Progressive Presentation of Type 2 Heparin-Induced Thrombocytopenia (HIT-2) in ESRD: An Illustrative Case Report

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Citation

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Abstract

Heparin-induced thrombocytopenia (HIT) is a well known side effect of heparin therapy. Type-1 HIT is a non-immune response that is relatively common in patients exposed to heparin. It is often transient, rarely deadly, and resolves quickly after heparin is withdrawn. Type-2 HIT is a more severe form of the syndrome that is immune-mediated and associated with systemic arterial and/or venous thrombosis. HIT commonly develops within fourteen days of initial heparin exposure, but delayed-onset cases are becoming increasingly reported. HIT can also develop in patients who have previously been exposed to heparin without subsequent development of the syndrome. We present a case of HIT-2 in a patient with ESRD who had been receiving unfractionated heparin therapy for a large proportion of the previous 7 months without development of thrombocytopenia. This case underscores the importance of continuous monitoring for HIT even after the patient has been receiving heparin treatment either periodically or continuously for extended periods of time.

INTRODUCTION

Heparin is the most commonly used anticoagulant drug for prevention and treatment of thromboembolic diseases. Heparin-induced thrombocytopenia (HIT) is a well-known complication of heparin therapy. There are two types of HIT: Type 1 (HIT-1) is a non-immune response while Type 2 (HIT-2) is an immune-mediated response. HIT-1, also known as heparin-associated thrombocytopenia, is more common and occurs in 10% to 20% of patients receiving heparin [1]. HIT-1 is mild and non-progressive; platelet counts usually do not fall below 100 x 10^9 /L. HIT-1 is not associated with bleeding or thrombosis and requires no treatment; platelet counts usually rise to pre-treatment levels within days of heparin discontinuation, and in some cases normalize without withdrawal of heparin [2].

Type 2 HIT is a less common, more severe type of HIT. It is an immune-mediated response occurring as a result of heparin therapy. It develops in about 1% to 3% of all patients who receive unfractionated heparin (UFH) and up to 0.8% of patients on low molecular-weight heparin (LMWH) [1]. The main complications associated with HIT-2 are bleeding and thrombosis. It can lead to either systemic arterial or, more rarely, venous thrombosis. The most common thrombotic events are deep venous thrombosis (DVT) and pulmonary embolism (PE). Other uncommon thrombotic events are occlusions of the limb artery, acute myocardial infarct, stroke, and skin necrosis [2].

HIT most commonly develops within 14 days of initiation of heparin therapy. However, reports of delayed-onset HIT cases (i.e. >2 weeks after heparin initiation) are becoming more prevalent in the literature [3]. Additionally, individuals who have not developed HIT while previously on heparin are not necessarily excluded from possibility of HIT development in the future [1]. In the current report we describe an interesting and unusual case of HIT-2 with skin necrosis in a patient with ESRD with onset during her eighth trial of heparin in the previous 7 months, during which she did not develop HIT. This case underscores the importance of continued monitoring for HIT in patients who are receiving heparin therapy who have not developed HIT during past heparin treatment courses.

CASE REPORT

A 48-year-old, morbidly obese, non-ambulatory female was transferred to our facility from a shelter for fall preceded by dizziness. She had a history of type 2 diabetes, hypertension,

hypercholesterolemia, depression, chronic anemia, and coronary artery disease (CAD) with subsequent coronary bypass surgery. She also had chronic renal insufficiency for the previous one year and was started on hemodialysis 7 months prior to current admission due to diabetic nephropathy. She had been hospitalized 7 times in the previous 7 months for complications related to end stage renal disease (ESRD). She had received heparin therapy at least 7 times prior to this admission, specifically while on hemodialysis both as an outpatient and inpatient and as prophylaxis for DVT during hospital admissions (See Table I for previous inpatient heparin exposure and related lab values).

