Recurrent thromboembolism as a hallmark of Cushing's syndrome

A. La Brocca*, M. Terzolo**, A. Pia**, P. Paccotti**, P. De Giuli*** and A. Angeli**

*Divisione di Medicina Interna e Servizio di Endocrinologia e Malattie del Metabolismo, Ospedale Civile di Giaveno, Torino; Dipartimento di **Scienze Cliniche e Biologiche, Cattedra di Medicina Interna e ***Servizio di Anatomia ed Istologia Patologica, Azienda Ospedaliera San Luigi Gonzaga, Università di Torino, Torino, Italy

ABSTRACT. The present report describes a 54-year-old woman with a history of recurrent thromboembolic events. The clinical and physical examination led to suspect Cushing's syndrome. Screening tests (urinary free cortisol excretion and 1 mg dexamethasone) were inconclusive, but a detailed endocrine work up confirmed the presence of ACTH-dependent hypercortisolism. The patient was cured by the removal of a ACTH-secreting microadenoma by transsphenoidal route. The present case provides a clinical demonstration of a previous experimental evidence that a hypercoagulable state is present in Cushing's syndrome.

(J. Endocrinol. Invest. *20:* 211-214, 1997)

INTRODUCTION

A hypercoagulable state and an increased incidence of thromboembolic complications are reported in Cushing's syndrome (1-3), mainly in the early postoperative period (4, 5).
The hypercoagulable state in Cushing's syndrome is due to an increase in plasma clotting factors, particularly factor VIII complex (5, 6), and the impaired fibrinolytic capacity associated with high plasma levels of fast-acting plasminogen activator inhibitor (PAI-1) and decreased plasma levels of tissue-type plasminogen activator (t-PA) (7).

CASE REPORT

The patient is a 54-year-old woman with a history of hypertension and obesity for more than twenty years. In 1992, she experienced a hypertensive crisis with concomitant paroxystic atrial fibrillation and pulmonary embolism shortly after surgery for umbilical hernia. Marked hypokalemia (2.3 mEq/l; n. r.=3.5-5.6) was apparent. After the discovery of a floating thrombus in the right popliteal vein, a caval filter was placed and anticoagulant therapy was started. In December 1994, the patient was referred to us for impressive edema and persistent aching pain at the left leg. Doppler ultrasound of the legs and abdominal CT showed a deep venous thrombosis of the left iliofemural region extending to the confluence between the external iliac and the hypogastric veins. No surgical treatment was amenable. Standard haemostatic parameters under oral anticoagulant tharapy were: partial thromboplastin time=28 seconds (n.v.=<35 sec), prothrombin activity=40% (n.v.=70-100%), and fibrinogen=705 mg/dl (n.v.=200-450). The recurrence of thromboembolic events together with hypertension, mild hypokalemia (3.0 mEq/l), round facies, tendency to centripetal obesity, depression and diffidence towards physicians, led to suspect the presence of hypercortisolism. Hormonal evaluation demonstrated the absence of the circadian profile of cortisol and ACTH. Serum cortisol ranged between 27.6 µg/dl at 08:00 and 31.4 µg/dl at 24:00 (mean of six samples over 24 hours: 28.8 µg/dl) and plasma ACTH ranged between 15.5 pg/ml at 08:00 and 53.4 pg/ml at 24:00 (mean of six samples over 24 hours: 20.3 pg/ml). Urinary free cortisol (UFC) excretion oscillated from normal values (29 µg/24h; 66 µg/24h; n.r.=<150) to supranormal ones (161 µg/24h; 200 µg/24h) on different occasions (mean value: 77 µg/24h). Cortisol suppressibility to 1 mg dexamethasone was maintained (2.8 µg/dl). Magnetic resonance imaging of the sella region was negative. Further diagnostic steps were performed by means of dynamic testing with high dose dexamethasone,

Key-words: Cushing's syndrome, ketoconazole treatment, recurrent thromboembolism.

Correspondence: Antonello La Brocca, M.D., Corso Laghi 261, 10051 Avigliana (TO), Italy.

Accepted March 10, 1997.

