

A CASE REPORT OF CUSHING'S SYNDROME INDUCED HYPERCOAGULABLE STATE

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PRESENTATION OF CASE

A 25-year-old female patient presented with complaints of swelling of the left lower limb associated with pain in the left leg for 15 days duration. Patient had history of weight gain and irregular menstrual bleeding. No history of breathlessness or giddiness. Patient has no similar complaints in the past and not on any chronic drug intake in the past. On examination, patient is conscious and oriented, pulse – 86/ minute, all peripheral pulses felt; Blood pressure -110/80 mm Hg and systemic examination normal. Examination of the left lower limb shows swelling of the entire lower limb with redness and warmth. Her complete haemogram revealed anaemia with Hb– 9.3 g% and thrombocytosis with platelet – 680000/ cu mm. Her renal function tests, liver function tests and serum electrolytes were normal. Electrocardiogram and chest X-ray revealed no abnormalities.

Cushing's syndrome, an endocrine disorder due to chronic glucocorticoids excess may be a result of exogenous glucocorticoid use for various conditions or, endogenous as in adrenal adenoma or secondary due to increase ACTH (Adrenocorticotrophic hormone) as in pituitary adenoma or ectopic ACTH production. Cushing's syndrome results in a wide range of clinical manifestations such as central obesity, easy bruising, osteoporosis, diabetes, hirsutism and depression. Cardiac complications are also common in patients with Cushing's syndrome and mortality is high in such patients. They include hypertension, myocardial infarction, stroke, heart failure and venous thrombosis. Various explanations are given for thrombosis occurring in Cushing's syndrome. Here we present a 25-year-old female patient with deep venous thrombosis of the left lower limb was diagnosed as a case of Cushing's syndrome.

DIFFERENTIAL DIAGNOSIS

Unilateral Limb Swelling

In a patient with unilateral leg swelling, common differential diagnoses are cellulitis, deep vein thrombosis (most important as may embolise to the lungs), lymphedema,

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varicose veins and ruptured popliteal cyst. In our case we further proceeded with a Doppler study of the left lower limb which showed thrombus formation involving the left femoral vein, superficial femoral vein, popliteal vein, anterior and posterior tibial veins extending into the great saphenous vein. Her d-Dimer was elevated 400 ng/ml. Diagnosis - Left lower limb Deep Venous Thrombosis (DVT)

Approach to DVT

A patient with deep venous thrombosis has to be evaluated for the underlying pathology causing DVT. DVT results from hypercoagulable state or venous stasis as in bedridden state.

Inherited	Acquired
1) Factor V Leiden	1) Increasing age
2) Prothrombin gene mutation	2) Previous thrombosis
3) Protein C deficiency	3) Immobilization
4) Protein S deficiency	4) Hormonal disturbances
5) Antithrombin III deficiency	5) Pregnancy and puerperium
6) Elevated F VIII	6) Obesity & smoking
UNKNOWN CAUSES	7) Infections
1) Elevated factor II, IX, XI	8) Drugs
2) Elevated (or) low levels of Thrombin-activatable fibrinolysis inhibitor	9) Activated protein C resistance (non-genetic)

Table 1. Showing the Inherited and Acquired Causes of Thrombophilia

As in our case, the patient was young we ruled out inherited causes of thrombophilia – protein C activity – 64% and protein S activity – 130% (normal range). Antithrombin III activity – 64% and prothrombin gene mutation – not detectable. As the patient was a young female we ruled out connective tissue disorders, anti- nuclear antibodies (ANA) by immunofluorescence and APLA (antiphospholipid antibody syndrome) were negative.

CLINICAL DIAGNOSIS

In a patient with unilateral leg swelling, non-pitting with warmth and calf muscle tenderness with no history of fever, our clinical suspicion should be DVT of the lower limbs. And on further searching for the aetiology, inspection, abdomen had purple stretch marks and morbid obesity with irregular menstrual cycles made us to suspect Cushing's syndrome and patient was evaluated.

PATHOLOGICAL DIAGNOSIS

Her 24 hours free urinary cortisol was 70 µg / 24 hrs (elevated). Her serum cortisol level was 7.4 µg/ dl and overnight dexamethasone suppression test (with 1 mg of tab. Dexamethasone at 11 pm) serum cortisol level in the morning was 2.3 µg/ dl which is elevated (expected value of < 1.8 µg/ dl). Serum ACTH levels was low- 4 pg/ml. CT adrenals showed features of bilateral nodular adrenal hyperplasia.

DISCUSSION OF MANAGEMENT

Patient was started on anticoagulants for deep vein thrombosis patient was started with inj. Heparin 5000 units IV 4 times a day with oral anticoagulants (tab. Acitrom 1 mg at 6 pm). Oral anticoagulants need to be bridged with heparin as in first 5 days of starting, they inhibit protein C and protein S (increasing thrombus formation). The dose of tab. Acitrom was adjusted according to her prothrombin time (PT) and Internationalised ratio (INR) values (target INR of 2-3).

Treatment for Cushing’s syndrome requires surgical removal of the adenoma. As our patient had DVT and morbid obesity, patient was treated symptomatically and planned later for bilateral adrenalectomy.

