CASE REPORT

Secondary Adrenal Insufficiency and Primary Antiphospholipid Syndrome

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Abstract

A woman with isolated ACTH deficiency and empty sella in a background of primary antiphospholipid syndrome (APS) is described. A 24-year-old woman was admitted for premature delivery at 30 weeks of gestation and was found to have severe pulmonary hypertension and right sided heart failure. A few hours after delivery, without excessive blood loss, she suddenly lost consciousness, and was found to be hypotensive and hypoglycemic. The findings on hormonal evaluation were consistent with isolated secondary adrenal insufficiency as both ACTH and cortisol levels were very low. Magnetic resonance imaging of the pituitary fossa showed an empty sella. Her severe cor pulmonale was found to be due to primary APS. The patient was given replacement of glucocorticoid and treated with frusemide, spironolactone, warfarin, sildenafil and inhaled iloprost for her pulmonary hypertension, after which her clinical status improved substantially. Follow-up tests of the hypothalamic–pituitary axis found normal serum LH, FSH, TSH, FT4 and prolactin secretion; serum ACTH and plasma cortisol levels remained low.

Key words: antiphospholipid syndrome, secondary adrenal insufficiency, empty sella

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Introduction

The antiphospholipid syndrome (APS) is an acquired thrombotic disorder characterized by recurrent venous or arterial thromboses and/or pregnancy morbidity, in association with the prolonged presence of serum antiphospholipid antibodies (aPL), namely anticardiolipin (aCL), anti-beta 2 glycoprotein I (anti-beta 2 GPI), and lupus anticoagulant (LA) (1). Antiphospholipid syndrome is usually associated with systemic lupus erythematosus but may occur as a primary disorder. In this condition, many organs may be involved by thrombosis. Hypopituitarism with empty sella (2-7), Addison’s disease resulting from adrenal hemorrhagic infarctions (8-10), hypothyroidism and hyperthyroidism (Graves’ disease) (11) have been reported as endocrine disorders associated with APS. In this report, we describe an unusual case of isolated secondary adrenal insufficiency associated with primary APS.

Case Report

A 24-year-old woman, G3P2+0, was admitted to a maternity hospital with premature delivery at 30 weeks of gestation. She was found to have signs of severe pulmonary hypertension and right sided heart failure (jaundice due to congested liver, high JVP with prominent V wave, loud P2, pansystolic murmur at left sternal border and significant bilateral lower limb edema) with no evidence of left side heart failure. She delivered a baby girl with a birth weight of 1.1 kg. A few hours after a delivery, she suddenly lost consciousness and was found to be hypotensive and hypoglycemic, blood glucose levels were 2.4 & 2.5 mmol/L (normal range 3.9-6.9). This event was not preceded by significant postpartum hemorrhage. Her serum Na level was 139 mmol/L (normal range 135-150). Her cortisol level 25 nmol/L was very low (normal range >550-950 during stress); serum ACTH was also depressed at 1.8 pg/mL (normal range 9-52). Other hormonal examinations revealed: Prolactin (PRL) >10,000.0 μIU/mL (normal range 72-511 in anon pregnant
Figure 1. Pituitary MRI revealed empty sella, top image is T1 weighted with gadolinium and bottom one is T2 weighted image.

