Pulmonary embolism in iatrogenic Cushing's syndrome: a case report

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ABSTRACT

Background: Patients with Cushing's syndrome have an increased risk of thrombosis due to acquired hypercoagulability.

Case Presentation: A 54-year-old obese female, with underlying iatrogenic Cushing's syndrome (ICS), presented with a sudden onset of dyspnea and circulatory collapse. Computed tomography pulmonary angiogram confirmed acute massive pulmonary embolism (PE). She showed marked improvement after treatment with anticoagulation.

Conclusion: This case demonstrates the clinical presentations and pathophysiology of Cushing's syndrome (CS). CS patients are prone to thrombosis due to disturbance in all three components of Virchow's triad. PE is one of the leading causes of mortality in CS. Clinicians should be aware of this serious, but less recognized, complication when a patient with CS presents with acute circulatory collapse. Anticoagulants remain the mainstay of treatment in ICS complicated by PE.

Keywords: Cushing's syndrome, corticosteroids, thrombosis, pulmonary embolism, anticoagulation, case report.

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Background

Iatrogenic Cushing's syndrome (ICS) occurs after exposure to a supraphysiological dose of exogenous glucocorticoids, used in the treatment of many nonendocrine diseases, most commonly in oral form. Exogenous glucocorticoids lead to increased circulating cortisol levels with subsequent suppression of the hypothalamus-pituitary-adrenal (HPA) axis [1]. Hypercortisolism is associated with a high risk of hypercoagulability due to abnormalities of coagulation and fibrinolytic systems [2]. However, there are no standard anticoagulation guidelines currently [2].

Case Presentation

A 54-year-old woman presented with sudden onset of dyspnea and circulatory collapse. Over the past few years, she has suffered from generalized weakness, easy fatigability, light bruising, somnolence, and progressive weight gain, especially in her abdomen. Her mobility was limited due to weakness and her weight. She has a history of bronchial asthma for which she has been taking oral dexamethasone irregularly by herself.

On arrival at the emergency department, she was dyspneic. Blood pressure was 90/60 mmHg, heart rate (HR) was 132 bpm, oxygen saturation was 79% on air, and 95% with oxygen 10 L with a non-rebreather mask. Capillary blood sugar was 293 mg/dl. Physical examination revealed a morbidly obese woman (BMI = 47.2, bodyweight = 250 lb, and height = 5 feet 1 inch) with a short neck, posterior neck fat pads (buffalo hump), and moon-like face. There were red-purple striae marks and purpura all over her body, mainly in the abdomen and limbs. She was fully conscious and oriented with no cognitive impairment. Motor examination of upper and lower limbs showed mild bilateral proximal muscle weakness with Medical Research Council grade 4/5. Deep tendon reflexes were symmetrical, 2+ with bilateral downgoing plantar reflexes. Sensory examination was unremarkable. A diagnosis of ICS was made based on her full-blown cushingoid morphology and history of exogenous steroid exposure.

Investigations

Portable chest radiography showed pulmonary congestion (Figure 1). Electrocardiography revealed sinus tachycardia with the S1Q3T3 pattern (Figure 2). Laboratory tests (Table 1) were normal except for elevated Troponin T, D-dimer (>1,600 ng/ml), liver enzymes, lipid profile, and glycosylated hemoglobin. Thyroid function, electrolytes,

