Adrenal Crisis Due To Bilateral Adrenal Hemorrhage in Primary Antiphospholipid Syndrome

Usanee Ringkananon, MD*, Weerapan Khovidhunkit, MD, PhD*,
Varaphon Vongthavaravat, MD*, Vitaya Sridama, MD*,
Siripon Lalitanantpong, MD**, Thiti Snabboon, MD*

** Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University*
*** Department of Radiology, Faculty of Medicine, Chulalongkorn University*

The authors report a case of a 56-year-old Thai woman with a history of recurrent venous thrombosis, spontaneous abortion and Graves' disease who presented with bilateral flank pain, nausea, vomiting and low-grade fever followed by hypotension. Adrenal crisis from bilateral adrenal hemorrhage was diagnosed by a low serum cortisol level during hypotension and bilateral hyperdense oval masses in each of the adrenal glands in a computerized tomographic study. Her hemostatic and serologic profile was compatible with primary antiphospholipid syndrome. Rapid improvement was observed after the administration of intravenous hydrocortisone. She was discharged on long-term glucocorticoid replacement for her primary adrenal insufficiency as well as an anticoagulant for prevention of thrombosis. The antiphospholipid syndrome should be suspected in a patient presenting with adrenal crisis without a distinct etiology.

Keywords: *Antiphospholipid syndrome, Adrenal hemorrhage and adrenal crisis*

J Med Assoc Thai 2005; 88(4): 534-7
Full text. e-Journal: *http://www.medassocthai.org/journal*

Adrenal hemorrhage (AH) is a rare cause of adrenal insufficiency. Because of its nonspecific manifestations, AH is often diagnosed accidentally or after an onset of hypotensive crisis. The incidence of this potentially fatal entity varies from 0.14% to 1.8% in unselected case autopsies[1], however, in critically ill patients, the incidence is much higher[2].

In the present report, we describe the first documented case of a Thai woman with adrenal crisis from spontaneous AH due to primary antiphospholipid syndrome.

Case Report

A 56-year-old woman was admitted for bilateral flank pain, nausea, vomiting and low-grade fever. Her past history was remarkable for a spontaneous abortion 20 years ago, Graves' disease in remission state after I-131 therapy 8 years ago, and 2 episodes of femoral vein thrombosis of both sides 6 years ago. Anticoagulant therapy was given for 2 years and discontinued 4 years prior. Physical examination revealed mild pallor and bilateral flank pain without rebound tenderness or palpable abdominal mass. Her laboratory tests showed a hematocrit of 28.2%; white blood cell count of 12,000/mm^3 (70% polymorphonuclear cells, 20% lymphocytes, 8% monocytes, 2% eosinophils) and a platelet count of 430,000/mm^3. Blood chemistry gave a serum sodium of 111 mEq/L with normal serum potassium. Urine analysis revealed a trace hematuria and 1^+ proteinuria. She was initially treated for presumed urinary tract infection; however, cystoscopy with retrograde pyelography and various bacteriological cultures were negative. Seven days after admission, the patient became confused and hypotensive. An urgent abdominal computerized tomographic (CT) scan (Fig. 1) demonstrated a hyperdense oval mass in each adrenal gland suggesting bilateral AH. Adrenal insufficiency was confirmed by a low level of cortisol at 0.48 (normal 5-18 ng/dL) during hypotension and rapid improvement after treatment with hydrocortisone. Hemostatic analysis

Correspondence to : Snabboon T, Department of Internal Medicine, Faculty of Medicine, Chulalongkorn University, Rama IV Rd, Patumwan, Bangkok 10330, Thailand. Phone: 0-2256-4101, Fax: 0-2652-5347, E-mail: fmedtsb @md.chula.ac.th

showed a hematocrit of 23%, normal platelet count and prothrombin time (PT). The activated partial thromboplastin time (aPTT), kaolin clotting time (KCT), diluted Russell viper venom clotting time, however, were all prolonged, which were not corrected by the addition of normal plasma. Lupus anticoagulant antibodies (LA) were positive but anticardiolipin (aCL) antibodies were negative. Further investigation showed falsely positive VDRL, negative antibodies for dsDNA and weakly positive antinuclear antibodies (ANA) at the titer of 1:20 with cytoplasmic staining. Due to lack of clinical evidence of other autoimmune diseases or malignancy, the diagnosis of primary APS was finally made. Upon discharge, the patient was maintained on cortisone acetate and warfarin. A repeated abdominal CT scan at 4 months after the admission (Fig. 2) revealed a decrease in the size of both adrenals but there was no recovery of adrenal function.

