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Bilateral adrenal hemorrhage: The unrecognized cause of hemodynamic collapse associated with heparin-induced thrombocytopenia

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Abstract

Objective—Heparin-induced thrombocytopenia is a common adverse effect of treatment with heparin resulting in paradoxical thromboses. An immunoglobulin G class "heparin-induced thrombocytopenia antibody" attaches to a heparin—platelet factor 4 protein complex. The antibody then binds to the FcγIIa receptor on the surface of a platelet, resulting in activation, consumption, and thrombocytopenia in the clinical syndrome of heparin-induced thrombocytopenia. In contradistinction to other drug-induced thrombocytopenias that lead to a risk of hemorrhage, the state of thrombocytopenia in heparin-induced thrombocytopenia leads to an acquired hypercoagulability syndrome. Bilateral adrenal hemorrhage associated with heparin-induced thrombocytopenia has become an increasingly documented association. The adrenal gland has a vascular construction that lends itself to venous thrombus in the setting of heparin-induced thrombocytopenia and subsequent arterial hemorrhage. A literature search revealed 17 reported cases of bilateral adrenal hemorrhage in the setting of heparin-induced thrombocytopenia uniformly presenting with complete hemodynamic collapse.

Data Sources—An Ovid MEDLINE search of the English-language medical literature was conducted, identifying articles describing cases of bilateral adrenal hemorrhage in the setting of heparin-induced thrombocytopenia.

Study Selection—All cases with this association were included in the review.

Data Extraction and Data Synthesis—A total of 14 articles were identified, describing 17 individual case reports of bilateral adrenal hemorrhage associated with heparin-induced thrombocytopenia. All cases confirmed known characteristics of heparin-induced thrombocytopenia and uniformly revealed hypotension due to adrenal insufficiency. There were five deaths, resulting in an overall mortality rate of 27.8%, and 100% mortality in the three cases where adrenal insufficiency went unrecognized.

Conclusions—The secondary complication of adrenal vein thrombosis leading to bilateral adrenal hemorrhage remains insufficiently recognized and undertreated. The nonspecific presentation of adrenal hemorrhage and insufficiency as a complication of heparin-induced thrombocytopenia, coupled with the catastrophic clinical course of untreated adrenal collapse, requires a high index of suspicion to achieve rapid diagnosis and provide life-saving therapy.

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Keywords

heparin; thrombocytopenia; adrenal insufficiency; adrenal hemorrhage; thrombosis; anticoagulation

Heparin-induced thrombocytopenia (HIT) is a common, well-documented adverse effect of treatment with heparin resulting in paradoxical arterial and venous thromboses. HIT occurs in up to 1% of patients receiving unfractionated heparin for postoperative antithrombotic prophylaxis, most frequently in orthopedic patients (4.8%) and more often with unfractionated heparin (4.8%) than with low molecular weight heparin (0.6%) (1,2).

HIT is an antibody-mediated effect in which an antibody forms against heparin when bound to a protein called platelet factor 4. These antibodies, predominantly immunoglobulin G class, can then attach directly to the heparin–platelet factor 4 complex. The antibody then binds to the FcγIIa platelet surface receptor, resulting in platelet activation, consumption, and thrombocytopenia in the clinical syndrome of HIT. The resulting immune complexes stimulate excessive thrombin formation, causing thrombosis, defining HIT with thrombosis syndrome (1).

HIT antibody seroconversion typically occurs between days 5 and 10 following heparin initiation, and thrombocytopenia occurs between days 5 and 14 (2). HIT should be suspected with recent heparin use, a platelet drop of >50% from baseline or to <100 K/μL, evidence of new thrombosis or extension of an old thrombus, and an absence of other causes of thrombocytopenia. To confirm HIT, a heparin–platelet factor 4 enzyme-linked immunosorbent assay (HIT antibody) or a serotonin release assay should be obtained (3).

In contradistinction to other drug-induced thrombocytopenias that lead to a risk of hemorrhage, thrombocytopenia in HIT leads to an acquired hypercoagulability syndrome secondary to platelet activation and thrombin generation. This environment promotes serious arterial and venous thromboses, including our reported complication of bilateral adrenal hemorrhage (BAH) secondary to venous occlusion (2). These prothrombotic complications necessitate immediate discontinuation of heparin and initiation of a thrombin inhibitor.

We present a case of HIT complicated by BAH from venous thrombosis that led to hemodynamic collapse with subsequent acute renal failure and myocardial infarction.

