Case Report

BILATERAL ADRENAL HEMORRHAGE WITH ADRENAL INSUFFICIENCY AFTER DALTEPARIN USE POST HIP ATHROPLASTIES

Robyn L. Houlden, MD, FRCPC; Azraa Janmohamed

ABSTRACT

Objective: Multiple case reports have implicated the use of heparin for deep vein thrombosis (DVT) prophylaxis with bilateral adrenal hemorrhage. Only 1 previous report has described this with the low molecular weight product, dalteparin. We report a case following bilateral hip arthroplasties.

Methods: Clinical and laboratory data are presented.

Results: A 69-year-old woman underwent bilateral total hip arthroplasties with dalteparin 5,000 international units subcutaneously daily for 30 days postoperatively. The patient's past medical history was unremarkable. She was discharged 5 days post-surgery and required readmission 1 day later for epigastric pain, nausea, and vomiting. Her platelet count was 91×10^9/L (normal, 150 to 400×10^9/L). She was discharged after 4 days with pain resolution. She presented 4 weeks later with nausea and vomiting for several days. Serum sodium was 123 mmol/L (normal, 133 to 145 mmol/L), potassium was 6.0 mmol/L (normal, 3.7 to 5.3 mmol/L), total calcium was 3.37 mmol/L (normal, 2.25 to 2.80 mmol/L), creatinine was 404 μmol/L (normal, 0 to 85 μmol/L), and her platelet count was normal. On short adrenocorticotropic hormone stimulation test, baseline plasma cortisol was 123 nmol/L and the peak was 129 nmol/L. She was treated with hydrocortisone, fludrocortisone, and 0.9% saline with resolution of symptoms and normalization of electrolytes, calcium, and renal function. Computed tomography showed bilateral adrenal masses. Core needle biopsy was consistent with necrosis. There were no bleeding disorders on hematologic work 3 months later. The most likely etiology of bilateral adrenal hemorrhage was heparin-induced thrombocytopenia from dalteparin.

Conclusion: This case highlights the importance of vigilance for the complication of bilateral adrenal hemorrhage with adrenal insufficiency in patients receiving dalteparin for DVT prophylaxis. **(AACE Clinical Case Rep. 2020;6:e141-e143)**

Abbreviations:
CT = computed tomography; **DVT** = deep vein thrombosis; **LMW** = low molecular weight

INTRODUCTION

Bilateral adrenal hemorrhage is a recognized cause of acute adrenal insufficiency (1). Major risk factors include the postoperative state (1), heparin therapy with heparin-induced thrombocytopenia (2,3), thromboembolic disease (1), hypercoagulable states (4), and sepsis (5). Patients typically present with hyperkalemia, hyponatremia, and volume contraction (1,3). The condition is difficult to recognize clinically and the diagnosis is often missed. We report a case of a woman with bilateral adrenal hemorrhage with adrenal insufficiency who had received dalteparin 5,000 international units subcutaneously daily for 30 days post-bilateral hip arthroplasties for deep vein thrombosis (DVT) prophylaxis ending 2 weeks prior to presentation to the emergency room. Multiple case reports have impli-

Submitted for publication September 26, 2019
Accepted for publication February 12, 2020
From the Department of Medicine, Queen's University, Kingston, Ontario, Canada.
Address correspondence to Dr. Robyn Houlden, Division of Endocrinology, Kingston General Hospital, 76 Stuart Street, Kingston, ON, K7L 2V7, Canada. E-mail: houldenr@queensu.ca.
DOI: 10.4158/ACCR-2019-0434
To purchase reprints of this article, please visit: www.aace.com/reprints.

cated the use of unfractionated heparin for DVT prophylaxis in the subsequent development of bilateral adrenal hemorrhage (2); however, only 1 previous case report has described dalteparin (a low molecular weight heparin) used alone with the presentation of bilateral adrenal hemorrhage (6).

CASE REPORT

A 69-year-old woman underwent bilateral total hip arthroplasties and was treated with dalteparin 5,000 international units subcutaneously daily for 30 days postoperatively. Her past medical history was unremarkable with the exception of osteoarthritis of her hips. Hemoglobin and platelet count were normal preoperatively. She was discharged 5 days post-surgery and required readmission 1 day later for epigastric pain, nausea, and vomiting. The pain was squeezing, tight, and heavy; rated 7 out of 10 by the patient; and radiated to the right upper quadrant. Her hemoglobin was low at 85 g/L (normal, 120 to 160 g/L) and she was transfused 1 unit of packed red blood cells. White blood cell (WBC) count was elevated at 14.3 $\times 10^9$/L (normal, 4.0 to 10.5 $\times 10^9$/L). Platelet count was 91 $\times 10^9$/L (150 to 400 $\times 10^9$/L). Cardiac investigations revealed no electrocardiogram changes and normal troponin levels. Coronary angiography showed no obstructive disease. She was discharged after 4 days with resolution of her pain and normalization of her platelet count to 154 $\times 10^9$/L.