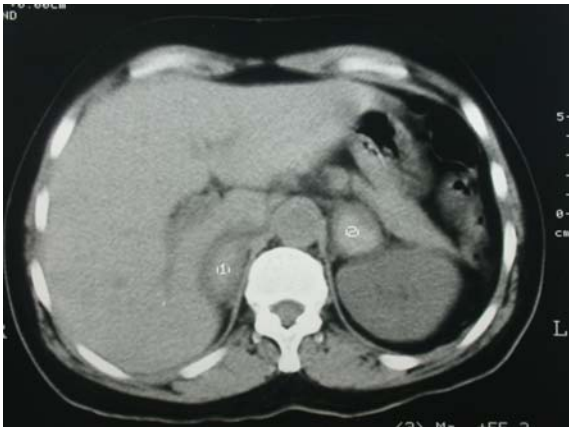

Fig. 1 An axial non-contrast CT scan of the upper abdomen shows enlarged both adrenal glands with an inhomogeneous increase in attenuation (47-55 Housfield Units), suggesting acute adrenal hemorrhage. The size of the adrenal glands is 2.5 x 4 cm on the right and 2.8 x 3 cm on the left side

Discussion

The authors describe a case of adrenal crisis as the manifestation of bilateral AH due to primary APS. The diagnosis of AH requires a high level of suspicion because its early clinical manifestations are nonspecific. Pain localized to the abdomen, flank, lower chest, or back is the most common feature. Evidence of occult hemorrhage with a fall of hematocrit (28.2% to 23%) together with adrenal crisis should raise a suspicion for AH. The radiographic finding typically shows a hyperdense or hyperintense mass in the adrenal gland CT scan (without contrast) or MRI (T1-weighted), respectively. AH usually occurs in association with severe stress such as sepsis, surgery, burns or shock, and adrenocorticotropic hormone (ACTH) administration but may also be a complication of a hemorrhagic diathesis from anticoagulant therapy or an acquired coagulation disorder, such as APS. Prompt and long-term corticosteroid replacement along with anticoagulant therapy to prevent further thrombosis is life-saving. Only a single case has been reported about the recovery of adrenal function after presenting as adrenal crisis from bilateral adrenal hemorrhage with APS[3].

APS is characterized by repeated episodes of arterial and/or venous thromboses, thrombocytopenia, and habitual abortion in combination with the presence of anti-phospholipid antibodies (aPL)[4]. It may be associated with a wide variety of conditions such as autoimmune diseases or malignancies (secondary APS) or may occur as an isolated disease (primary

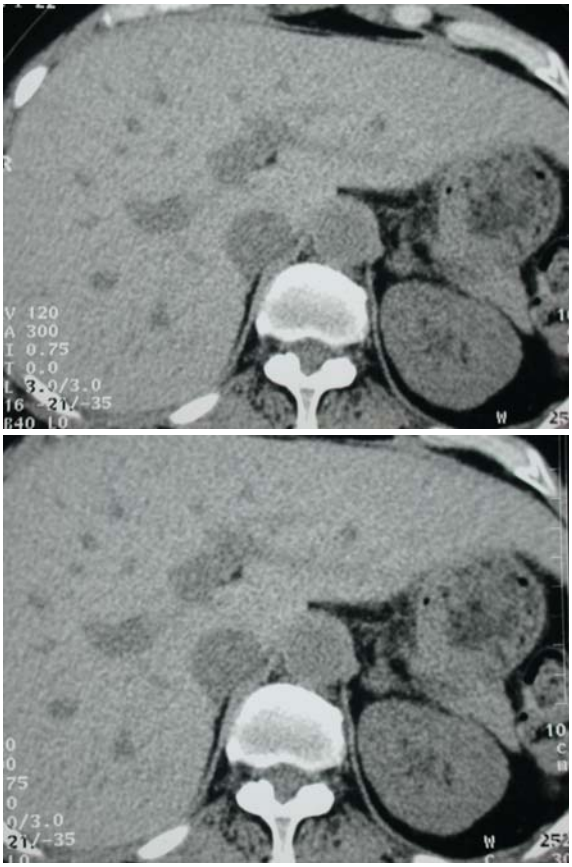

Fig. 2 The follow up axial CT scan performed 4 months after the admission shows markedly decrease in size of both adrenal glands with normal attenuation

APS). Tests to confirm the existence of aPL include prolonged aPTT and KCT (which were not corrected by the addition of normal plasma), positive LA, anti-β_2 glycoprotein I (β_2BPI) antibodies[5] or aCL antibodies, and falsely positive VDRL. AH in APS occurs as a result of focal microthrombosis or post-infarction hemorrhage rather than vasculitis[6]. Thrombosis in the adrenal vein can cause intraglandular hemorrhage due to its multiple small arterial supplies but only a single vein, constituting a "vascular dam". Additionally, thick longitudinal muscle bundles of the veins make it prone to the formation of platelet thrombi.

aPL are related to thrombosis in APS with unknown pathogenic mechanism. Recently, lysobisphosphatidic acid (LBPA), an anionic phospholipid presenting in the late endosomes, has been shown to be a target for aPL, causing accumulation of cholesterol in the adrenal fascicular cell[7]. Binding of LBPA to aPL in endothelial cells leads to a redistribution of regulatory proteins such as C1-M6PR, causing secretion of lysosomal proteinases such as cathepsin D, which can locally activate endothelial cells and induce a procoagulant state. Human aPL can also induce the express vascular cell adhesion molecule-1 (VCAM-1) or E-selectin in vitro cultured endothelial cells, suggesting endothelial damage and increasing leukocyte adhesion to endothelial cells[8].

