Prevention of thrombosis with prostaglandin E_1 in a patient with catastrophic antiphospholipid syndrome

[Prévention de la thrombose avec la prostaglandine E_1 chez une patiente atteinte du syndrome antiphospholipidique catastrophique]

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Purpose: Catastrophic antiphospholipid syndrome (CAPS) is a variant of antiphospholipid syndrome and presents with life-threatening symptoms of multiorgan failure due to thrombosis. We present a patient with CAPS secondary to an ovarian cancer. In such cases, it is believed that the thrombotic risk disappears after surgical removal of the cancer. The intraoperative management was challenging because of the risks of two opposing complications: catastrophic exacerbation of the thrombotic tendency triggered by the surgical stimulus and major bleeding due to the necessary anticoagulation. We describe the intraoperative management of hemostasis in a patient with CAPS.

Clinical features: A 44-yr-old female patient with CAPS underwent resection of an ovarian cancer, which was suspected to be associated with her coagulation abnormality. She had both arterial and venous thromboembolism, including cerebral infarction, embolic gangrene, and pulmonary emboli. Serological examinations revealed increased anticardiolipin IgG antibody and decreased protein C activity. Before surgery, an inferior vena cava filter was placed to prevent perioperative pulmonary embolism. Prostaglandin E_1 (PGE_1; 100 $ng \cdot kg^{-1} \cdot min^{-1}$) was given intraoperatively to suppress platelet aggregation and thrombin generation and to maintain arterial blood flow. No apparent coagulation abnormalities were observed during surgery, neither hypercoagulation nor a tendency to bleed. No additional thrombotic symptoms developed during a six-month follow-up.

Conclusion: The use of PGE_1, an inhibitor of thrombin formation and platelet function, and placement of an inferior vena cava filter were associated with the uneventful surgical resection of an ovarian cancer in a patient with CAPS.

Objectif : *Le syndrome antiphospholipidique catastrophique (SAPC), variante du syndrome antiphospholipidique, présente des symptômes graves de défaillance multiorganique causés par une thrombose. Nous présentons un cas de SAPC secondaire à un cancer ovarien. Le traitement peropératoire a été difficile à cause des risques de deux complications opposées : l'exacerbation catastrophique de la tendance à la thrombose déclenchée par le stimulus chirurgical et l'important saignement lié à la nécessaire anticoagulation. Nous décrivons la prise en charge peropératoire de l'hémostase.*

Éléments cliniques : *Une patiente de 44 ans atteinte du SAPC, qu'on croyait associé à une anomalie de la coagulation, a subi la résection d'un cancer ovarien. Elle présentait une thrombo-embolie artérielle et veineuse, comprenant un infarctus cérébral, de la gangrène embolique et une embolie pulmonaire. Les examens sériques ont révélé une augmentation d'anticorps anticardiolipine IgG et une réduction de l'activité des protéines C. Avant l'opération, un filtre a été placé dans la veine cave inférieure pour prévenir l'embolie pulmonaire périopératoire. De la prostaglandine E_1 (PGE_1 ; 100 $ng \cdot kg^{-1} min^{-1}$) a été administrée pendant l'opération pour supprimer l'agrégation plaquettaire et la génération de thrombine et maintenir le débit sanguin artériel. Aucune anomalie apparente de la coagulation n'a été observée pendant l'opération, ni d'hypercoagulation ou de tendance au saignement. Aucun symptôme thrombotique additionnel ne s'est développé pendant le suivi postopératoire de six mois.*

Conclusion : *L'usage de PGE_1, un inhibiteur de la formation de thrombine et de la fonction plaquettaire, et la mise en place d'un filtre parapluie dans la veine cave inférieure ont été combinés à la résection chirurgicale sans incident d'un cancer ovarien chez une patiente atteinte du SAPC.*

