Case Report

Multiple Deep Vein Thromboses After Curative Surgery for Cushing Disease: A Case Presentation and Review

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Article info

Article history:
Received 4 March 2022
Received in revised form 14 July 2022
Accepted 1 August 2022
Available online 5 August 2022

Key words:
Cushing syndrome
thrombosis
thromboprophylaxis

Abstract

Background/Objective: Cushing syndrome (CS) is a prothrombotic state associated with an increased risk of postoperative venous thrombosis. We aim to present the case of a patient with Cushing disease who underwent pituitary surgery and subsequently developed acute lower extremity deep venous thromboses after anticoagulation was stopped.

Case Report: We present the case of a 57-year-old woman who was admitted for intra-abdominal abscesses after a gastric bypass surgery and was found to have evidence of severe CS. Her 24-hour urinary free cortisol level was 898.6 μg/24 h. She was diagnosed with Cushing disease and underwent trans-sphenoidal resection of a pituitary adenoma, with an appropriate postoperative drop in the cortisol level. She received thromboprophylaxis during hospitalization; however, this was discontinued upon discharge, on postoperative day 9, because she was ambulating. Five days after hospital discharge and 14 days after her surgery, she developed left lower extremity edema and was found to have 4 deep venous thromboses.

Discussion: As previously described, thrombotic risk can be elevated for at least 1 month after surgery for CS, and thromboprophylaxis can decrease this risk.

Conclusion: This case highlights the need for clear recommendations for the duration of postoperative thromboprophylaxis in patients with CS. Clinicians should consider continuing thromboprophylaxis for at least 1 month after surgery for CS.

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Introduction

Cushing syndrome (CS) is caused by excessive glucocorticoid action. Cushing disease (CD) is a form of CS caused by overproduction of adrenocorticotropic hormone (ACTH) by the pituitary gland. This glucocorticoid excess in patients with CS results in a wide range of pathological changes, including multiple alterations in their coagulation profile.1,2 Previous studies on CS have demonstrated a clear risk of thromboembolic disease; however, the guidelines for prophylaxis are not clear and practice patterns remain variable. Herein, we present the case of a patient with CD who underwent pituitary surgery and subsequently developed 4 acute lower extremity deep venous thromboses (DVTs) after anticoagulation was stopped.

Case Report

A 57-year-old woman with a medical history of type 2 diabetes and hypertension presented to our institution with progressive abdominal pain 1 month after a gastric bypass surgery for weight loss. The patient had been diagnosed with type 2 diabetes and hypertension 2 years prior to presentation. Abdominal computed tomography showed multiple intra-abdominal abscesses, and therefore, she was started on treatment with intravenous antibiotics and abscess drainage. During hospitalization, she was noted to have hypertension while on her home antihypertensive regimen (160-175 mm Hg/70-95 mm Hg) and hypokalemia, with potassium...
levels of 1.9 mmol/L, unresponsive to a supplemental potassium chloride level of 60 mEq/d; therefore, the endocrinology service was consulted. On review of systems, she was found to endorse a 2-week history of hirsutism, difficulty climbing stairs, and easy bruising. Her physical examination result was significant for coarse hair on her chin, central adiposity, scattered ecchymoses, and proximal muscle weakness. She had small, supracervical fat pads and a slight dorsocervical hump. No abdominal striae were noted. Further workup revealed a random cortisol level of 45 μg/dL, an ACTH level of 114 pg/mL, and an elevation of urinary free corticotropin-releasing hormone, the ACTH level rose to 302 pg/mL.

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Clinical Relevance
This case illustrates that there is an increased risk of thrombosis in patients with Cushing syndrome (CS) after surgery. We review evidence for prolonged thrombosis risk after surgery for CS. This report demonstrates the need for research on risk factors and updated guidelines on postoperative thromboprophylaxis in patients with CS.