Table 1 - *Dynamic testing of the hypothalamic-hypophysis-adrenal axis.*

CRH test (100 µg oCRH)			
	ACTH (pg/ml)		Cortisol (µg/dl)
basal	16	basal	24.3
peak (at +20 min)	69	peak (at +45 min)	32.1
Dexamethasone Suppression Test (8 mg overnight)			
Cortisol: 5.3 µg/dl			
Metyrapone Test (2 g overnight)			
Cortisol		3.4 µg/dl	
11-Deoxycortisol		383 ng/ml	

Petrosal Sinus Sampling with oCRH			
ACTH (pg/ml)	Right Inferior Petrosal Sinus	Left Inferior Petrosal Sinus	Peripheral Blood
basal	>1450	373	315
peak (at + 10 min)	>1450	517	413

metyrapone and oCRH (Table 1). The test results coupled with the patient's history and the clinical picture were suggestive for the presence of Cushing's disease. Inferior petrosal sinus catheterization with selective sampling for ACTH after oCRH stimulation displayed a significative center to periphery ratio (3.5) and a right to left gradient as well (2.8). Ketoconazole (200 mg daily) was then started with a progressive tapering of the dose up to 600 mg daily. Two months later, serum cortisol as well as UFC excretion were normalized (ACTH=114 pg/ml; cortisol=19.3 µg/dl; UFC=15.2 µg/24h). During ketoconazole treatment, a sustained increase of the total plasmatic creatin-phosphokinase (CPK) was observed (peak level: 558 U/l; n.v.=<180), but the myocardial isoenzyme (MB) was always normal. In July 1995, transsphenoidal surgery was performed and a pituitary microadenoma was found in the right-sided part of the gland and removed. The microscopic pattern in hematoxylin-eosin was mixed, both trabecular (sinusoidal) and solid (diffuse). The tumor cells were poligonal, with round nucleus and a variable amount of citoplasm, amphophilic and acidophilic. Mitoses were absent (Fig. 1). Immunohistochemistry demonstrated strong reactivity for ACTH and weak staining for GH and prolactin (Fig. 2).

The postoperative course was uneventful. Glucocorticoid supplementation was necessary since clinical hypocortisolism ensued although morning cortisol after 24-hour discontinuation of steroid supplementation was normal one month later (11.1 µg/dl). At that time UFC was 15.8 µg/24h. Signs and symptoms of Cushing's syndrome disappeared almost completely in 4-6 weeks: arterial blood pressure fell so that antihypertensive therapy was reduced and depressive mood improved remarkably. Serum potassium and total creatin-phosphokinase normalized, peripheral edema resolved, and a significant weight loss was observed (about 10 kg in 3 months). At that time, basal evaluation of HPA axis was normal. Steroid supplementation was discontinued five months after surgery. Nine months after surgery, the patient was free from any symptomatology with normal laboratory data. She is under anticoagulant therapy and low doses of antihypertensive drugs.

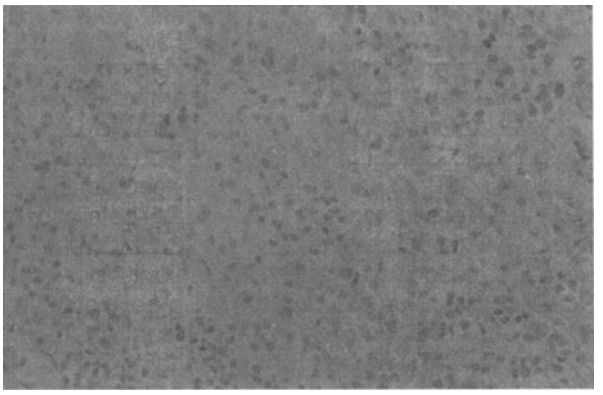

Fig. 1 - *Pituitary microadenoma: trabecular and solid pattern of the tumor (hematoxylin-eosin, X250).*