She presented 4 weeks later to the emergency room with a several-day history of nausea, vomiting, decreased oral intake, weight loss, and a decreased level of consciousness. Serum sodium was 123 mmol/L (normal, 133 to 145 mmol/L), serum potassium was 6.0 mmol/L (normal, 3.7 to 5.3 mmol/L), serum chloride was 88 mmol/L (normal, 97 to 110 mmol/L), serum bicarbonate was 21 mmol/L (normal, 19 to 27 mmol/L), the anion gap was 14 (normal, 8 to 12), serum creatinine was 404 μmol/L (normal, 0 to 85 μmol/L), the estimated glomerular filtration rate was 9 mL/min/1.73 m^2 (normal, 60 to 150 mL/min/1.73 m^2), and serum total calcium was 3.37 mmol/L (normal, 2.25 to 2.80 mmol/L). The platelet count was normal at 209 $\times 10^9$/L. Her 6-week course of dalteparin ended 2 weeks prior to her presentation to the emergency room.

Workup revealed a new onset of primary adrenal insufficiency. A short adrenocorticotropic hormone (ACTH) stimulation test (250 mcg of cosyntropin intravenous bolus) revealed a baseline plasma cortisol of 123 nmol/L, a 30-minute plasma cortisol of 129 nmol/L, and a 60-minute plasma cortisol of 122 nmol/L. The parathyroid hormone level was 1.4 pmol/L (normal, 2.0 to 9.4 pmol/L). The ACTH level was undetectable but was drawn after she had started hydrocortisone 12 hours earlier. Other pituitary hormones including prolactin, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone were normal. A diagnosis of new onset of primary adrenal insufficiency was made and she was treated with intravenous fluids, hydrocortisone 100 mg intravenously every 8 hours and fludrocortisone 0.1 mg orally once daily with rapid improvement in her symptoms and normalization of serum electrolytes, calcium, and renal function. Computed tomography (CT) showed bilateral adrenal masses measuring 3.5 cm in the left and 3.6 cm in the right with a noncontrast attenuation of 30 Hounsfield units.

A core needle biopsy of the left adrenal gland was performed as the CT scan report raised the possibility of the adrenal masses representing metastases, and was consistent with necrosis with degenerated blood and inflamed connective tissue. Hematologic workup performed 3 months after the diagnosis of adrenal insufficiency revealed no bleeding disorder abnormalities. These included a prothrombin time (PT test) of 11.6 seconds (normal, 10.7 to 13.0 seconds); an international normalized ratio (INR test) of 1.0 (normal, 0.9 to 1.1); a partial thromboplastin time (PTT test) of 23 seconds (normal, 21 to 29 seconds); a thrombin time of 16.1 seconds (normal, <18.0 seconds); negative cardiolipin, lupus anticoagulant, B2 glycoprotein, antinuclear and extractable nuclear antigen (double stranded deoxyribonucleic acid, chromatin, ribosomal protein, SS-A52, SS-A60, SS-B, SM, SMRNP, ribonucleoprotein A, ribonucleoprotein 68, Sci-70, Jo-1, centromere B) antibodies; and negative heparin-induced thrombocytopenia testing (anti-PF4/heparin EIA screen).

DISCUSSION

Bilateral adrenal hemorrhage is a relatively uncommon occurrence, but has previously been associated with anticoagulation, coagulopathy, sepsis, and acute medical or surgical illnesses (7). Symptoms include abdominal pain, fever, and hypotension, as well as laboratory findings of hyponatremia, leukocytosis, metabolic acidosis, hyperkalemia, azotemia, and a fall in hemoglobin (7). For our patient, it is possible that the admission for epigastric pain and nausea 6 days postoperatively was her initial presentation of bilateral adrenal hemorrhage. Epigastric pain has been described in other case reports (8).

Heparin-induced thrombocytopenia is a well-known potential adverse effect of the use of heparin products for DVT prophylaxis postoperatively. Heparin-induced thrombocytopenia occurs when heparin-platelet-factor 4 antibodies bind to the heparin-platelet-factor 4 complex resulting in activation and consumption (2). This in turn leads to thrombocytopenia, and an acquired state of hypercoagulability. Heparin-induced thrombocytopenia is often associated with bilateral adrenal hemorrhage due to thrombosis of the central adrenal vein which leads to subsequent hemorrhagic infarct of the adrenal glands (2).

Heparin-induced thrombocytopenia and bilateral adrenal hemorrhage have been reported previously in asso-

ciation with unfractionated heparin (9-11); low molecular weight (LMW) heparin products including dabigatran (12), enoxaparin (13), and fondaparinux (14); and with warfarin (8); however, there has been only 1 previous case report with the low molecular weight heparin product, dalteparin, used alone (6); and 1 case report when used after fractionated heparin and warfarin (15). In the other case with dalteparin used alone, a 54-year-old female presented with severe abdominal pain, anorexia, and high-grade fever 11 days after hip surgery with a prophylactic dose of dalteparin postoperatively (6). On admission, she had an elevated WBC count, thrombocytopenia, and hyponatremia. A CT scan revealed bilateral adrenal hemorrhage (6). A heparin-induced antibody panel was strongly positive. It is possible that a panel for PF4-heparin antibodies might have been abnormal in our patient if performed closer to diagnosis as antibodies disappear 2 to 3 months after resolution of heparin-induced thrombocytopenia (16).