Discussion
This is the case of a patient with CD who had an appropriate decrease in the cortisol level and was ambulatory at the time of discharge but developed 4 lower extremity DVTs 14 days after discharge. Hypercoagulability has been clearly described in patients with CS.4,5 After surgery for CS, the risk of venous thromboembolism (VTE) is particularly elevated. The patient in the current case report had also undergone a gastric bypass surgery 1 month prior to presentation; furthermore, the risk of VTE in the general population that has undergone bariatric surgery ranges from 0.2% to 2%, with the highest risk occurring in the first month.5

Unlike for orthopedic procedures, there are no clear guidelines for the appropriate treatment for the prevention of VTE in patients with CD. Although some authors recommend prophylaxis for nonambulatory patients only,6 many reviews of perioperative management of CS did not address the risk of VTE. Two major guidelines (by the American Association of Clinical Endocrinologists/American College of Endocrinology and the European Society of Endocrinologists/European Network for the Study of Adrenal Tumors) for the management of adrenal incidentaloma also did not address perioperative thromboprophylaxis. Although the 2015 Endocrine Society guidelines recommend that patients with CS be evaluated for risk factors for VTE and that those undergoing surgery receive perioperative prophylaxis for VTE,7 these do not provide specific recommendations for risk stratification or the duration of postoperative thromboprophylaxis. However, there may be a shift toward greater recognition of thrombotic risk in patients with CD.5,6 In a recent statement by the Pituitary Society, prophylactic anticoagulation was recommended for individuals with a history of embolism, abnormal coagulation test results, severe hypercortisolism, poor mobility, extended hospital stay, high postoperative cortisol concentrations, or cortisol overreplacement and for those currently using estrogen or oral contraceptive pills.5 In addition, in a recent review, Varlamov et al9 recommended thromboprophylaxis for 2 to 6 weeks before surgery in patients with CD, with regimens of 2 to 3 months for patients with the highest thrombotic risk. However, the identification of highest-risk patients remains a challenge, and practice patterns still vary significantly among pituitary experts who report prescribing anticoagulation after surgery for anywhere from 1 to 2 days of hospital stay to 2 to 3 months.5

The risk of thrombotic events in patients with CS has been reported to be up to 10 to 18 times higher than that in the general population.4,10,11 This risk appears to increase substantially after surgery,12 and in retrospective studies of postoperative patients, VTE occurred in 3% to 20%1,10,13 of untreated individuals who underwent remission with surgery. The risk of arterial thromboses (myocardial infarction and stroke) is also increased.14 Some studies have shown that most complications occur in the first month. Semple and Laws15 reported 4 cases of DVT that occurred between 2 and 4 weeks after transsphenoidal surgery for CD, whereas Babic et al15 found that VTE occurred in 2.6% of 310 patients who underwent adrenalectomy for CS within 23 days after surgery. It is possible that these studies missed more delayed VTEs given that a retrospective study of 208 patients found that patients with CS have an elevated risk of thromboembolism during 30 to 60 days of the postoperative period.14 Several others have also described cases of VTEs occurring 2 to 3 months after curative surgery.16

Glucocorticoid excess induces multiple changes in coagulant and thrombotic factors that promote clotting and are likely to be exacerbated during the postoperative state. CS is associated with reduced aPTT; increased activation of several clotting factors,
including F8, factor IX, and von Willebrand factor (vWF); increased levels of antithrombin III (ATIII), protein S and C, plasminogen activator inhibitor 1 (PAI-1) antigen and activity, D-dimer, fibrinogen, α(2) antiplasmin, and thrombin-antithrombin complex; and increased clot lysis time. Increases in F8 and vWF levels are predominant changes in patients with CS, explaining the prolongation of aPTT seen in patients with CS. Notably, shorter aPTT has been consistently observed in individuals with CS who develop VTE.