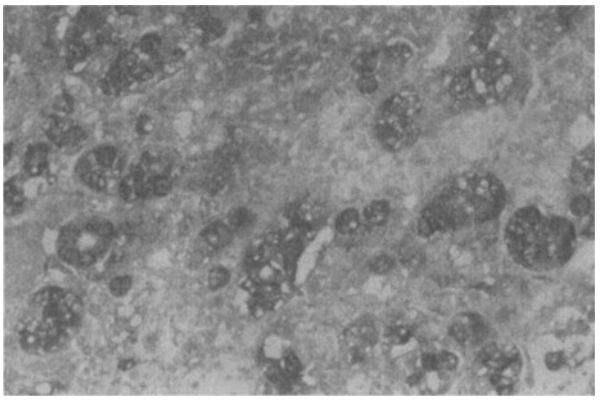

Fig. 2 - *Pituitary microadenoma: ACTH immunostaining (ABC method, X250).*

METHODS

Serum and urinary cortisol were measured by a specific RIA (Sorin Biomedica, Saluggia, Italy) and ACTH by a specific IRMA (Nichols, San Juan Capistrano, US) with intra- and interassay coefficients of variation always below 10%. All samples were run in duplicate in the same session.
Routinely processed tissues were sectioned and stained by hematoxylin-eosin and Pas. Immunostaining was performed using antisera to ACTH, GH and prolactin (Avidine-Biotine-Peroxidase Complex method).

DISCUSSION

The hypercoagulable state of Cushing's syndrome is due to an increase in the plasmatic levels of clotting factors II, V, IX, XII, and especially, factor VIII complex (2). The increase in von Willebrand factor is key to this process (5). It was indeed demonstrated as elevated plasma cortisol levels are able to induce the synthesis of a vast array of blood proteins (8).
Several factors could contribute to the rise in circulating clotting factors in Cushing's syndrome also because of the frequent association with diabetes or hypertension. These two conditions are *per se* characterized by hypercoagulability (9-10). Pertinently, a significant correlation between diastolic or mean arterial blood pressure and the concentration of some contact phase coagulation factors plus factor VIII complex, was found in Cushing's syndrome (10, 11). Hypertension could stimulate the activation of the contact phase of coagulation on the vascular endothelium (3).
A further role in development of the prothrombotic state in Cushing's syndrome is played by the alteration of the fibrinolytic system (7). The impaired fibrinolytic capacity observed in some Cushing's patients is due to both increased synthesis and release of plasminogen, alpha$_2$-antiplasmin (3) and fast-acting plasminogen activator inhibitor (12, 13) and to the impaired release of tissue-type plasminogen activator (tPA) (14, 15). In fact, defective fibrinolysis is often involved in the pathogenesis of venous thrombosis (16, 17). Impaired release of t-PA or high plasma levels of PAI-1 is strongly correlated with venous thromboembolic disease, and represent a further risk factor for thromboembolism especially after hypophysial or adrenal surgery.
Recently, Casonato et al. (5) have confirmed that in Cushing's syndrome all these hemostatic abnormalities are maximally operative shortly after surgery, when thrombotic complications more often occur. Their results suggest the need for an accurate monitoring of hemostasis in patients with Cushing's syndrome, especially during the postoperative period. Moreover, they advocate the necessity of an anticoagulant prophylaxis in the preoperative and postoperative periods.
The present case is of interest because of some peculiar clinical findings. First, the suspicion of Cushing's syndrome was mainly based on the recurrence of thromboembolic events in the absence of a full blown cushingoid habit. Second, screening test, like UFC and overnight 1 mg dexamethasone tests, were inconclusive. Fluctuation of UFC excretion around normal values is not infrequent in mild Cushing and may be also explained by periodic hormonogenesis (18, 19). Cortisol suppressibility to 1 mg dexamethasone have been observed in some patients with Cushing's disease, presumably due to the exquisite sensitivity of glucocorticoid feedback as well as the occasionally intermittent nature of the hypercortisolism (20). The occurrence of normal cortisol suppression after dexamethasone and inconsistent elevation of UFC should not exclude the possibility of hypercortisolism in an appropriate clinical setting. Moreover, the present case provides a clinical demonstration of experimental evidence that a hypercoagulable state is present in Cushing's syndrome.

REFERENCES

1. Sjoberg H.E., Blomback M., Granberg P.O.
Thromboembolic complications, heparin treatment and increase in coagulation factors in Cushing's syndrome.
Acta Med. Scand. *199:* 95, 1976.
2. Dal Bo Zanon R., Fornasiero L., Boscaro M., Cappellato G., Fabris F., Girolami A.
Increased factor VIII associated activities in Cushing's syndrome: a probable hypercoagulable state.
Throm. Haemostas. *47:* 116, 1982.
3. Patrassi G.M., Dal Bo Zanon R., Boscaro M., Martinelli S., Girolami A.
Further studies on the hypercoagulable state of patients with Cushing's syndrome.
Thromb. Haemostas. *54:* 518, 1985.
4. Blichert-Toft M. Bagerskov A., Lockwood K., Hasner E.
Operative treatment, surgical approach, and related complications in 195 operations upon the adrenal glands.
Surg. Gynecol. Obstet. *135:* 261, 1972.
5. Casonato A., Pontara E., Bertomoro A., Scarpa E., Sonino N., Girolami A.
Abnormalities of primary haemostasis with consequent hypercoagulable state in patients with Cushing's syndrome.