Conclusion

The presented case illustrates that the investigation for APS should be considered in any patient having adrenal crisis without distinct etiology[9]. Diagnosis in such a patient requires a high index of suspicion and should be confirmed by a CT scan or MRI of the abdomen. Treatment with glucocorticoid to correct adrenal insufficiency, and anticoagulant therapy to prevent further thrombosis should be initiated as soon as possible.

Acknowledgement

The authors wish to thank Dr. Nittaya Suwanwela for providing us with invaluable diagnostic information.

References

1. Rao RH. Bilateral massive adrenal hemorrhage. Med Clin North Am 1995; 79: 107-29.
2. Russell P. The adrenal glands in shock. Pathology 1972; 4: 5-8.
3. Vengrove MA, Amoroso A. Reversible adrenal insufficiency after adrenal hemorrhage. Ann Intern Med 1993; 119: 489.
4. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. N Engl J Med 2002; 346: 52-63.
5. McNeil HP, Simpson RJ, Chesterman CN, Krilis SA. Antiphospholipid antibodies are directed against a complex antigen that includes lipid-binding inhibitor of coagulation: β_2-glycoprotein I (apolipoprotein H). Proc Natl Acad Sci USA 1990; 87: 4120-4.
6. Espinosa G, Santos E, Cervera R, Piette JC, de la Red G, Gil V, et al. Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients. Medicine (Baltimore) 2003; 82: 106-18.
7. Galve-de Rochemonteix B, Kobayashi T, Rosnoblet C, Lindsay M, Parton RG, Reber G, et al. Interaction of anti-phospholipid antibodies with late endosomes of human endothelial cells. Arterioscler Thromb Vasc Biol 2000; 20: 563-74.
8. Berneis K, Buitrago-Tellez C, Muller B, Keller U, Tsakiris DA. Antiphospholipid syndrome and endocrine damage: why bilateral adrenal thrombosis? Eur J Haematol 2003; 71: 299-302.
9. Caron P, Chabannier MH, Cambus JP, Fortenfant F, Otal P, Suc JM. Definitive adrenal insufficiency due to bilateral adrenal hemorrhage and primary antiphospholipid syndrome. J Clin Endocrinol Metab 1998; 83: 1437-9.

ต่อมหมวกไตชั้นนอกทำงานต่ำเฉียบพลันเนื่องจากมีเลือดออกภายในต่อมหมวกไตทั้งสองข้างในผู้ป่วยโรคแอนติฟอสโฟไลปิดชนิดปฐมภูมิ

อุษณีย์ ริงคะนานนท์, วีรพันธุ์ โชวิฑูรกิจ, วราภณ วงศ์ถาวราวัฒน์, วิทยา ศรีดามา, ศิริพร ลลิตอนันตพงษ์, ธิติ สนับบุญ

ผู้ป่วยหญิงไทยอายุ 56 ปี รับไว้ในโรงพยาบาลจุฬาลงกรณ์ เนื่องจากมีอาการปวดบริเวณบั้นเอวทั้งสองข้าง คลื่นไส้ อาเจียน และ มีไข้ต่ำ ๆ ต่อมาเกิดภาวะช็อกจากต่อมหมวกไตชั้นนอกทำงานต่ำเฉียบพลันอันมีสาเหตุมาจากการมีเลือดออกภายในต่อมหมวกไตทั้งสองข้างโดยการตรวจทางรังสี อาการของผู้ป่วยดีขึ้นภายหลัง จากการให้ยาสเตียรอยด์ การวินิจฉัยโรคพื้นฐานของผู้ป่วยคือโรคแอนติฟอสโฟไลปิดชนิดปฐมภูมินั้น อาศัยประวัติที่ผู้ป่วยเคยแท้งบุตร หลอดเลือดดำอุดตัน และผลการตรวจทางโลหิตวิทยา ซึ่งจำเป็นต้องได้รับยาป้องกันเลือดแข็งตัวไปตลอดชีวิตเพื่อป้องกันการอุดตันของหลอดเลือดในส่วนต่าง ๆ ของร่างกาย จากรายงานฉบับนี้แพทย์ผู้ดูแลควรคำนึงถึงโรคแอนติฟอสโฟไลปิดในกลุ่มผู้ป่วยที่มีภาวะต่อมหมวกไตชั้นนอกทำงานต่ำเฉียบพลันที่ยังไม่ทราบสาเหตุ