Vitek et al. showed that 6 months after successful transphenoidal management of CD, the levels of both fibrinogen and D-dimer remained elevated despite normalization of cortisol levels. However, in another study comparing preoperative and postoperative coagulative parameters in patients with CS, Manetti et al. found that after successful surgical treatment, the levels of vWF, thrombin-antithrombin complex, ATIII, PAI-1, α(2) and antithrombin as well as aPTT normalized at 12 months after surgery. In their study, 3 patients (7.5%) who developed VTE had elevated levels of fibrinogen, vWF, PAI-1, and ATIII, with low aPTT, compared with healthy controls. The patient described herein had a shortened aPTT and an increased F8 level, a pattern consistent with thrombophilia caused by hypercortisolism. This abnormality in the F8 level persisted for 2 months but improved by 6 months.

Not surprisingly, studies have shown that a longer duration of thromboprophylaxis after surgery for CS decreases VTE complications. In a retrospective analysis of 307 postoperative patients, among individuals who underwent surgery between 1972 and 1981 without receiving anticoagulants, 15 patients (20%) experienced VTE and 8 (11%) died. In contrast, among individuals who underwent surgery between 1982 and 2000 and received postoperative subcutaneous unfractionated heparin (15 000–22 500 units daily) until clotting parameters normalized, only 6% developed postoperative VTE and only 1 (0.4%) died. Similarly, Barbot et al. found that there were no postoperative VTEs among 44 patients who received enoxaparin with graduated stockings and early ambulation for 30 days compared with 3 VTEs (among 34 individuals) in those who received only heparin until discharge (or 14 days).

Studies assessing risk factors for VTE have reported inconsistent findings and were limited by small numbers of outcomes and a mix of perioperative and nonperoperative patients. In 1 cohort of 176 patients with active CS, 20 individuals who developed VTE were more likely to have elevated F8 levels, elevated late-night salivary cortisol levels, elevated UFC levels (>10 times the upper limit of normal), shortened aPTT, elevated fibrinogen levels, heterozygosity for factor V Leiden mutation, higher midnight plasma cortisol levels, a previous cardiovascular event, comorbid acute severe infections, reduced mobility, bilateral adrenalectomy, swollen legs and/or varicose veins, obesity, cancer, hypertension, or diabetes mellitus; be older; be men; and be using oral contraceptive pills or and/or varicose veins, obesity, cancer, hypertension, or diabetes mellitus; be older; be men; and be using oral contraceptive pills or.
15. Babic B, De Roulet A, Volpe A, Nilubol N. Is VTE prophylaxis necessary on discharge for patients undergoing adrenalectomy for Cushing syndrome? *J Endocr Soc*. 2019;3(2):304–313. https://doi.org/10.1210/js.2018-00278.

16. van der Pas R, Leebeek FW, Hofland LJ, De Herder WW, Feelders RA. Hypercoagulability in Cushing’s syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol (Oxf)*. 2013;78(4):481–488. https://doi.org/10.1111/cen.12094.

17. Barbot M, Daidone V, Zilio M, et al. Perioperative thromboprophylaxis in Cushing’s disease: what we did and what we are doing? *Pituitary*. 2015;18(4):487–493. https://doi.org/10.1007/s11102-014-0600-y.

18. Manetti L, Bogazzi F, Giovannetti C, et al. Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing’s syndrome: results from a prospective study before and after surgery. *Eur J Endocrinol*. 2010;163(5):783–791. https://doi.org/10.1530/EJE-10-0583.

19. Zilio M, Mazzai L, Sartori MT, et al. A venous thromboembolism risk assessment model for patients with Cushing’s syndrome. *Endocrine*. 2016;52(2):322–332. https://doi.org/10.1007/s12020-015-0665-2.

20. Witek P, Zielinski G, Szamotulska K, Wittek J, Kamiński G. Cushing’s disease: fibrinogen and D-dimer levels fail to normalize despite early postoperative remission—a prospective, controlled study. *Endokrynol Pol*. 2016;67(1):283–291. https://doi.org/10.5603/EJ.a2016.0034.

21. Koutroumpi S, Daidone V, Sartori MT, et al. Venous thromboembolism in patients with Cushing’s syndrome: need of a careful investigation of the prothrombotic risk profile. *Pituitary*. 2013;16(2):175–181. https://doi.org/10.1007/s11102-012-0398-4.