state); thyroid stimulating hormone (TSH) 13.5 μIU/mL (normal range 0.27-4.2); free triiodothyronine (FT3) 1.01 pmol/L (normal range 2.8-7.1); free thyroxin (FT4) 10.7 pmol/L (normal range 12-22); luteinizing hormone (LH) 0.17 mIU/mL (normal range before menopause 1.0-34.9); follicle stimulating hormone (FSH) <0.1 mIU/mL, (normal range before menopause 2.0-14). The patient was treated with IV hydrocortisone 100 mg Q 8 hours and IV frusemide. After few days, she was transferred to our hospital for further workup. On further questioning, the patient admitted that she was well until the last three months before her delivery, when she started to have progressive shortness of breath and progressive swelling in her legs, however, she did not seek medical advice nor had antenatal care since she lives in a desert. She denied any history of headache, nausea or vomiting, visual deterioration, polyuria or polydipsia, syncopal attacks or postural dizziness before her delivery. The patient had never taken any steroid therapy before. She had no history of significant blood loss in her previous pregnancies. On physical examination, her vital signs were stable and she continued to have the signs of pulmonary hypertension with right sided heart failure but normal breathing sounds. She was not hyperpigmented and her thyroid gland was not enlarged. Glucocorticoids were tapered over 4 days and then stopped to re-assess her hormonal profile. About 60 hours after stopping hydrocortisone, the patient developed nausea, vomiting, hypotension and hypoglycemia. Adrenal crisis was suspected and 100 mg IV hydrocortisone was given after taking a blood sample for hormonal measurements. The results showed: cortisol 42 nmol/L; ACTH 1.4 pg/mL; PRL 1.100.0 μIU/mL; TSH 10.1 μIU/mL; FT3 3.2 pmol/L; FT4 18 pmol/L; LH 0.21 μIU/mL; FSH 0.18 μIU/mL; estradiol (E2) 147 pmol/L; growth hormone (GH) 6.5 mU/L (normal range 0-13); insulin-like growth factor 1 (IGF-1) 169 μg/L (normal range 90-360). Synacthen test was done after holding hydrocortisone for 24 hours using 250 mcg of IV cosyntropin, approximately one month after her collapse. Her cortisol failed to be stimulated; the levels were 25 nmol/L at 0 minutes, 35 nmol/L at 30 minutes and 40 nmol/L at 60 minutes. Magnetic resonance imaging (MRI) of pituitary gland disclosed “empty sella” and deviation of optic chiasm (Fig. 1). Evaluation for pulmonary hypertension and right side heart failure included an echocardiogram which revealed normal systolic function with normal mitral valve; pulmonary artery pressure was elevated to 100 mmHg with severe tricuspid regurgitation. Spiral CT scan of the chest and Doppler ultrasound of the lower limbs did not show any evidence of pulmonary embolism or deep vein thrombosis respectively. She had positive IgG anticardiolipin antibody (aCL) by ELISA on two occasions, three months apart, 40 and 50 GPL units/mL respectively (normal, <14 GPL units/mL). The following investigations were normal or negative: serum urea and electrolytes, Rheumatoid factor, ANA, anti-DNA, AMA, ASMA, C3, C4, C & P-ANCA, platelets, PT, PTT, lupus anticoagulant, protein C, protein S, factor V Leiden, antithrombin III, D-dimer, anti TPO antibody and hepatitis B & C serology.

Based on the above findings, she was diagnosed with primary antiphospholipid syndrome, secondary adrenal insufficiency, empty sella syndrome and right side heart failure due to severe pulmonary hypertension. We assumed that recurrent small thromboses, which are characteristic of APS, were the culprit for all her presentations; secondary adrenal insufficiency, empty sella and pulmonary hypertension. The patient was maintained on prednisone 5 mg once daily and treated with frusemide, spironolactone, warfarin, sildenafil and inhaled iloprost for her pulmonary hypertension. She gradually recovered and was discharged from hospital with a satisfactory physical and psychological condition.

Three months later, the patient’s menstrual period resumed and she was advised to use contraception and thus an intrauterine contraceptive device was placed. During follow-up, after more than two years, the patient continued to enjoy good health with preservation of other pituitary hormones, apart from ACTH deficiency, has regular menses and no symptoms or signs of right side heart failure. Recent hormonal profiles were as follows: PRL 400 μIU/mL; TSH 2 μIU/mL; FT4 18 pmol/L; LH 10 μIU/mL; FSH 9 μIU/mL and estradiol 200 pmol/L. The summary of her hormonal profile is shown in Table 1.