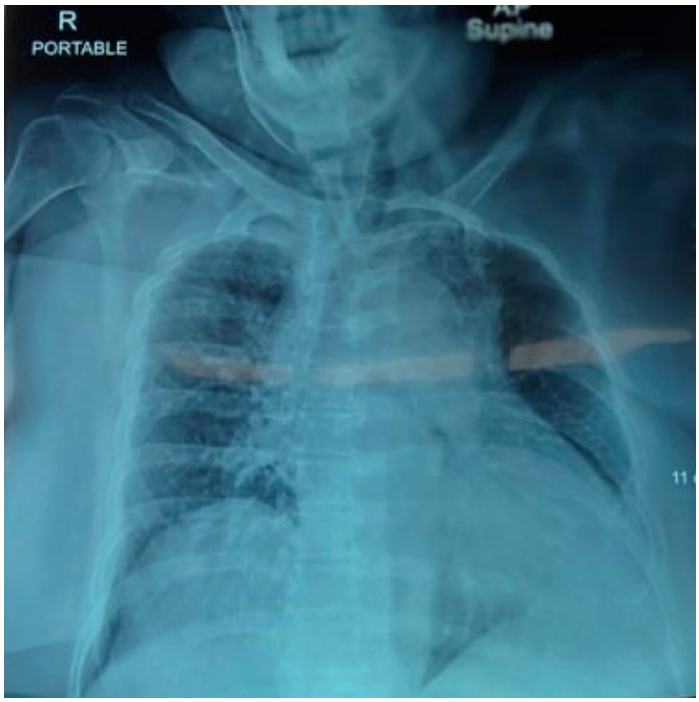

Figure 1. *CXR showing pulmonary congestion.*

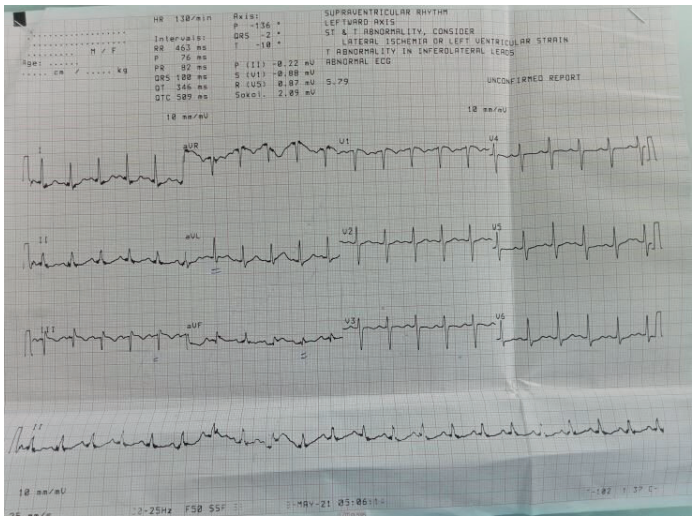

Figure 2. *ECG showing sinus tachycardia with the S1Q3T3 pattern.*

and renal function were all within normal range, apart from mild hypokalemia.

Bedside echocardiography showed dilated right atrium and right ventricle. Modified Wells criteria for pulmonary embolism (PE) was six points (tachycardia, limited mobility, other diagnoses less likely than PE), which means high risk (78%) of PE. Accordingly, CT pulmonary angiogram was done which showed PE in right and left main pulmonary arteries extending into both ascending and descending branches of pulmonary arteries (Figure 3).

Treatment

The patient was started on subcutaneous low-molecular-weight heparin, enoxaparin (1 mg/kg twice daily) for 7 days and then transitioned to a direct oral anticoagulant, Rivaroxaban. She was prescribed intravenous hydrocortisone initially, and then changed to oral prednisolone until HPA axis recovery. Blood sugar was controlled with insulin during her hospital stay and then changed to oral antidiabetic medications when discharged. She showed marked clinical improvement and was discharged on day 7 of hospital stay with blood pressure = 120/80 mmHg, HR = 69 bpm, oxygen saturation = 98% on room air. At 2 months' follow-up, she reported feeling much better with 5 kg weight loss. Oral anticoagulation was continued for 3 months, and the steroid was weaned off completely. The patient was educated about lifestyle modification, such as weight loss and staying active. She was also counseled about the hazards of steroids misuse.