At current admission, physical examination revealed multiple black maculo-papular lesions on all areas of the body and pitting edema over both legs. Vital signs were normal. Labs revealed abnormal kidney and liver function values, as suspected, due to her multiple pre-existing illnesses. Additionally, P-natriuretic peptide was greater than 35,000 (N: 0.0-5.0), hemoglobin was 8.4 g/dL (12.0-16.0 g/dL) and hematocrit was

Figure 1

Table I. Lab values during the patients 7 previous admissions

Day	Platelet Count	Prothrombin Time (PT)	INR	Partial Thromboplastin Time (PTT)	Other Tests	Heparin received?
Admission 1						
7 months + 1 week prior	215	33.6	3.9	>120	-	SQ Heparin (1 day)
Day 2	207	14.6	1.3	22.3	-	Levonox Discharged
Admission 2						
6 months prior	182	-	-	-	-	SQ Heparin (1 day)
Day 2	169	-	-	-	-	Discharged
Admission 3						
5 months prior	167	-	-	-	-	SQ Heparin (1 day)
Day 2	167	-	-	-	-	-
Day 4	131	-	-	-	-	-
Day 6	150	-	-	-	-	-
Day 9	275	-	-	-	-	SQ Heparin
Day 13	267	14.6	1.3	42	-	
Day 16	310	-	-	-	-	
Day 21	248	-	-	-	-	
Day 24	225	-	-	-	-	
Day 28	240	-	-	-	-	Discharged
Admission 4						
3 months + 3 weeks prior	255	-	-	-	P-N peptide > 35,000	Heparin SQ
Day 2	205	14.2	1.2	31.7	-	
Day 3	188	-	-	-	-	Discharged
Day	**Platelet Count**	**Prothrombin Time (PT)**	**INR**	**Partial Thromboplastin Time (PTT)**	**Other Tests**	**Heparin received?**
Admission 5						
2 months + 2 weeks prior	163	12.6	1.1	20.9	-	SQ Heparin
Day 2	189	-	-	-	-	
Day 5	-	18.6	1.9	>120	-	IV Heparin
Day 6	227	17.7	1.8	>120	-	
Day 7	192	15.2	1.4	50.8	-	
Day 9	-	15.5	1.5	70.0	-	
Day 10	143	17.4	1.7	32.0	-	-
Day 13	157	19.5	2.0	98.8	-	-
Day 15	149	17.0	1.7	43.9	-	-
Day 17	136	14.9	1.4	40.0	-	Discharged
Admission 6						
1 month + 2 weeks prior	176	16.6	1.6	34.6	-	SQ Heparin
Day 2	166	14.2	1.3	26.0	-	
Day 3	144	17.1	1.6	32.8	-	IV Heparin
Day 4	131	15.8	1.5	31.7	-	
Day 5	135	15.7	1.5	34.5	-	
Day 6	125	14.6	1.4	>120	-	
Day 8	137	16.6	1.6	>60	-	
Day 10	139	15.7	1.5	25.9	-	
Day 11	-	25.9	2.9	>120	-	
Day 12	-	32.9	4.0	147.1	-	
Day 14	169	36.4	4.5	52.7	-	Discharged
Admission 7						
2 weeks prior	229	16.8	1.6	30.4		SQ Heparin
Day 5	228	-	-	-		
Day 7	208	-	-	-		
Day 9	194	-	-	-		
Day 12	-	-	-	-	-	Discharged

Normal Ranges: Platelets: 130,000-400,000/μL, prothrombin time: 10.4-13.7 sec., INR: 1.0-3.5, and partial thromboplastin time: 21.4-38.6 sec. P-N Peptide = 0-5

Figure 2

Table II. Lab values during current admission (admission 8) associated with a diagnosis of HIT.

Day	Platelet Count	Prothrombin Time (PT)	INR	Partial Thromboplastin Time (PTT)	Other Tests	Heparin received?
1	199	18.9	1.9	38.0	P-N peptide > 35,000	IV Heparin
2	183	20.2	2.1	53.1	D-Dimer = 788	↓
3	168	20.6	2.1	38.1	-	↓
5	139	-	-	-	-	-
7	118	19.5	2.0	41.5	-	-
8	140	19.1	2.0	48.6	-	SQ Heparin
10	96	18.5	1.9	45.7	-	Argatroban
11	73	16.6	1.6	42.8	-	↓
12	61	16.5	1.6	45.3	HIT antibody test positive	↓
13	42	16.2	1.5	38.8	-	↓
14	78	15.7	1.5	36.3	-	↓
15	97	-	-	-	-	↓
16	123	>60	8.3	>120	-	↓
17	160	>60	8.3	>120	-	↓
19	-	43.2	5.7	80.0	-	↓
`	141	25.9	2.9	55.0	-	↓
22	-	>60	8.3	106.5	-	↓
23	119	18.9	1.9	41.9	-	↓
24	-	-	-	-	-	↓
26	151	17.0	1.7	39.9	-	
27	150	-	-	-	-	
28	-	-	-	-	-	Patient expired

