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) suggested pulmonary embolism and low molecular weight heparin was therefore introduced.

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 80 U/L), ascites, as well as stasis 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

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

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), and platelet count, renal and liver function tests were normal. Chest X-ray showed heart enlargement with peripherally 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/L), lactate dehydrogenase (6157 U/L), aspartate aminotransferase (295 U/L), alanine aminotransferase (424 U/L), gamma-glutamyltransferase (118 U/L), alkaline phosphatase (233 U/L), GGT (80 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 pericardial 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 pericardial 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.

APS = antiphospholipid syndrome
CAPS = catastrophic APS
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.

**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-associated 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 aggressive 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].

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References


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Capsule

Effects of treatment: animal experiments vs. clinical trials

Perel et al. examined the concordance between treatment effects in animal experiments and clinical trials. Data were extracted on study design, allocation concealment, number of randomized animals, type of model, intervention, and outcome. Corticosteroids did not show any benefit in clinical trials of treatment for head injury but did show a benefit in animal models (pooled odds ratio for adverse functional outcome 0.58, 95% confidence interval 0.41–0.83). Anti-fibrinolytics reduced bleeding in clinical trials but the data were inconclusive in animal models. Thrombolysis improved outcome in patients with ischemic stroke. In animal models, tissue plasminogen activator reduced infarct volume by 24% (95% CI 20%–28%) and improved neurobehavioral scores by 23% (17–29%). Tirilazad was associated with a worse outcome in patients with ischemic stroke. In animal models, tirilazad reduced infarct volume by 29% (21–37%) and improved neurobehavioral scores by 48% (29–67%). Antenatal corticosteroids reduced respiratory distress and mortality in neonates, whereas in animal models respiratory distress was reduced but the effect on mortality was inconclusive (odds ratio 4.2, 95% CI 0.85–20.9). Bisphosphonates increased bone mineral density in patients with osteoporosis. In animal models the bisphosphonate alendronate increased bone mineral density by 11.0% compared with placebo (95% CI 9.2%–12.9%) in the combined results for the hip region. The corresponding treatment effect in the lumbar spine was 8.5% (5.8–11.2%) and in the combined results for the forearms (baboons only) 1.7% (-1.4% to 4.7%). The authors conclude that the discordance between animal and human studies may be due to bias or to the failure of animal models to mimic clinical disease adequately.

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Capsule

Hyperactive antimicrobials

Rosacea is a painful acne-like skin disorder, characterized by dilated blood vessels and persistent redness of the face. Yamasaki et al. provide evidence that cathelicidin peptides – which are chemotactic, angiogenic, and bactericidal, and are important for innate immune responses in the skin – are involved in the pathogenesis of rosacea. Skin biopsies of patients with rosacea had elevated levels of cathelicidin and cathelicidin mRNA. Processing of the cathelicidin precursor involves cleavage of the propeptide by the kallikrein family protease stratum corneum tryptic enzyme (SCTE); rosacea samples had elevated levels of SCTE and protease activity. The abundant cathelicidin fragment LL-37 stimulated interleukin-8 production in cultured human keratinocytes and caused erythema, vascular dilation, neutrophil infiltration, thrombosis, and hemorrhage when injected subcutaneously into mice; injection of SCTE caused similar symptoms. In mice deficient for the gene Camp, which encodes cathelicidin, inflammation was substantially less than normal after application of a contact skin irritant or physical abrasion.

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