Table 1. *Laboratory test results.*

NAME OF TEST	PATIENT VALUE	REFERENCE RANGE
Total white cells count	10.96	4.00-11.00 $\times 10^9$/l
Hemoglobin	11.6	11.0-16.5 g/dl
Platelet	233	150-400 $\times$ 10^9/l
Troponin T	163.1	≤14 pg/ml
Urea	5.4	2.7-8.0 mmol/l
Sodium	142	135-145 mmol/l
Potassium	3.54	3.60-5.20 mmol/l
Chloride	106.8	98.0-107.0 mmol/l
Bicarbonate	26.8	22.0-29.0 mmol/l
Creatinine	75	44-84 micromol/l
eGFR	74	≥60 ml/minute/1.73 m^2
C-reactive protein (CRP)	12.88	≤5.00 mg/l
D-dimer	>1,600	<198 ng/ml
Total bilirubin	0.374	≤1.2 mg/dl
Alkaline phosphatase	87	35-105 U/l
Alanine aminotransferase	43.7	≤33 U/l
Aspartate aminotransferase	104.4	≤32 U/l
Gamma-glutamyl transferase	106	6-42 U/l
Total cholesterol	276.2	≤200.0 mg/dl
Triglyceride	195.5	≤150 mg/dl
High-density lipoprotein	48.4	45.0-65.0 mg/dl
Low-density lipoprotein	219.5	≤130.3 mg/dl
Uric acid	329	143-339 micromol/l
Free T3	5.43	3.10-6.80 picomol/l
Free T4	19.94	12.00-22.00 picomol/l
Thyroid-stimulating hormone	1.44	0.270-4.200 microIU/ml
Glycosylated hemoglobin	7.7	4.8%-5.9 %

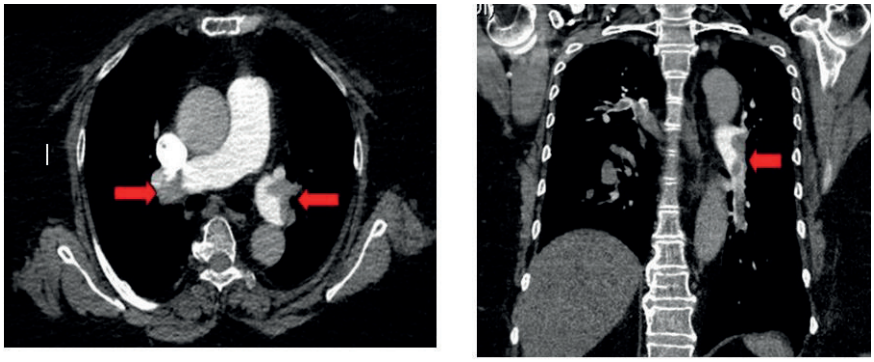

Figure 3. *Pulmonary embolism in right and left main pulmonary arteries extending into both ascending and descending branches of pulmonary arteries.*

Discussion

Pathophysiology of CS

CS occurs after chronic exposure to a supraphysiological dose of glucocorticoids, either endogenous or exogenous. Corticotropin-releasing hormone from the hypothalamus stimulates the anterior pituitary gland to release adrenocorticotrophic hormone (ACTH), which, in turn, induces the adrenal cortex to secrete glucocorticoids. [1] Endogenous CS can be classified as ACTH-dependent (ACTH-secreting pituitary adenoma or ectopic ACTH secretion) or ACTH-independent (autonomous adrenal gland secreting excess cortisol). While endogenous CS is rare, exogenous or iatrogenic (drug-related) CS is common in clinical practice.

Oral corticosteroid therapy is the most common cause of iatrogenic CS, but it can happen with any route (inhaled, topical, or intra-articular). In any person taking even a

low dose (evening/ bedtime dose of ≥5 mg prednisolone equivalent per day) for more than a few weeks, adrenal suppression should be anticipated through HPA feedback mechanism [1]. Synthetic glucocorticoids, with a rare exception of dexamethasone, have cross-reactivity with standard cortisol assays [3]. Hence, in our case, the serum cortisol level was not measured because there was a strong history of exogenous steroid use and the patient was already on intravenous hydrocortisone for suspected Addisonian crisis.