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CATASTROPHIC antiphospholipid syndrome (CAPS) is a variant of antiphospholipid syndrome (APS), which is characterized by the presence of antiphospholipid antibodies (APA) resulting in arterial and venous thromboembolism.[1–3] Patients with CAPS present with life-threatening symptoms of multiorgan failure. APS, including CAPS, is usually associated with autoimmune diseases, such as systemic lupus erythematosus.[3] However, there are several reports of ASP associated with malignancy.[4–6]

Patients with malignant disease have an increased incidence of thromboembolic complications, commonly referred to as Trousseau's syndrome.[7] In addition to Trousseau's syndrome, the presence of APA in cancer patients has recently been proposed as another mechanism that enhances hypercoagulability.[4–6] In those patients with cancer-associated APS, APA and the thrombotic risk are believed to disappear only after surgical removal of the malignancy.[4] However, the thrombotic tendency is temporarily enhanced by surgical procedures and the discontinuation of anticoagulant treatment.[2,8–11] The intraoperative management for cancer resection is challenging because of the competing risks of complications: exacerbation of thrombosis triggered by surgery *vs* significant bleeding due to anticoagulation. In this report, we describe the intraoperative use of prostaglandin E_1 (PGE_1) as an antithrombotic agent in a patient with cancer-related CAPS.

Case report

A previously well, 44-yr-old woman was admitted to our hospital with general fatigue, paresthesia in her right leg, and recurrent episodes of transient loss of consciousness. Furthermore, she presented dyspnea, pyrexia, lower abdominal pain, and embolic gangrene of the right foot. She had tendencies to both arterial and venous thrombosis and her symptoms were life-threatening. On admission, her blood pressure was 100/60 mmHg. Laboratory data were significant for a hemoglobin concentration of 7.3 $g \cdot dL^{-1}$; C-reactive protein 16.1 $mg \cdot dL^{-1}$ (normal < 0.06 $mg \cdot dL^{-1}$). Enzyme-linked immunosorbent assay (ELISA) of anticardiolipin IgG antibody (Mesacup Cardiolipin Test, Medical & Biological Laboratories Co., Ltd, Nagoya, Japan) revealed increased anticardiolipin IgG antibody (15 $U \cdot mL^{-1}$, cut-off value: 10 $U \cdot mL^{-1}$). ELISA of protein C (Asserachrom Protein C, Diagnostica Stago, Inc., NJ, USA) revealed decreased protein C activity (16%, normal: 70–130%). The platelet count, activated partial thromboplastin time (aPTT), serum concentration of creatinine, blood urea nitrogen were all within the normal range. An anti-DNA antibody was negative. A pulmonary perfusion scintigram showed multiple pulmonary perfusion defects. Ultrasound echocardiograms revealed the presence of a thrombus on the mitral valve. No right-to-left shunt was detected on a colour-flow Doppler echocardiogram. Magnetic resonance imaging of the head demonstrated multiple cerebral infarctions. Her symptoms were diagnosed as CAPS with multiorgan failure. Although APS is often associated with connective tissue disorders, the investigations excluded autoimmune diseases and systemic lupus erythematosus. Warfarin was started immediately. The initial dose was 1 $mg \cdot day^{-1}$, and the dose was increased up to 3 $mg \cdot day^{-1}$ to obtain an international normalized ratio (INR) of 2.0. While anticoagulation was effective against the pulmonary emboli, her pyrexia, embolic gangrene of the right lower extremity, and increasing abdominal pain did not respond to the oral warfarin. Computed tomography scans of the abdomen revealed a pelvic mass consistent with an ovarian cancer. The pelvic mass was suspected of being the cause of the CAPS. An operation to resect the mass was planned.