CASE REPORT

A 69-yr-old man with biopsy-proven invasive gastric adenocarcinoma underwent a technically uncomplicated gastrectomy, Roux-en-Y esophagojejunostomy, and cholecystectomy. Beginning on the day of surgery, unfractionated heparin (5000 units subcutaneously three times daily) was initiated for venous thromboembolism prophylaxis. His platelet count preoperatively was 252 K/μL, and on postoperative day 5 his platelet count began to decline, reaching a nadir of 60K/μL on postoperative day 10. HIT was suspected, heparin discontinued, hematology consulted, and treatment with therapeutic fondaparinux instituted due to mild liver dysfunction and normal kidney function. Heparin antibodies eventually returned to positive.

On postoperative day 11, unexplained abdominal and flank pain, tachypnea, tachycardia, hypotension, and oliguria developed, necessitating intensive care unit transfer and vasopressor therapy. The patient was euvolemic on workup but suffered a non-ST elevation myocardial infarction with troponin peaking at 3.99 ng/mL. Despite adequate fluid resuscitation, his hypotension persisted, and he continued to require vasopressor support. He

subsequently developed oliguric renal failure, with urine electrolytes revealing acute tubular necrosis, necessitating argatroban substitution for fondaparinux to continue venous thrombosis prophylaxis and treatment of HIT.

The patient was afebrile, without leukocytosis, and showed no clinical evidence of sepsis. All cultures were negative, and the chest radiograph showed no infiltrate. Concern for a surgical complication in light of continued postoperative abdominal pain prompted a computed tomography (CT) of the abdomen and pelvis. This revealed no evidence of anastomotic leak or abscess but did demonstrate significant bilateral adrenal gland enlargement, new compared to a prior CT (Figs. 1 and 2) and consistent with BAH. In addition, a 250-μg corticotropin-stimulation test was performed, as was routine in our intensive care unit at the time, to evaluate for adrenal insufficiency due to BAH. The basal plasma cortisol level was 6.1 μg/dL and failed to rise appropriately in response to the corticotropin-stimulation test at either 30 or 60 mins (6.3 and 6.2 μg/dL, respectively).

The patient was started on parenteral hydrocortisone 50 mg every 6 hrs, with rapid improvement in hemodynamic status allowing the discontinuation of vasoactive agents within 24 hrs. His renal failure rapidly resolved, and he demonstrated general rapid clinical improvement. After recovery of his thrombocytopenia, he was transitioned from argatroban to warfarin and was subsequently discharged to home on postoperative day 21 on oral hydrocortisone 40 mg daily for initial treatment of adrenal insufficiency. He was maintained on warfarin 3 mg daily for one month, completing his treatment course. The patient remains well 10 months postoperatively and continues to require exogenous steroid replacement. His 10-month postoperative AM cortisol was measured at 8.7 and adrenocorticotropic hormone at 736. His endocrinologist expressed he would require lifetime replacement as these values suggest his adrenal function will not completely recover.

LITERATURE REVIEW

First formally described by Findling et al in 1987 (9) with a report of two cases, BAH associated with HIT has become increasingly well-documented. A literature search revealed 17 reported cases of BAH in the setting of HIT (4–17). Characteristics of these case reports and our currently presented case are summarized in Table 1.

Demographics and Presentation

Of the 18 cases, there are seven females and 11 males with a mean age of 61.8 yrs (range 42–76). The majority are postsurgical patients (16 of 18), patients following orthopedic procedures (12 of 16), cardiovascular procedures (2 of 16), and intra-abdominal surgery (2 of 16). The majority of cases occurred with unfractionated heparin (16 of 18 cases), while one case each was associated with enoxaparin and dalteparin.

Thrombocytopenia presented between days 7 and 12 (mean day 8) after initiation of heparin therapy. The platelet count dropped to an average of 69.1 K/μL, with a range of 29 K/μL–115 K/μL. All 18 cases displayed a platelet drop of >50% with an average decrease of 73% (range 57% to 91%). Signs and symptoms typically presented within a few days following the nadir in platelet count and were primarily due to subsequent adrenal insufficiency. The most common manifestations were fever and abdominal pain, present in 14 and 11 cases, respectively. Altered mentation was seen in eight cases, vomiting in three, and dizziness in two. Hypotension was uniformly present. Hyponatremia was present in 15 cases, while hyperkalemia and hypokalemia were reported in five and two cases, respectively.

Diagnosis and Treatment

Diagnosis of adrenal insufficiency was uniformly elusive to ascertain. In the setting of fever, abdominal pain, nausea, vomiting, and associated hypotension, a workup for sepsis ensued in over half the cases. In 12 cases a corticotropin-stimulation test identified or confirmed adrenal insufficiency, with CT revealing adrenal hemorrhage in 14 cases. CT was the primary radiographic modality used to identify adrenal hemorrhage; however, magnetic resonance imaging revealed BAH in one case, and in three cases BAH was discovered at autopsy.