Discussion

Previously, adrenal insufficiency was reported in APS as primary adrenal infarction/hemorrhage (9-11). Recently many cases of APS associated with secondary adrenal failure as a part of pan hypopituitarism with empty sella have been reported (2-8). Interestingly, most of these cases were diagnosed at the post partum period (2-4, 6). The reason for this is not very clear but could be attributed to two factors:
first, hypercoagulability state of pregnancy and second, related to blood loss post delivery, both of these factors in a background of APS can interfere with the blood supply to the pituitary gland and hence lead to pituitary infarction. To our knowledge, this case is the first report of “isolated” ACTH deficiency with empty sella associated with APS. Our diagnosis of APS is definite based on International consensus statement on the classification criteria for definite antiphospholipid syndrome (1). These include premature delivery of a morphologically normal neonate at 30 weeks of gestation as a result of placental insufficiency, as evident by the low birth weight of the baby, and positive IgG aCL antibody on two occasions 12 weeks apart. Other prominent features of APS in this case were non-thromboembolic pulmonary hypertension and empty sella. Both of those two conditions were described previously in patients with APS (3, 6, 12). These complications could occur in APS as a result of recurrent small thromboses.

We believe that the empty sella and isolated ACTH deficiency in the present case are secondary to pituitary gland infarction due to vascular thromboses as a part of her APS. The time at which she developed pituitary injury is not very clear, but the presence of an empty sella on neuro-imaging during the acute presentation and the failure of her cortisol to be stimulated by high dose ACTH stimulation test support the possibility of an earlier (past) injury to her pituitary which might have caused subclinical secondary adrenal insufficiency that became clinically evident this time possibly due to a recent pituitary infarction.

During the acute presentation, many of her pituitary hormones were abnormal which subsequently normalized during the follow-up, except for ACTH deficiency, so it became evident that she has an isolated ACTH deficiency with preservation of other pituitary hormones. Her prolactin level was high right after delivery, as expected, and then dropped to a normal level subsequently. Her high TSH and low T3 and T4 in the beginning, which were normalized subsequently, are probably explained by sick euthyroid syndrome. Her FSH, LH and estradiol were low initially which is expected after delivery and they returned to normal levels subsequently and her menses resumed a few months later, indicating recovery of her hypothalamic pituitary gonadal axis.

The reason for isolated ACTH deficiency in this patient is not clear but it is not surprising. Indeed, there are many reports of isolated ACTH deficiency and primary empty sella (13-16). Also isolated secondary adrenal insufficiency has been described in lymphocytic hypophysitis (17). In lymphocytic hypophysitis there is lymphocytic infiltration and enlargement of the pituitary (17) and it most often occurs in late pregnancy or the postpartum period. The typical appearance of pituitary MRI in lymphocytic hypophysitis is increased stalk thickness and diffuse homogenous contrast enhancement of the pituitary (18, 19), both of those findings were not seen in the present patient. It was reported that empty sella may be the final outcome in lymphocytic hypophysitis, but this requires many years before it develops (20).

Classical Sheehan’s syndrome due to postpartum hemorrhage is another possibility, but the present patient had no history of substantial blood loss after any of her deliveries. In addition, Sheehan’s syndrome is usually associated with pan hypopituitarism rather than isolated secondary adrenal insufficiency (21, 22). Another differential diagnosis in this case is infarction of undiagnosed pituitary adenoma which results in secondary empty sella and deviation of the optic chiasm, but the patient had no history of precedent headache or visual problems and the MRI showed no evidence of residual tumor. Furthermore, dislocation of the optic nerve and optic chiasm have been reported with empty sella syndrome (23). Undeniably, all of the fore-mentioned diagnoses are possible in this case but APS is the only diagnosis that could explain all her clinical and radiological findings; empty sella, secondary adrenal insufficiency, and severe pulmonary hypertension.

### Conclusion

The present case illustrates a few important points; first, isolated adrenal insufficiency in the setting of antiphospholipid syndrome can be primary or secondary. Second, screening for primary APS may be warranted in evaluating patients with empty sella and a history of thrombosis.
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References


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