and IgM anti-β2GPI, lupus anticoagulant negative). Extensive thrombosis together with thrombocytopenia suggest extensive platelet aggregation.

Reduced dose of hirudin (12 mg Refludan® in i.v. bolus followed by 4.5 mg/hr dose), fresh frozen plasma and blood transfusions were administered. We instituted parenteral nutrition. Generalized bleeding continued and respiratory failure developed, which necessitated assisted respiration. The neurological status progressed to coma. Heparin-induced thrombocytopenic thrombosis was not confirmed (platelet count 42,000/µl, INR 2.23, APTT 108 sec), therefore, low dose sodium heparin therapy (100 U/hr) was initiated and the patient continuously received fresh plasma and blood transfusions. Despite this therapy, the patient's clinical status deteriorated and bradycardia and hypotension followed by shock developed on the fourth day after her admission to our department. Resuscitation was unsuccessful.

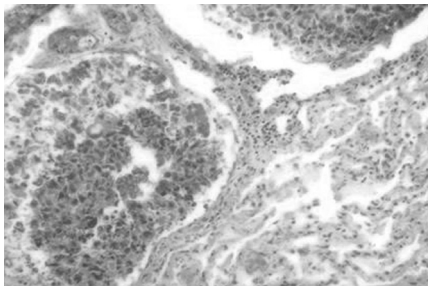
Autopsy revealed multiple thromboses of the pelvic veins, portal vein [Figure A], hepatic veins and the right jugular vein. Histology of the internal organs indicated liver necrosis with signs of regeneration [Figure B], microthrombi and lymphoid depletion in the spleen. Hematoxylin-eosin staining indicated the metastasis of the previous endometrial cancer in the lungs [Figure C]. This specimen also exhibited cytokeratin-7 positivity (not shown). Autopsy did not indicate the relapse of the primary cancer.



[A] Portal vein thrombosis (arrow).



[B] Histology of the liver showing liver atrophy, extensive necrosis and regenerative activity in the remaining liver tissue. (hematoxylin-eosin).



[C] Metastases of endometrial cancer in the lungs. Reactivation of endometrial cancer (hematoxylin-eosin).

Comment

Catastrophic antiphospholipid syndrome, also known as Asherson's syndrome, is a very rare, rapidly progressing form of APS, leading eventually to death in many cases [2,3]. In CAPS, the dramatic clinical events are associated with increased serum antiphospholipid antibody levels [2]. Asherson et al. [2] claim that precipitating factors can be identified in about 60% of CAPS cases. Regarding the molecular pathogenesis of CAPS, the role of microbial molecular mimicry in CAPS was suggested.

Regarding tumor-asociated CAPS, in a recent review Miesbach et al. [4] analyzed the relationship of CAPS to malignancies. Of the 262 patients included in the CAPS registry, underlying malignancy could be identified in 9% of the cases. Associated tumors included hematological malignancies (26% of tumor-associated CAPS cases), lung cancer (17%), colon cancer (9%) and other types of cancer. We also published a case of CAPS associated with gastric cancer [5]. Among immunological factors, none of the cancer-associated CAPS cases were APA negative [4]. Histopathological examination showed thrombosis in the larger vessels leading to infarcts in the brain, myocardium, spleen, kidney and in 50% of the CAPS patients [4].

Despite agressive therapy, CAPS is fatal in more than half the cases. Rapidly progressing multiorgan failure is the most common feature leading to death. Higher mortality is associated with increased age and multiple organ involvement. Altogether, 65% of recovered CAPS cases had some clinical manifestations of APS later. Recurrent CAPS is very rare [2,4,5].

Prophylaxis is crucial in all APS cases. Any infection should be treated promptly with antibiotics. The first-line treatment protocol includes intravenous heparin for 7–10 days followed by oral anticoagulation. INR should be adjusted to 3. Corticosteroids should be administered for at least 3 days, sometimes longer. Second-line specific therapy may include high dose intravenous immunoglobulin, plasmapheresis and/or rituximab. The use of fresh frozen plasma is also required. Third-line specific agents including cyclophosphamide or defibrotide have been used only in sporadic, refractory cases. Secondary, non-specific treatment modalities include hemodialysis in renal insufficiency. Acute respiratory distress syndrome may require the use of a respirator, while heart failure should be treated with positive inotrope agents [2]. Unfortunately, even with the most aggressive therapeutic regimen, CAPS still has a fatal outcome in more than half the cases [2].

APA = antiphospholipid antibody
Ig = immunoglobulin
GP1 = glycoprotein 1
INR = international normalized ratio
APTT = activated partial thromboplastin time

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