Fifteen patients obtained the adrenal insufficiency diagnosis and received corticosteroid replacement therapy. Eleven patients received hydrocortisone, eight with concomitant fludrocortisone, and the remaining four received an unspecified steroid treatment. The time frame between the initiation of steroid replacement and resolution of symptoms was uniformly described as dramatic, prompt, and rapid, with three cases describing the discontinuation of vasopressors within 6–24 hrs (8,10,16) All three undiagnosed patients progressed rapidly to mortality as described below.

Mortality and Morbidity

Twelve of 18 patients suffered serious secondary thrombotic events, including eight pulmonary embolisms (5–9,11,14,15), three deep vein thromboses (7,11,15), and one case of lower extremity ischemia (15). In addition to our patient, who developed acute renal failure and myocardial infarction, one patient developed acute renal failure (12), and another patient suffered a myocardial infarction (15). One patient had undiagnosed BAH and adrenal insufficiency for 2 yrs with multiple hospital admissions for nausea, vomiting, and abdominal pain (9).

There were five deaths, resulting in an overall mortality rate of 27.8%, and in three cases, where adrenal insufficiency was undiagnosed, mortality was 100% (6,12,14–16). In two of the five mortalities, the diagnosis of adrenal insufficiency was made and steroid replacement initiated; however, mortality ensued on postoperative day 31 and 1 month following intensive care unit discharge, respectively (15,16).

The remaining three mortalities occurred in patients where the diagnoses of BAH and adrenal insufficiency were made postmortem. One had a presumed diagnosis of HIT but no described treatment beyond the discontinuation of heparin (6). In the second, the diagnosis of HIT was made and treatment with ethyl biscoumacetate for anticoagulation was initiated. In this case, the patient had sudden worsening of hemodynamic status, with a failure to diagnose adrenal hemorrhage, and died shortly after transfer to the intensive care unit (12). The third mortality was without recognition of either HIT or adrenal insufficiency. This patient's platelet count dropped from 277 K/μL to 85 K/μL, but was heparin continued. The patient became dizzy, febrile, hypotensive, and hypoxic and underwent a CT scan revealing bilateral adrenal enlargement. Suspecting a pulmonary embolism, a heparin bolus was given. Within a few hours, the patient suffered cardiopulmonary arrest with postmortem findings of both massive pulmonary embolism and BAH (14).

DISCUSSION

HIT is not an infrequent complication that is commonly overlooked in postoperative patients. This diagnosis must be considered and treated appropriately as the complications related to the prothrombotic state are severe. Shock associated with HIT must raise the suspicion of adrenal insufficiency and BAH. This insidious disorder if left untreated is fatal.

Treatment of HIT

In the setting of HIT, direct thrombin inhibitors and the factor Xa inhibitors are used for anticoagulation and treatment for prevention of prothrombotic complications. Danaparoid, argatroban, lepirudin, fondaparinux, and bivalirudin all are accepted methods of anticoagulation in the setting of HIT (2,3). The acute state typically lasts weeks to months, necessitating anticoagulation either by direct thrombin inhibition (argatroban, lepirudin, bivalirudin) or by indirect inhibition via factor Xa inhibition (danaparoid, fondaparinux). The duration of therapy is guided on the basis of the presence of thrombotic complications and recovery of platelets.

Adrenal Hemorrhage

BAH is a well-documented complication now being associated with the prothrombotic state of HIT and evidence of HIT with thrombosis. It is a serious condition as the resulting adrenal insufficiency leads to life-threatening hemodynamic collapse if unrecognized (18). The adrenal gland has a vascular construction that lends itself to venous thrombus and subsequent arterial hemorrhage. The gland has up to 60 arterioles that supply a rich subcapsular plexus, while venous drainage occurs through a single central vein, which is susceptible to outflow obstruction. It is presumed that central vein thrombosis leads to hemorrhage within the gland (19,20). In this series, a single case described the autopsy findings of the adrenal vasculature and confirmed venous rather than arterial pathology (15).

In 1857, Goolden described the first case of BAH as postmortem hemorrhagic “cavities” in the suprarenal capsules in a patient with circulatory collapse and subsequent mortality. BAH has been associated with numerous disease processes, including trauma, antiphospholipid syndrome, meningococcemia and sepsis, thermal injuries, and anticoagulation (18). Its reported incidence in postmortem studies is between 0.14% and 1.8%, although autopsies may be less frequently pursued after the death of a critically ill patient when hypotension is attributed to the primary disease process, likely underestimating the prevalence of BAH (21–23).