Heparin-induced thrombocytopenia has been reported with both unfractionated heparin and LMW heparin. A meta-analysis of 13 studies comparing unfractionated versus LMW heparin in 5,275 medical patients with venous thromboembolism found no difference in the risk of heparin-induced thrombocytopenia according to the type of heparin used (17). The 4Ts score can be used to estimate the probability of heparin-induced thrombocytopenia based on the degree of thrombocytopenia, the timing relative to heparin exposure, the presence of thrombosis, and other causes for thrombocytopenia (18). In our patient, her platelet count fell greater than 50% (2 points), with an onset between 5 and 10 days of dalteparin exposure (2 points), the bilateral adrenal hemorrhage may have been related to thrombosis of the central adrenal vein (1 point), and there were no other apparent causes for thrombocytopenia (2 points), giving a total score of 7 points and a high probability of heparin-induced thrombocytopenia.

CONCLUSION

The most likely etiology of bilateral adrenal hemorrhage in our patient was heparin-induced thrombocytopenia from dalteparin use post-hip arthroplasty. The case highlights the importance of ruling out adrenal insufficiency secondary to bilateral adrenal hemorrhage in patients receiving dalteparin postoperatively who present with nausea, vomiting, dehydration, and electrolyte disturbance.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES

1. **Rao RH, Vagnucci AH, Amico JA.** Bilateral massive adrenal hemorrhage: early recognition and treatment. *Ann Intern Med*. 1989;110:227-235.
2. **Rosenberger LH, Smith PW, Sawyer RG, Hanks JB, Adams RB, Hedrick TL.** Bilateral adrenal hemorrhage: the unrecognized cause of hemodynamic collapse associated with heparin-induced thrombocytopenia. *Crit Care Med*. 2011;39:833-838.
3. **Kovacs KA, Lam YM, Pater JL.** Bilateral massive adrenal hemorrhage. Assessment of putative risk factors by the case-control method. *Medicine*. 2001;80:45-53.
4. **Carron P, Charbonnier MY, Campus JP, Fortenfant F, Otal P, Suc JM.** Definitive adrenal insufficiency due to bilateral adrenal hemorrhage and primary antiphospholipid syndrome. *J Clin Endocrinol Metab*. 1998;83:1437-1439.
5. **Margaretten W, Nakai H, Landing BH.** Septicemic adrenal hemorrhage. *Am J Dis Child*. 1963;105:346-351.
6. **Kurtz LE, Yang S.** Bilateral adrenal hemorrhage associated with heparin induced thrombocytopenia. *Am J Hematol*. 2007;82: 493-494.
7. **Siu SC, Kitzman DW, Sheedy PF 2nd, Northcutt RC.** Adrenal insufficiency from bilateral adrenal hemorrhage. *Mayo Clinic Proceedings*. 1990;65:664-670.
8. **Bharucha T, Broderick C, Eason N, Roberts C, Moore D.** Bilateral adrenal haemorrhage presenting as epigastric and back pain. *JRSM Short Rep*. 2012;3:15.
9. **Maag RL, Chuang CH.** Uncommon complications of heparin-induced thrombocytopenia. *Am J Med*. 2013;126:e5-e6.
10. **Kurtz LE, Yang S.** Bilateral adrenal hemorrhage associated with heparin induced thrombocytopenia. *Am J Hematol*. 2007;82: 493-494.
11. **Namias N.** Chance favors the prepared mind: the association between heparin-induced thrombocytopenia and bilateral adrenal hemorrhage. *Crit Care Med*. 2011;39:912-913.
12. **Best M, Palmer K, Jones QC, Wathen CG.** Acute adrenal failure following anticoagulation with dabigatran after hip replacement and thrombolysis for massive pulmonary embolism. *BMJ Case Rep*. 2013.
13. **Park KJ, Bushmiaer M, Barnes CL.** Bilateral adrenal hemorrhage in a total knee patient associated with enoxaparin usage. *Arthroplast Today*. 2015;1:65-68.
14. **Alsaleh KA, Al-Nasser SM, Bates SM, Patel A, Warkentin TE, Arnold DM.** Delayed-onset HIT caused by low-molecular-weight heparin manifesting during fondaprinux prophylaxis. *Am J Hematol*. 2008;83:876-888.
15. **Maag RL.** Dalteparin sodium/heparin. *Reactions Weekly*. 2014;18:1492.
16. **Kelton JG.** Heparin-induced thrombocytopenia: an overview. *Blood Rev*. 2002;16:77-80.
17. **Morris TA, Castrejon S, Devendra G, Gamst AC.** No difference in risk for thrombocytopenia during treatment of pulmonary embolism and deep venous thrombosis with either low-molecular-weight heparin or unfractionated heparin: a metaanalysis. *Chest*. 2007;132:1131-1139.
18. **Lo GK, Juhl D, Warkentin TE, Sigoui CS, Eichler P, Greinacher A.** Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4:759-765.