An inferior vena cava filter (Neuhaus Protect; Toray, Tokyo, Japan) was put in place two days before surgery. The oral warfarin was replaced by the infusion of unfractionized heparin (15,000 $U \cdot day^{-1}$) the day before surgery. The INR and aPTT the day before surgery were 1.88 and 35.8 sec (cont 31.6 sec) respectively. After five minutes of oxygenation, general anesthesia was induced with propofol and vecuronium and maintained with sevoflurane, nitrous oxide, fentanyl, and vecuronium. Monitoring during anesthesia included an electrocardiogram, direct arterial blood pressure, oxygen saturation, end-tidal carbon dioxide values, and the bispectral index. A PGE_1 infusion (100 $ng \cdot kg^{-1} \cdot min^{-1}$) was started at the time the patient entered the operating room and used intraoperatively to obtain an antithrombotic effect. The heparin infusion was discontinued two hours prior to surgery. We measured the activated clotting time with Hemochron 401 (Soma Technology, Inc., CT, USA) every hour after the induction of general anesthesia. The activated clotting time remained slightly prolonged, 125 to 143 sec (normal: 90–130 sec). The operation lasted three hours and the intraoperative course was uneventful.

We did not observe any signs suggesting the development of pulmonary emboli (e.g., hypotension, deoxygenation or sudden decrease of end-tidal carbon dioxyde) or cerebral infarction (e.g., anisocoria). We did not observe uncontrollable bleeding during surgery. Thus, no apparent coagulation abnormalities were observed, neither hypercoagulation nor a tendency to bleed. Total intraoperative blood losses were 720 mL. No allogenic blood products were used perioperatively.

The trachea was extubated with the patient fully awake and there were still no signs of thromboembolic complications. The patient was transferred to the intensive care unit. After confirming that she had no postoperative bleeding, the heparin infusion was restarted and the PGE_1 infusion was stopped. Heparin was changed to coumadin ten days after the operation. The pathological diagnosis confirmed clear cell carcinoma of the ovary. Her general condition continued to improve. Anticardiolipin IgG antibody disappeared after removal of the malignancy. The pulmonary emboli and mitral valve thrombus disappeared one month after resection of the cancer. No additional thrombotic symptoms developed during six months of follow-up.

Discussion

Cancer patients have an increased incidence of thromboembolic events, traditionally known as Trousseau's syndrome.[7] Deep vein thrombosis and pulmonary emboli are the most commonly encountered clinical symptoms. Cancer-related arterial thromboembolism in multiple organs and elevated serum APAs, such as lupus anticoagulants or anticardiolipin antibodies, are rare. Recently, the symptoms have been recognized as those of secondary APS associated with malignancy.[4–6] In this patient, the catastrophic symptoms of multiorgan failure associated with both arterial and venous thromboembolism, positive anticardiolipin IgG antibodies, and the presence of a pelvic mass consistent with a cancer suggested the diagnosis. Although surgery enhances the thrombotic tendency in APS,[8–11] surgical removal of the cancer is regarded as the only treatment to eliminate thromboembolism and APA.[4]

The anesthetic management of APS associated with autoimmune diseases has been reported previously.[8,12] As far as we know, however, there has been no reported case of cancer-related CAPS in the anesthetic literature. In this case, the ovarian cancer was resected uneventfully with the use of PGE_1 and placement of an inferior vena cava filter, in spite of the potential risks of developing thromboembolism triggered by the surgical procedure or significant bleeding during surgery.

Asherson named the severe manifestation of APS presenting with an accelerated form of thromboembolism in multiple organs "catastrophic" APS.[1] The precise pathophysiology of CAPS remains unclear, although recent studies have revealed some potential mechanisms.[2] One of the mechanisms involves endothelial cell activation, which leads to the development of thrombosis in the microcirculation.[13] APAs recognize proteins such as $ß_2$-glycoprotein I and prothrombin bound to the phospholipid surface of endothelial cells, platelets, and monocytes.[14] The bonding of APAs to the protein on the cell surface triggers activation of the involved cells. Activated endothelial cells express adhesion molecules on their surface, which induce leukocyte-endothelial adhesion and promote a procoagulant state. The activation of platelets triggers platelet aggregation, which may lead to thromboembolism. Another possible mechanism is the perturbation of the protein C and S regulatory systems.[15] This disturbance inhibits the downregulation of activated factors V and VIII, and leads to the increased generation of thrombin.