Normal Ranges: Platelets: 130,000-400,000/μL, prothrombin time: 10.4-13.7 sec., INR: 1.0-3.5, and partial thromboplastin time: 21.4-38.6 sec. P-N Peptide = 0-5, D-Dimer < 500 FEU μg/L.

25.7% (37.0%-47.0%) with RDW=18.3 (11.5-14.5), MCV 100.3fL (81-99fL), and Troponin 0.046 ng/mL (0.0-0.03 ng/mL). Platelet counts, INR's, partial thromboplastin times (PTT) and prothrombim times (PT) throughout admission are displayed in Table II; all were normal at admission with the exception of PT (18.9 sec.; N=10.4-13.7 sec.). Chest x-ray revealed cardiomegaly and congestion in the lungs.

The patient was initially managed for fluid overload with lasix and hemodialysis with repeat hemodialysis every two days. On day 2, the patient's blood pressure dropped from 120/70mm-Hg to 80/50mm-Hg; she also developed tachycardia, mild respiratory distress and leg swelling. Pulmonary embolism was suspected. CT pulmonary angiogram was not possible due to ESRD and ventilation-perfusion scan was not possible due to pulmonary edema. Patient was placed on heparin drip for suspected pulmonary embolism. On day 4, venous duplex of the lower extremities was negative.

Platelet counts fluctuated within the normal range over the first five days of admission. On admission day 6, the patient started having severe abdominal pain with abdominal distension and abdominal wall edema and development of some vilaceous reddish-black skin lesions on the left paraumbilical and umbilical areas. She also had high grade fever and low blood pressure. Abdomen was distended, rigid and tender. CT of the abdomen and pelvis was significant for diffuse subcutaneous edema throughout the abdominal wall and ascites without any evidence of intestinal obstruction. She was started on broad spectrum antibiotics and vasopressors for septic shock, and fresh frozen plasma and vitamin K for subsequent coagulopathy. She also received steroid for relative adrenal insufficiency and septic shock.

The patient's platelet count dropped to 96,000 on day 10. Heparin was discontinued, venodyne boots were placed, and anti-thrombin (Argatroban®) medication was started. Heparin-free hemodialysis was also started. Multiple necrotic areas began to develop on the leg and thigh. On day 12, HIT antibody result came back positive. Platelets continued to fall to a low of 42,000 on day 13. Multiple necrotic areas became more prominent and appeared dark, diffuse and tender with irregular margins (Figure 1). The patient developed dark, curly, string-like areas on the thigh and belly, suggestive of venous thrombosis (Figure 1). Venogram was negative for superior vena cava thrombosis. Platelets improved to 160,000 on day 16. She experienced one episode of gastrointestinal bleed on day 24, therefore antithrombin drip was discontinued. The patient was persistently hemodynamicaly unstable due to multiple co-morbid conditions. Her condition gradually worsened and she died on the 28 th day of admission. The family refused an autopsy.