J. Endocrinol. Invest. *18* (Suppl. no. 5): 75, 1995, abstract number 256.

6. Ikkala E., Myllyla G., Pelkonen R., Rasi V., Viinikka L., Ylikorkala O.
Haemostatic parameters in Cushing's syndrome.
Acta Med. Scand. *217:* 507, 1985.
7. Patrassi G.M., Sartori M.T., Viero M.L., Scarano L., Boscaro M., Girolami A.
The fibrinolytic potential in patients with Cushing's disease: a clue to their hypercoagulable state.
Blood Coagul. Fibrinolysis *3:* 789, 1992.
8. Simmons P.S., Miles J.M., Gerich J.E., Haymond M.W.
Increased proteolysis. An effect of increased in plasma cortisol within the physiological range.
J. Clin. Invest. *73:* 412, 1984.
9. Huges A., McVerry B.A., Wilkinson L., Goldstone A.H., Lewis D., Bloom A.
Diabetes, a hypercoagulable state? Haemostatic variables in newly diagnosed type 2 diabetic patients.
Acta Haematol. *69:* 254, 1983.
10. Boneu B., Durand D., Connilon F., Charlet J.P., Bierme R., Suc G.M.
Increased level in factor VIII complex in severe arterial hypertension.
Haemostasis *7:* 332, 1978.
11. Patrassi G.M., Fallo F., Martinelli S., Mantero F., Boeri G., Girolami A.
The contact phase of blood coagulation and renin activation in essential hypertension before and after captopril.
Eur. Heart J. *5:* 561, 1984.
12. Jorgensen M., Bonnevie-Nielsen V.
Increased concentration of the fast-acting plasminogen activator inhibitor in plasma associated with familial venous thrombosis.
Br. J. Haematol. *65:* 175, 1987.
13. Engesser L., Brommer E.G.P., Kluft C., Briet E.
Elevated plasminogen activator inhibitor (PAI), a cause of thrombophilia? A study in 203 patients with familial or sporadic venous thrombophilia.
Thromb. Haemostas. *62:* 673, 1989.
14. Patrassi G.M., Sartori M.T., Viero M., Boscaro M., Boeri G., Girolami A.
Venous thrombosis and tissue plasminogen activator release deficiency: a family study.
Blood Coagul. Fibrinol. *2:* 231, 1991.
15. Petaja J., Rasi V., Myllyla G., Vahtera E., Hallman H.
Familial hypofibrinolysis and venous thrombosis.
Br. J. Haematol. *71:* 393, 1989.
16. Korninger C., Lechner K., Neissner H., Gossinger H., Kundi M.
Impaired fibrinolytic capacity predisposes for recurrence of venous thrombosis.
Thromb. Haemostas. *52:* 127, 1984.
17. O'Connor N.T.J., Cederholm-Williams S.A., Fletcher E.W., Allington M., Sharp A.A.
Significance of idiopathic deep venous thrombosis.
Postgrad. Med. J. *60:* 275, 1984.
18. Atkinson A.B., Kennedy A.L., Carson D.J., Hadden D.R., Weaver J.A., Sheridan B.
Five cases of cyclical Cushing's syndrome.
Br. Med. J. *292:* 1453, 1985.
19. Schweikert H.U., Fehm H.L., Fahlbusch R., Martin R., Kolloch R., Higuchi M., Kruck F.
Cyclic Cushing's syndrome combined with cortisol suppressible, dexamethasone non-suppressible ACTH secretion: a new variant of Cushing's syndrome.
Acta Endocrinol. (Copenh.) *110:* 289, 1985.
20. Sheeler L.R., Bay J.W.
Normal overnight dexamethasone suppression tests (ODST) in patients with proven Cushing's disease.
In: Landolt A.M. et al. (Eds.), Advances in Pituitary Adenoma Reserch (Advances in the Biosciences, vol. 69).
Pergamon Press, New York, 1988, p. 373.