CASE REPORT

Arterial thrombosis as primary presentation of endogenous Cushing's syndrome

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SUMMARY

Cushing's syndrome is known to present with a characteristic set of clinical manifestations and complications, well described in literature. However, hypercoagulability remains an under recognised entity in Cushing's syndrome. A 31-year-old woman from Southern India presented with history of fever, left upper quadrant pain and progressive breathing difficulty for 3 weeks. Clinical examination revealed discriminatory features of Cushing's syndrome. Laboratory investigations showed biochemical features of endogenous ACTH-dependent Cushing's syndrome. Imaging of the abdomen revealed splenic collection, left-sided empyema and extensive arterial thrombosis. Gadolinium enhanced dynamic MRI of the pituitary gland revealed no evidence of an adenoma while a Ga-68 DOTATATE positron emission tomography CT scan ruled out an ectopic Cushing's. A diagnosis of endogenous Cushing's syndrome causing a prothrombotic state with extensive arterial thrombosis was made. She was initiated on oral anticoagulation and oral ketoconazole for medical adrenal suppression. She subsequently underwent bilateral adrenalectomy and was well at follow-up.

BACKGROUND

Cushing's syndrome is a prothrombotic state with elevated levels of factor VIII and von Willibrand Factor (vWF) that can result in venous thrombosis.¹ Most thrombotic events have been reported to occur in the perioperative period warranting prophylactic anticoagulation, with venous thrombosis more in occurrence than arterial events.² However, widespread arterial thrombosis as a presenting manifestation of ACTH-dependent Cushing's syndrome has not been described previously. Here we report one patient with endogenous Cushing's syndrome that was detected when she presented to us with extensive arterial thrombosis and secondary infection of the infarcted tissue.

CASE PRESENTATION

A 31-year-old woman from Southern India presented with fever, recurrent abdominal pain and left sided pleuritic pain for 3 weeks. Her medical history was significant for irregular menstrual cycles, progressive weight gain of 15 kg and proximal lower limb weakness, all for 3 years. She also had diabetes mellitus and hypertension for 3 months. She was initially evaluated in another hospital for these complaints, where imaging CT thorax and abdomen done revealed extensive

arterial thrombosis involving the abdominal aorta, complete thrombotic occlusion of the splenic artery, hepatic artery, celiac trunk and superior mesenteric artery with infarcts involving the spleen and both kidneys. She presented to our centre for further management of the same.

Physical examination revealed a Cushingoid habitus with centripetal pattern of fat distribution, supraclavicular and dorsocervical pads of fat, round plethoric facies, wide non-tapering purplish abdominal striae, hirsutism and features of easy bruisability without significant hyperpigmentation. She was also noted to have absent breath sounds in the left mammary and infra-axillary regions with minimal intercostal tenderness, and mild splenomegaly. The diagnosis of *Cushing's syndrome* with left sided pleural effusion and splenomegaly due to a disseminated infection such as tuberculosis or disseminated malignancy were considered at this point.

INVESTIGATIONS AND DIFFERENTIAL DIAGNOSIS

Baseline investigations revealed leucocytosis with left shift, and mild hypokalaemia with metabolic alkalosis. Blood counts done revealed Hb 10.9 g/dL, white cell count $11.3 \times 10^9/L$ and platelet count $350 \times 10^9/L$. Serum sodium, potassium and bicarbonate were 136 mEq/L, 3.1 mEq/L and 28 mEq/L respectively. She was noted to have poor glycaemic control with HbA1c of 11.9 g %.

In view of the extensive intra-abdominal arterial thrombosis, our initial evaluation was aimed at ruling out a prothrombotic state in a young woman. Inherited thrombophilias and acquired prothrombotic states secondary to an underlying malignancy were considered in our differentials.

Chest radiograph revealed a left sided pleural effusion and imaging of the abdomen revealed splenic collection (850 cc). Cross sectional imaging of the thorax and abdomen was done to look for evidence of a neoplastic aetiology. This revealed left sided loculated collection ([figure 1](#)), splenic collection with extensive arterial thrombosis involving the abdominal aorta, complete thrombotic occlusion of the splenic artery, hepatic artery, celiac trunk and superior mesenteric artery ([figures 2 and 3](#)) with infarcts involving the spleen and both kidneys ([figure 4](#)). However, there was no evidence of any mass lesion. Despite the extensive nature of arterial thrombosis, she did not develop clinical signs or symptoms of bowel ischemia. CT angiography

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Figure 1 Contrast CT of the thorax showing empyema on the left side.

revealed extensive collateralisation of arterial arcade compensating for the thrombosed vessels.

Given the poor glycaemic control, differentials of infective endocarditis, disseminated tuberculosis and melioidosis were considered. Work-up for the same was negative. There was no evidence of atrial fibrillation or valvular dysfunction. Echocardiography revealed normal valve structure, function and normal left ventricular systolic function. The differentials considered for the prothrombotic process were procoagulant state secondary to Cushing's syndrome, infective endocarditis with septic emboli, or an unrelated prothrombotic state.