Figure 3

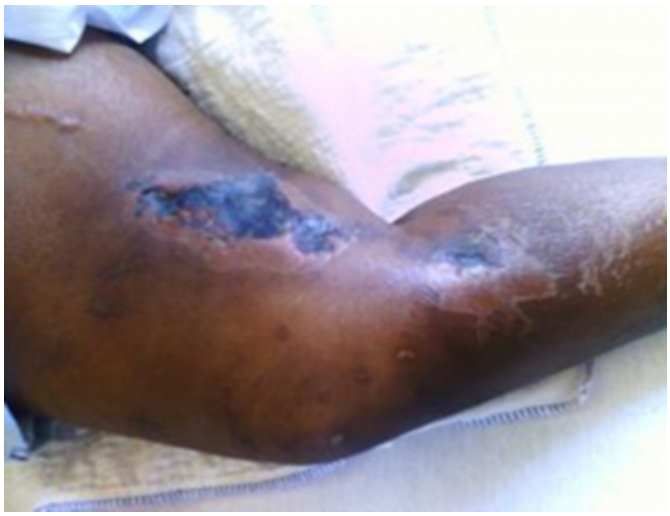
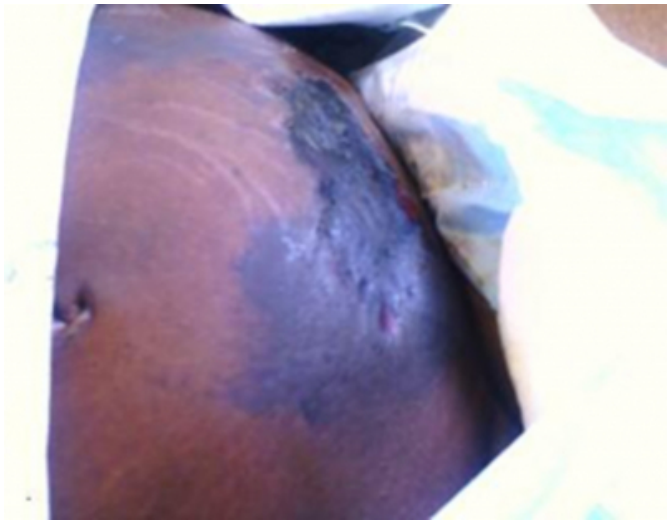


Figure 4

Figure 1. On day 13, multiple necrotic areas became prominent and appeared dark, diffuse and tender with irregular margins (top). Dark, curly, string-like areas on the thigh and belly, suggestive of venous thrombosis, also developed (bottom).



DISCUSSION

PATHOPHYSIOLOGY AND RISK FACTORS

HIT-2 is an immune-mediated reaction. Following heparin administration, factor-4 platelets (PF-4) bind to heparin and form PF-4-heparin complexes. The patient develops immunoglobulin G (IgG), M (IgM) and A (IgA) antibodies to these complexes. IgG is pathogenic; binding of IgG antibodies to PF-4-heparin complexes results in activation of platelets, platelet aggregation and release of microparticles with procoagulant. The microparticles initiate thrombin generation and results in thrombotic events. These activated platelets are removed prematurely from circulation, leading to development of thrombocytopenia [4]. Relative decreases in platelets (i.e. platelet count decrease more than 50% from baseline, or to <100 X 10^9 /L) after heparin therapy is the main criteria for diagnosis of HIT-2 [2].

Risk for development of HIT-2 depends mostly on type of heparin used, patient medical conditions and duration of heparin therapy. Patients receiving (UFH) are at greater risk than those receiving porcine or LMWH. In addition, patients undergoing orthopedic or cardiac surgery are at increased risk [1]. Onset of HIT-2 is typically between 5 and 14 days following the start of heparin therapy; however, onset may be sooner if there has been previous exposure to heparin [5]. There have been reports of HIT-2 onset 3 weeks to 3 months or more after heparin therapy; this is known as delayed-onset HIT-2 [6].

PRESENTATION AND DIAGNOSIS

Patients with thrombocytopenia caused by medications usually present with bleeding complications, but in cases of HIT-2, thrombotic events (with or without bleeding) are also usually present. DVT and PE are the most common thrombotic complications of HIT-2, but can also include cerebral dural sinus thrombosis, adrenal hemorrhagic infarction, acute thrombotic stroke, myocardial infarction, aortic occlusion and thrombosis of limb, mesenteric, renal and/or spinal arteries. Routine vascular Doppler of lower limb is indicated. Skin lesions (e.g. erythema, purpura, painful red plaque, skin necrosis) at heparin injection site are also frequent. The skin manifestations in our patients were quite severe and included skin necrosis. Disseminated intravascular coagulation, acute adrenal infraction and global amnesis are very uncommon in HIT [2,7-8]. Due to our patients numerous co-morbidities, several diagnostic techniques were not available. Venous duplex, however, was able to rule-out venous thrombosis.