Cushing’s syndrome, a constellation of clinical features due to chronic exposure to excess glucocorticoids of any aetiology. This disorder may be due to exogenous glucocorticoid excess as used in wide range of diseases; or endogenous as in adrenal adenoma (or) secondary due to increase in Adrenocorticotrophic hormone (ACTH) as in pituitary adenoma or ectopic ACTH syndrome. Most of the cases of Cushing’s syndrome may be due to excess glucocorticoids usage as therapy. In patients with endogenous overproduction around 90% of cases are ACTH dependent.^{1,2}

Clinical features of Cushing’s syndrome are diverse as glucocorticoids have impact on almost all cells of the body. They include obesity (central with rounded face), easy bruising, diabetes, diastolic hypertension, oedema and electrolyte imbalance (mineralocorticoid activity), proximal myopathy, depression and in severe cases patients may develop paranoid psychosis. The genital symptoms are hirsutism and amenorrhoea and in males decreased libido. In the cardiovascular system, it causes hypertension, coronary artery disease and heart failure. These patients are also at risk of deep vein thrombosis.^{1,2}

- 1) MRI Pituitary- CT adrenals for adrenal tumour corticotrophin releasing hormone test or bilateral adrenal hyperplasia high dose DEX test positive in pituitary adenoma
- 2) Ectopic ACTH Production.

Overt Cushing’s syndrome if untreated, has poor prognosis. Oral agents used in CS are tab. metyrapone 500 mg thrice (max-6g/day) and tab. Ketoconazole 200 mg thrice (max- 1200 mg/day). In severe cases, etomidate can be used. In adrenal adenoma treatment is surgical removal of the tumour. In ACTH dependent CS in pituitary adenoma surgical removal by transsphenoidal approach is done and regular followup of these patients is needed as relapse can occur. In ectopic ACTH syndrome identify and remove the source of ACTH production. If not possible then try medical management or bilateral adrenalectomy.^{2,3}

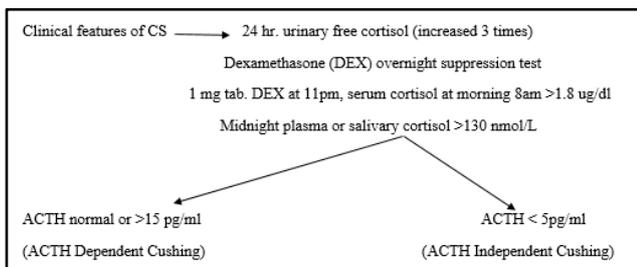
Hypercoagulable State in Cushing’s Syndrome

Patients with Cushing’s Syndrome (CS) are at increased risk of arterial and venous thrombosis. Thrombus formation increases by fourfold in patients with Cushing’s syndrome and cardiac complications remain the important factor of mortality in these patients. The cardiac complications of CS are myocardial infarction, stroke, heart failure and venous thromboembolism. The theory of Virchow’s Triad (hypercoagulability, endothelial damage and blood stasis) explains thrombus formation in CS. Also, presence of obesity, hypertension, diabetes, dyslipidaemia, surgery, age also increase the risk of thrombosis in these patients. Various studies show presence of significant carotid artery disease in most cases of CS, even 1 year after successful treatment.^{4,5,6}

Hypercoagulability- In recent studies, various coagulation abnormalities were observed in CS. Prothrombin Time (PT) and Thromboplastin Time (aPTT) were found to be decreased in most studies. Fibrinogen, a platelet aggregator and activator of fibrin formation, is elevated in CS. Platelet count is also increased in patients of CS as seen in this patient. However, platelet function has been found to be normal. Increase in P selectin is seen in patients treated with high dose dexamethasone. However, it has no role in endogenous CS. Clotting factors, factor VIII and Von Willebrand Factor (vWF) are elevated in patients with Cushing’s syndrome.⁷ These factors were increased even after 3 months of curative surgery. Decreased fibrinolytic activity is seen in Cushing’s – Plasminogen activator inhibitor type 1 activity is elevated in CS in various studies. All these factors increase chance of VTE but which factor is responsible for thrombosis still remains unclear in patients with CS.^{8,9,10}

Blood stasis- Polycythaemia and obesity play a main role for stasis activating thrombus formation.

Endothelial damage- Cortisol causes concentric ventricular remodeling and hypertrophy in patients of CS. Hypertrophic remodeling also occurs in resistance arteries. Vascular remodeling occurs independent of hypertension in CS. It is suggested in various studies that vascular



Work Up of Cushing’s Syndrome

remodeling occurs through mineralocorticoid signaling pathway.^{6,7}

Attempts were made to detect the occurrence of thromboembolism prior to the event in CS. Thrombin Antithrombin complexes (TAT), Prothrombin fragment 1+2, fibrinopeptide A, plasmin α 2 antiplasmin (PAP) and D-dimer were exclusively studied in various studies but still no marker is approved for clinical use. The most recent of these markers is endogenous thrombin potentials (ETP).^{11,12}

Treatment of Cushing's syndrome involves surgery and even after successful treatment, venous thromboembolism (VTE) and cardiac complications occur. Also, surgery can provoke thromboembolism. Prophylactic anticoagulation is not recommended in patients with CS and should be based on individual patients and presence of risk factors (obesity, hypertension, etc.). Postsurgical patients of CS are advised for anticoagulation for at least 3 months in various studies.^{4,11,12}

To conclude patients with CS are at increased chance of arterial and venous thrombosis and presence of additional risk factors increase the chance and they remain the mainstay of cause of mortality in CS. Various markers have been studied to assess risk of VTE but still not in clinical use. Most of the cardiac complications persists even after successful treatment in patients of Cushing's syndrome. Treatment is of other cases of VTE and prophylactic anticoagulation depends on individual patient risk.

FINAL DIAGNOSIS

Left lower limb deep vein thrombosis secondary to ACTH independent Cushing's syndrome with bilateral adrenal hyperplasia.

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