As BAH presents with nonspecific signs and symptoms, it is of utmost importance to maintain a high clinical suspicion. Commonly, clinical deterioration is attributed to an infectious cause and the diagnosis of BAH is not made until discovery intraoperatively, by CT scan, or postmortem (21,23). The most reproducible symptoms of BAH include abdominal pain, fatigue, nausea, vomiting, anorexia, and dizziness. Clinical signs are fever, tachycardia, and significant hypotension unresponsive to fluids and vasopressors. Laboratory abnormalities include hyponatremia, hyperkalemia, hypoglycemia, and an unexplainable drop in hemoglobin or hematocrit out of proportion to that lost in the adrenal glands (18,21–23). Our series of HIT associated with BAH exhibited signs, symptoms, and laboratory results consistent with those previously described.

It is recommended the diagnosis of BAH be confirmed both anatomically and hormonally (22). The anatomical diagnosis of BAH may be suggested radiologically by CT or magnetic resonance imaging, revealing uniform, rounded enlargement of the adrenals with homogeneous enhancement (18,21–24). The hormonal diagnosis of adrenal insufficiency from BAH is confirmed by a serum cortisol level in conjunction with a corticotropin-stimulation test.

Adrenal insufficiency is an inadequate response to stress with low basal and stress levels of plasma cortisol and can lead to cardiovascular collapse and death. The cosyntropin-stimulation test is the standard laboratory test for adrenal insufficiency (25). A 250 μg dose of cosyntropin is administered, and the serum cortisol level is measured 30 and 60 mins later. If a cortisol level is >34 μg/dL, adrenal insufficiency is unlikely. Conversely, a cortisol

level of <15 μg/dL makes adrenal insufficiency highly likely. An increased risk of death has been shown with only a small increase from the baseline cortisol level (<9 μg/dL) (25).

Treatment of BAH

Treatment is primarily aimed at repletion of deficient glucocorticoids. If there is clinical suspicion of adrenal crisis, an immediate bolus dose of 50 mg of hydrocortisone should be administered. This large dose of hydrocortisone obviates the need for supplemental mineralcorticoids. Intravenous dosing of 50 mg of hydrocortisone should be given every 6 hrs until there is clinical improvement, and then steroid dosage may be tapered (25). For long-term treatment following BAH, the mainstay remains hydrocortisone, averaging 20–30 mg/day in divided doses to mimic the normal diurnal rhythm of the adrenals. Additionally, 0.05–0.2 mg of the mineralocorticoid fludrocortisone should be given daily (25).

CONCLUSION

Isolated HIT is well-documented and widely recognized as a complication of heparin use; however, the secondary complication of adrenal vein thrombosis leading to BAH remains insufficiently recognized and undertreated. The nonspecific presentation of adrenal hemorrhage and insufficiency as a complication of HIT, coupled with the catastrophic clinical course of untreated adrenal collapse, requires a high index of suspicion to achieve rapid diagnosis and provide life-saving therapy.

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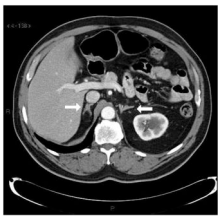

Figure 1.
Abdominal computed tomography, before heparin-induced thrombocytopenia, revealing normal adrenal glands bilaterally (*arrowheads*).

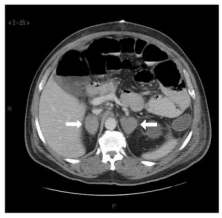

Figure 2.
Abdominal computed tomography revealing homogeneous, smooth, bilateral adrenal enlargement (*arrowheads*) consistent with bilateral adrenal hemorrhage.

Table 1

Case reports of bilateral adrenal hemorrhage associated with heparin-induced thrombocytopenia by year