HIT is initially diagnosed based on clinical presentation and medical history of patient. The 4T Scoring System, which is widely utilized for formalizing the diagnosis of HIT, is based on: (1) a significant drop in platelet count, (2) the amount of time elapsed between heparin exposure and development of symptoms, (3) the presence of new or worsening thrombosis, and (4) the presence of alternative caused of symptoms. During the previous admissions there were no significant indicators of development of HIT.

Laboratory finding of heparin antibodies are useful to support the diagnosis. Different specific assays are available to aid in diagnosis of HIT, including PF-4-heparin enzyme linked immunabsorbent assay (ELISA) and C-serotonin release assay (C-SRA). PF-4-heparin ELISA measures presence of heparin dependent antibodies. ELISA is readily available, rapid and easy. It has about 90% sensitivity and 80% specificity. C-SRA measures the release of C-serotonin from platelets. It is expensive and requires more time, but it is about 90% sensitive and 98% specific [9]. In our case, P-natriuretic peptide was greater than 35,000 (N: 0.0-5.0), which is highly associated with HIT [9]. P- natriuretic peptide was also greater than 35,000 at a previous admission, which could have prompted earlier suspicion for the possibility of development of HIT-2 during subsequent admissions. HIT antibody test was positive, confirming our diagnosis of HIT-2.

TREATMENT

Treatment of HIT-2 requires immediate withdrawal of heparin. The main pathophysiology is increased thrombin generation, so the medical treatment of choice is a direct thrombin inhibitor (lepirudine, argatroban, bivalirudin). Factor Xa inhibitors (danaparoid) are also used for treatment HIT-2. These medical treatments are used until there is a stabilization of normal platelet counts [7-8,10]. In our case, heparin was immediately withdrawn and argatroban was started for treatment of HIT-2. Due to an upper GI bleed, argatroban had to be discontinued on day 24 and the patient died four days later, presumably due to complications related to HIT-2.

Lepirudin is a USFDA approved agent for HIT-2 treatment. It is a recombinant hirudin that is excreted (90%) via kidney; the plasma half-life is 1-2 hours. Lepirudin leads to rapid platelet count recovery [2,11]. Argatroban is also USFDA approved for HIT-2 treatment. Argatroban is a synthetic direct thrombin inhibitor, excreted via the liver [2]. Argatroban was used in our patient due to her ESRD. Bivalirudin is approved in United State for anticoagulation during percutaneous coronary intervention. It is a synthetic hirudin analogue (highly specific thrombin inhibitor) that inhibits both free and clot-bound thrombin; it has a half-life of 30 minutes. Bivalirudin has no cross-reactivity with HIT anti-bodies. All of these direct thrombin inhibitors have a side effect of bleeding and that can be easily monitor using aPPT. Danaparoid, a heparinoid, is not available in the United States, but is used in Canada and Europe. Danaparoid has a half-life of 24 hours and is excreted via the kidneys [3,7-8,10].

LMWH should be avoided in patients with HIT-2 because it has cross reactivity with UFH. Vitamin K antagonists can cause protein C decline with further hypercoagulations. Platelet transfusion should be avoided unless there is life-threatening bleeding. It was used in our patient due to severe GI bleed. Once platelet counts are normal, warfarin can be used in patients at high risk of thrombosis; it is suggested that warafin therapy for anticoagulation should be continued for at least 2 to 3 months after resolution of acute HIT-2 symptoms [3,7-8,10].

CONCLUSION

In the current case report we present a female with a history of numerous medical conditions, including ESRD with hemodialysis, and a 7 month history of at least 7 exposures to heparin. During current admission she developed HIT-2. The case underscores the need for close monitoring for HIT even when the patient has been treated with heparin in the past without development of symptoms of HIT. A p-natriuretic peptide greater than 35,000 during heparin therapy when no HIT symptoms are present may be an indicator of risk for later development.

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