She was evaluated for a secondary prothrombotic state. Approach to evaluation of a patient with hypercoagulability includes stepwise search for inherited and acquired causes.

Figure 2 CT angiography showing eccentric thrombus in the aorta with complete occlusion of the celiac trunk and non-visualisation of the splenic artery and common hepatic artery.

Figure 3 CT angiography showing partial thrombosis of superior mesenteric artery.

Though literature describes a clear distinction in the causes of arterial and venous thrombosis, there is significant overlap in the aetiologies. Important inherited causes include activated protein C resistance, factor V Leiden mutation, protein C/S deficiency, antithrombin deficiency and hyperhomocysteinaemia. Important acquired factors include solid and haematological malignancies, pregnancy, antiphospholipid antibody syndrome, paroxysmal nocturnal haemoglobinuria, and nephrotic syndrome. It is important to remember that atherosclerosis and risk factors of atherosclerosis are responsible for most cases of acquired arterial thrombosis. Lupus anticoagulant, beta 2 glycoprotein (IgM and IgG) tested negative. There was no evidence of hyperviscosity or panmyelosis. Coagulation profile done revealed elevated factor VIII and vWF levels, with normal levels of protein C and S. Serum homocysteine was noted to be well within normal limits. Genetic tests for factor V Leiden mutation and prothrombin mutation tested negative.

Further evaluation was aimed at localising the source of endogenous cortisol. 8 am Serum cortisol was 38 µg/dL (ref:10–25 µg/dL), 8am plasma ACTH was 56 pg/mL (ref: 10–50 pg/mL) and

Figure 4 CT angiography (coronal) showing wedge shaped infarct in the right kidney.

Figure 5 A T2-weighted flair MRI of the brain showing normal pituitary with no evidence of adenoma.

24 hour estimation of urine free cortisol (UFC) was 1330 µg (ref: <100 µg). Midnight measurement of serum cortisol and plasma ACTH were 25.7 µg/dL and 50.7 pg/mL respectively. Overnight dexamethasone suppression test (1mg) followed by measurement of 8 am cortisol (serum) was 36.4 µg/dL and high dose dexamethasone suppression test (8mg) followed by measurement of 8 am cortisol (serum) was 9.2 µg/dL.

Clinical features, along with the biochemical workup for Cushing's syndrome confirmed the diagnosis of an ACTH-dependent Cushing's syndrome. The differentials of Cushing's disease or an ectopic ACTH-secreting lesion were then considered. The next step in the diagnostic algorithm was imaging of the pituitary to look for a pituitary adenoma. Conventional MRI was performed initially, followed by dynamic gadolinium enhanced MRI brain with sections through the pituitary as per institutional protocol for neuroimaging for suspected Cushing's disease. However, imaging revealed no evidence of adenoma (figure 5). Towards localisation of the ectopic source, Ga-68 DOTATATE positron emission tomography (PET) CT was done which was negative. Though she had undergone initial imaging with thin slice contrast enhanced CT scan of the thorax and abdomen, subsequent imaging with Ga-68 DOTATATE PET CT for localisation was preferred due to its superior positive predictive accuracy.³ For further evaluation of the pituitary as the likely aetiology, she was advised to undergo inferior petrosal sinus venous sampling. However, she was unwilling for undergoing the procedure.

TREATMENT

Drainage of the splenic collection was done under radiological guidance and intercostal drain was inserted on the left side. Pus culture from both sites grew pan-sensitive *Pseudomonas aeruginosa*, for which she was given appropriate antibiotic therapy. Serial blood cultures drawn following admission showed no growth. The patient was initially started on vitamin K antagonist which was changed over to rivaroxaban for ease of management of anticoagulation in the perioperative period. As soon as need for surgery was

anticipated, the choice of oral anticoagulation was changed from vitamin K antagonist to rivaroxaban. Low molecular weight heparin was administered once daily. The patient had a labile INR with one episode of melaena during her admission. Combination therapy with antiplatelet agent and anticoagulation, though warranted in an ideal setting, was deferred due to high risk of bleeding in this patient. She was also initiated on oral ketoconazole at a dose of 400 mg/day for suppression of adrenal steroidogenesis. There was an initial reduction in 24 hours estimation of UFC within a few weeks of initiation of oral ketoconazole (baseline: 1330 µg, after ketoconazole: 702 µg). However, the UFC level failed to normalise with medical therapy alone.

OUTCOME AND FOLLOW-UP

She was kept on close follow-up following discharge. In view of failure of normalisation of urine cortisol levels and urgent need for control of endogenous hypercortisolism due to increased risk of potentially fatal thromboembolic events, bilateral adrenalectomy was chosen as the next best line of management. She was well on follow-up.