Clinical features of CS

Typically, CS presents with some of the following symptoms: central obesity, a moon face, supraclavicular fat accumulation, thinned skin with red-purple striae, proximal myopathy, osteoporosis, hypertension, hyperglycemia, and dyslipidemia. Glucocorticoids cause hyperglycemia and diabetes by impaired insulin secretion, reduced incretin effect, and increased hepatic gluconeogenesis. Moreover, glucocorticoids stimulate lipolysis, free fatty acid production, very low-density lipoprotein synthesis, and accumulation of lipids in the liver and muscles [4]. Suppression of the humoral and adaptive immune systems in CS also makes them susceptible to infection, which is one of the leading causes of mortality [5]. However, the clinical manifestations of CS do not always correlate with the severity of hypercortisolism [6]. CS is associated with multisystem morbidity and mortality. Mortality was twice as high in CS patients when compared with the normal population, and venous thromboembolism event (VTE), myocardial infarction, stroke, and infections were the leading causes.

Mechanism of vascular thrombosis in CS

Chronic hypercortisolism leads to low-grade inflammation. It also increases the risk of thrombosis by inducing all three components of Virchow's triad: endothelial injury, hypercoagulability, and venous stasis. Elevated endothelin-1, homocysteine, osteoprotegerin, cell adhesion molecules, vascular endothelial growth factor, and impaired endothelium-dependent flow-mediated vasodilatation in CS lead to endothelial dysfunction and atherosclerosis. Moreover, through mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK)-dependent pathways, glucocorticoids activate rapid mineralocorticoid receptor signaling in vascular smooth muscle cells, causing vascular remodeling and fibrosis of small arteries. This is independent of the circulating aldosterone level. Cortisol induces the upregulation of coagulation factors [factor VIII, von Willebrand factor (VWF), fibrinogen] and antifibrinolytic factors [plasminogen activator inhibitor 1(PAI-1) and antifibrinolytics α2-antiplasmin]. This imbalance between coagulation and fibrinolytic systems potentiates thrombosis [7]. Increased platelet counts, secondary polycythemia, and venous stasis due to decreased mobility also play a role. Two prospective, observational studies showed that patients with CS had elevated FVIII, VWF, and antifibrinolytics α2-antiplasmin when compared with controls, and the 24-hour urinary-free cortisol levels correlated positively with FVIII level and VWF levels [8,9].

Obesity and thrombosis

Obesity is one of the common manifestations of CS. Extreme obesity or class III obesity is defined as a BMI greater than 40 kg/m^2 and is associated with multisystem morbidities such as insulin resistance, hypertension, dyslipidemia, cardiovascular disease, gall bladder disease, and cancer. BMI is one of the prognostic indicators in the diagnosis and treatment of PE [10]. There are many supposed mechanisms by which obesity may cause thrombosis: increased adipocytokines secreted from adipose tissues, imbalance between coagulation and fibrinolytic cascades, increased inflammation, increased oxidative stress, endothelial dysfunction, and in association with metabolic syndrome. Adipose tissues secrete many substances which are potentially involved in the thrombosis, such as leptin, PAI-1, tissue factor (TF), nonesterified free fatty acids (NEFAs), tissue necrosis factor α (TNFα), transforming growth factor β (TGFβ), and interleukin 6 (IL-6). Leptin promotes platelet aggregation in response to its agonists: adenosine diphosphate and thrombin. Increased PAI-1 and increased TF-mediated coagulation led to thrombosis. A large amount of NEFAs, secreted from adipocytes, causes insulin resistance which induces a pro-thrombotic state. Moreover, increased pro-inflammatory cytokines IL-6 and TNFα, TGFβ, and acute-phase proteins, such as C-reactive-protein (CRP) and fibrinogen, lead to chronic low-grade inflammation and endothelial dysfunction [11]. Recently, many studies have shown that morbid obesity itself is a risk factor for thrombosis [12]. Moreover, the Hoorn study by Beijer et al. [13] showed that individuals with impaired glucose or type 2 DM are at high risk of thrombosis due to higher thrombin generation by central adiposity and low-grade inflammation.

Our patient had been self-medicated with a potent glucocorticoid, dexamethasone for a long time. Hence, our assumption is that a drug-induced hypercoagulable state associated with other metabolic morbidities, like obesity, impaired glucose intolerance, and limited mortality, synergistically played a role in PE.