In the perioperative setting, the thrombotic tendency may be enhanced temporarily. Yamamoto *et al.* reported a catastrophic exacerbation of APS after biopsy of a lung adenocarcinoma.[9] One of the authors has reported an intraoperative myocardial infarction in a patient with APS.[16] Therefore, to prevent thromboembolic events, anticoagulation is necessary in the perioperative period. The anesthetic management of cancer resection for such patients includes preventing both excessive bleeding due to anticoagulation and catastrophic exacerbation of thrombosis. Preventing these opposing potential complications makes the procedure challenging.

As newer therapeutic agents for anticoagulation in APS, Triplett and Asherson have suggested the use of prostacyclin, streptokinase, tissue plasminogen activator, or urokinase, although these agents require further investigation.[2] Prostacyclin, an eicosanoid, both inhibits hemostasis and is a potent vasodilator.[17] PGE_1, another eicosanoid, has properties similar to those of prostacyclin[18] and has been used clinically to induce hypotension with the aim of reducing intraoperative bleeding.[19] Yukioka *et al.* demonstrated a significant decrease of systolic blood pressure from 136 mmHg to 93 mmHg during PGE_1 infusion.[20] They also showed decreased blood losses and blood transfusion during surgery in patients with PGE_1 infusion. We considered the use of PGE_1 suitable both for anticoagulation and to reduce blood losses in our patient.

PGE_1 has two major properties. First, it inhibits hemostasis. PGE_1 is a potent antagonist of platelet activation and functions via the platelet prostaglandin receptor by up-regulating adenylate cyclase production of intracellular cyclic adenosine monophosphate.[18] PGE_1 also inhibits tissue factor/factor VIIa-dependent thrombin formation,[21] impairing thrombus formation. Second, PGE_1 induces dilatation of smooth muscle,[18] which results in mild hypotension. In spite of its hypotensive effect, cerebral, coronary, and renal blood flows are maintained with the use of PGE_1.[22,23]

We determined the dosage of PGE_1 according to previous reports. At the dosage of 100 $ng \cdot kg^{-1} \cdot min^{-1}$, PGE_1 reduces blood pressure by relaxing the vascular smooth muscle.[19,20] Koga *et al.* have shown that PGE_1, at clinically relevant concentrations, inhibits aggregation of platelets in platelet-rich plasma under synergic interaction with endothelial cell-derived factors.[24] At this dosage, we considered that PGE_1 has both smooth muscle relaxing and anti-aggregation effects.

Theoretically, PGE_1 is a suitable agent for controlling the thrombotic tendency of surgical patients with APS. PGE_1 has been used safely in various clinical situations, however, its use in patients with APS is not generally accepted since there have been no prospective studies of this rare disease. Further investigation is needed to establish its effectiveness and adequacy in improving thrombo-resistance in these patients.

In the patient described, the heparin infusion was discontinued prior to surgery. Although intraoperative heparin has been used successfully, the preoperative evaluation of this patient revealed a hypervascular tumour, which could have led to uncontrolled bleeding if an intraoperative heparin infusion had been used. After discussing intraoperative anticoagulation with the gynecologists, it was decided to discontinue the heparin infusion two hours before surgery, to eliminate the risk of significant bleeding. Finally, to prevent pulmonary emboli during the operation, we placed an inferior vena cava filter preoperatively. A vena cava filter is indicated for prophylaxis in high-risk patients with uncontrolled thromboembolism.[25]

In summary, we describe our experience with a patient suffering from multiple thromboemboli due to cancer-related CAPS. The intraoperative use of PGE_1 was associated with the uneventful surgical resection of the patient's ovarian cancer and the absence of thrombotic complications in the perioperative period.

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