DISCUSSION

Cushing's syndrome is an endocrine disorder with complex and varied presentations. Delay in diagnosis and failure to initiate appropriate therapy can prove catastrophic. Over the counter use of oral glucocorticoids resulting in exogenous Cushing syndrome is the most common cause of the same encountered in clinical practice, especially in India where these drugs may be obtained easily without a prescription.⁴ Endogenous Cushing's syndrome is a rare entity with an annual incidence of 0.7–2.4 in one million population.⁵ Pituitary adenomas account for over two-thirds of patients diagnosed with endogenous Cushing's syndrome. Remaining cases have rarer causes such as ectopic ACTH secreting tumours, autonomous adrenal adenomas and pigmented macronodular adrenal hyperplasia.

Cushing's syndrome has been associated with a wide variety of complications including metabolic, neuropsychiatric, infectious and coagulation related complications.⁶ The incidence of opportunistic infections in Cushing's syndrome is estimated to be approximately 11%–17%. Higher the serum cortisol, more profound is the immunosuppression. Hence, ectopic ACTH related Cushing's syndrome is associated with opportunistic infections more often than Cushing's disease.⁷ Common pathogens associated with infections in these patients include *P. jirovecii*, *Cryptococcus neoformans*, *Aspergillus* and *Nocardia* species.⁸

Cushing's syndrome is associated with a prothrombotic state resulting in venous and arterial thromboembolic events.^{9 10} Thrombotic events are of paramount importance as these are predictors of morbidity and mortality.⁹ While deep venous thrombosis and pulmonary thromboembolism are commonly noted venous disorders, important arterial events include myocardial infarction and strokes.¹¹

Though it is clear beyond doubt that a procoagulant state in Cushing's syndrome exists, the pathogenetic mechanisms behind the same remain unclear. Multiple causes have been postulated to be causative resulting in a chaotic and dysregulated coagulation system. Some of the causes mentioned in literature include atrial fibrillation, valvular heart disease, persistent and poorly controlled hyperglycaemia, dyslipidaemia, hypertension, accelerated atherosclerosis and occurrence of opportunistic

infections.^{6 12} Several investigators have attempted to explain these phenomena at the cellular and factor levels. High levels of circulating glucocorticoids have been associated with the generation of a prothrombotic microenvironment. Large number of coagulation abnormalities has been documented to occur in these patients. Most consistent among these has been elevated levels of factor VIII and von Willebrand factor.¹³ Accelerated thrombin generation along with concomitantly delayed fibrinolytic activity occurs as an end result of these changes in the haemostatic system.

This prothrombotic state predisposes patients with Cushing's syndrome to develop thromboembolic events, especially in the perioperative period and during admissions for inferior petrosal sinus sampling.¹⁴

Dal Bo Zanon *et al*¹⁵ reported that levels of Factor VIII which are elevated at diagnosis, return to baseline 4 months after surgical resection of pituitary adenoma. Casonato *et al*¹ have documented similar findings with respect to levels of factor VIII, vWF concentration and vWF ristocetin cofactor activity. While the levels of factor VIII and vWF may return to normal, an increased occurrence of cardiovascular events seems to persist upto 5 years after successful therapy of Cushing's syndrome.¹¹

The American College of Physicians (ACP) and American Society of Hematology (ASH) recommend against routine screening for hypercoagulable state in the setting of acute thrombosis because the protein levels are altered and interpretation of test results become difficult.^{16 17} However, genetic mutation analysis as those done to detect Factor V Leiden mutation and prothrombin mutation are unaffected. Its is also interesting to note that both ACP and ASH recommend against screening for hypercoagulable states because a positive result need not predict the risk of recurrence risk.^{16 17}

Most of literature on hypercoagulability in Cushing syndrome mentions venous events. Arterial thrombosis is a rare occurrence in the setting of endogenous Cushing syndrome. Takayasu *et al*² reported the case of a 65-year-old woman who presented with acute abdomen and was also diagnosed with endogenous Cushing syndrome. She was diagnosed with acute mesenteric ischaemia and hepatic infarction. Kim *et al*¹⁸ reported a case of thoracoabdominal aortic thrombosis in an 82-year-old woman with iatrogenic Cushing syndrome.

A retrospective-prospective observational study by Small *et al*¹⁹ looked at 43 patients with endogenous Cushing syndrome. Arterial thrombosis was noted in 9% cases (n=4) and venous events in 11% (n=6) cases. However, there is a dearth of literature reporting arterial events. It is, however, interesting to note that none of the cases reported in previously published literature presented with extensive arterial thrombosis in isolation, as in our case.

Our patient did well with therapeutic anticoagulation along with medical therapy with ketoconazole, followed by surgical adrenalectomy. This case highlights the complex and uncommon presentation of endogenous ACTH-dependent Cushing's syndrome with extensive arterial thrombosis. Though the exception rather than the rule, a high index of suspicion and meticulous clinical evaluation is crucial in making a timely diagnosis and avoiding catastrophic outcomes.

Learning points

- ▶ Cushing's syndrome is an endocrine disorder with complex and varied presentations.
- ▶ Venous thromboembolism is a well-known complication of Cushing's syndrome.
- ▶ Arterial thrombosis, less common than venous events, can be a presenting manifestation of the disease.
- ▶ Delay in diagnosis and failure to initiate appropriate therapy can prove catastrophic.

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