Wagner et al. [14] reported that the calculated odds ratio of VTEs in patients with CS was 17.82 compared to that of the general population. We also reviewed the published case reports of CS complicated by arterial and venous thrombosis, which are summarized in Table 2.

Anticoagulation in CS

Thromboprophylaxis is recommended in all CS patients who undergo surgery. Boscaro et al. [15] reported that

***Table 2**. Published case reports of CS complicated by thrombosis (2004-2019).*

AUTHOR, YEAR OF PUBLICATION	AGE/ GENDER	DIAGNOSIS	PRESENTATION	TREATMENT	OUTCOMES
Alexander et al., 2019	31 F	Endogenous ACTH-dependent CS	Extensive arterial thrombosis	Anticoagulation + bilateral adrenalectomy	Well on follow-up
Yoshimura et al., 2004	30 F	CS due to left adrenal tumor	Cerebral lateral sinus thrombosis	Heparin followed by warfarin + laparoscopic left adrenalectomy	Uneventful recovery
Al-Khalaf et al., 2016	21 M	ICS due to topical steroid clobetasol propionate	Superior sagittal, left transverse, and sigmoid venous thrombosis extending to the left jugular vein	SC low-molecular-weight heparin, followed by warfarin	Uneventful recovery
Kim et al., 2014	82 F	ICS due to long-term glucocorticoid for rheumatoid arthritis	Massive thoraco-abdominal aortic thrombosis	Anticoagulation	Improve, decrease thrombus burden
McDow et al., 2017	61 F	CS due to adrenal adenoma	Portal vein thrombosis	Heparin, followed by warfarin + Laparoscopic left adrenalectomy	Uneventful recovery
Yang et al., 2019	25 F	ACTH secreting bronchial carcinoid	Bilateral subsegmental PE	Heparin followed by Rivaroxaban + treatment of bronchial carcinoid	Improve

postoperative antithrombotic prophylaxis significantly reduced VTE-associated morbidity and mortality. Patients with CS are also highly vulnerable to nonoperative VTE risk. However, there is no standard guideline for nonsurgical candidates. In our case, after counseling the risks and benefits of warfarin and Rivaroxaban, the patient chooses Rivaroxaban. In all CS patients, thrombotic risk should be individualized by careful assessment of risk factors (age, obesity, impaired glucose tolerance, hypertension, dyslipidemia, smoking, immobility, prior thrombotic events, malignancy, family history, and medications), laboratory testing (full blood count, PT, aPTT, FVIII, VWF, D-dimer, fibrinogen, PAI-1, and α2-antiplasmin), ECG, echocardiography, and Doppler studies. Decision on thromboprophylaxis should be balanced between thrombosis and bleeding risks.

Conclusion

Drug-induced CS is common in clinical practice. This case demonstrates the importance of careful monitoring in patients with exposure to any form of corticosteroids, whether it is injected, oral, inhaled, topical, or intravenous. Health education about the risks and benefits of steroids is extremely important. Patients with CS are at high risk of thrombosis, VTE, and PE. The presence of other prothrombotic conditions potentiates the risk. Clinicians should be aware of this fatal complication, PE, when a CS patient presents with dyspnea. Further large, prospective studies are needed to determine which patient will benefit from thromboprophylaxis and the choice, dose, and duration of anticoagulation.

What is new?

CS is associated with multisystem morbidities and mortality.
PE is one of the serious, less recognized, complications.

List of Abbreviations

HPA Hypothalamus-pituitary-adrenal
ICS Iatrogenic Cushing's syndrome
PE Pulmonary embolism
VTE Venous thromboembolism

Conflict of interest

The author declares that there is no conflict of interest regarding the publication of this article.

Funding

None.

Consent for publication

Written informed consent to publish/present this case was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	Female, 54-year-old
2	**Final diagnosis**	Iatrogenic Cushing's syndrome with pulmonary embolism
3	**Symptoms**	Acute dyspnea and circulatory collapse
4	**Medications**	SC LMWH, followed by oral Rivaroxaban
5	**Clinical procedure**	CT pulmonary angiogram
6	**Specialty**	Internal medicine, Endocrinology, Cardiovascular medicine