Reference	Year	Age (yrs)/ Sex	Indication for Heparin	Heparin Type	Platelet Reduction (K/μL)	Signs/Symptoms and Lab Results	Dx	Differential Diagnosis	Treatment/Outcome
Findling et al (9) (two cases)	1987	42/F	PE	Heparin (unspecified therapy)[a]	232 → 86	T, V, HypoNa, HypoTN	CT	Unreporte	Hydrocortisone, fludrocortisone
		44/M	Ortho Sx, PE	Heparin (unspecified therapy)[a]	202 → 67	AP, V, HypoTN, HypoNa, HyperK	CT	Thyroid dysfunction, Addison's disease	Hydrocortisone, fludrocortisone
Delhumeau et al (6) (three cases)	1989	62/M	Ortho Sx	SQ calcium heparinate[a]	466 → 43	T, AP, HypoNa, HypoTN	Autopsy	Massive PE	No replacement, mortality before diagnosis
		74/M	Ortho Sx	SQ calcium heparinate[a]	249 → 90	T, AP, C, HypoNa, HypoTN	"Abdominal scanography"	Unreported	Unspecified steroid replacement
		76/F	Ortho Sx	SQ calcium heparinate[a]	Unknown → 65	T, AP, C, HypoNa, HypoTN	"Abdominal scanography"	Unreported	Unspecified steroid replacement
Case record of Massachusetts General Hospital (15)	1989	71/M	Colectomy, postoperative deep vein thrombosis	Treatment dose IV heparin[a]	226 → 29	C, HypoNa, HypoTN	Autopsy	Septic shock	Unspecified corticosteroid, subsequent mortality
Ernest and Fisher (8)	1991	68/F	THA	SQ heparin, 5000 units twice a day	170 → 58	T, HypoNa, hypokalemia, HypoTN	CT	Presumed septic shock	Hydrocortisone
Souied et al (16)	1991	63/F	THA	SQ heparin, 5000 units q8; then Lovenox	233 → 38	T, HypoNa, HyperK, HypoTN	CT	Bacteremia, septic shock	Hydrocortisone, cortisone, fludrocortisone, cardiac arrest, mortality
Bleasel et al (5)	1992	69/F	Total knee arthroplasty revision	SQ heparin, porcine, 5000 units q8	284 → 60	T, V, C, HypoNa, hypokalemia, HypoTN	CT	Syndrome of inappropriate secretion of antidiuretic hormone	Hydrocortisone, fludrocortisone
Hardwicke and Kisly (10)	1992	63/F	Total knee arthroplasty, bilateral	SQ heparin, 4500 units q8	349 → 84	T, AP, C, dizziness, HypoNa, HyperK, HypoTN	CT	Presumed sepsis	Dexamethasone, hydrocortisone, fludrocortisone
Delhumeau et al (7)	1993	74/M	THA, acute ischemia of LE	SQ heparin, 3750 units q8	290 → 90	T, AP, HypoNa, HypoTN	CT	Acute acalculous cholecystitis	Hydrocortisone, fludrocortisone
Leschi et al (12)	1994	63/M	Aortofemoral bypass graft	Heparin, 25000 units IO; SQ heparin, 50000 units q8; Lovenox, 40 mg (enoxaparin)	266 → 85 → 30	C, comatose, HypoNa, HyperK	Autopsy	Disseminated intravascular coagulation	No replacement, mortality before diagnosis
Rowland et al (14)	1999	50/M	Ortho Sx	Calciparine, 5000 units twice a day	277 → 85	T, AP, dizziness, HypoNa, HypoTN	CT	PE, metastases, bilateral pheochromocytoma, lymphoma	No replacement, mortality before diagnosis
Weyrich et al (17)	2001	56/M	Atrial fibrillation	IV heparin[a]	Unknown → 36	AP, C, HypoNa, HyperK, HypoTN	Magnetic resonance imaging	Cerebral thromboembolic event	Hydrocortisone

Reference	Year	Age (yrs)/ Sex	Indication for Heparin	Heparin Type	Platelet Reduction (K/μL)	Signs/Symptoms and Lab Results	Dx	Differential Diagnosis	Treatment/Outcome
Bakaeen et al (4)	2005	51/M	Coronary artery bypass graft	IV heparin, Lovenox[a]	266 → 115 → 40	T, AP, diarrhea, HypoTN	CT × 2	Presumedintra-abdominalinfection	Hydrocortisone
Kurtz and Yang (11)	2007	54/F	THA	SQ dalteparin[a]	Unknown → 73 → 49	T, AP, orthostatic syncope	CT	Presumedintra-abdominalinfection	Unspecified steroid replacement
Mongardon et al (13)	2007	64/M	THA	SQ heparin[a]	339 → 76	T, AP, C, HypoTN	CT	Unreported	Hydrocortisone, fludrocortisone
Present case	2008	69/M	Total gastrectomy	SQ heparin, 5000 units q8	252 → 87	HypoNa, HypoTN	CT × 2	Presumed septic shock	Hydrocortisone, fludrocortisone

M, male; F, female; PE, pulmonary embolism; Ortho Sx, unspecified orthopedic surgical procedure; THA, total hip arthroplasty; T, fever; AP, abdominal pain; V, vomiting; C, confusion; HypoTN, hypotension; HypoNa, hyponatremia; HyperK, hyperkalemia; CT, computed tomography; IV, intravenous.

[a]Unspecified dose.