

Heparin-Induced Thrombocytopenia and Hemodialysis

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Abstract

Hemodialysis-related-heparin-induced thrombocytopenia (HD-HIT) is a drug-induced, immunoglobulin-mediated disorder that it is suspected in dialysis patients with an unexpected fall in the platelet count, and/or unexplained thrombotic events, particularly visible clotting in the circuit under an adequate heparin dose, that begins between 5 and 10 days (nadir between 7 and 30 days, mostly by the third to fifth session) after heparin initiation. Although a positive result for anti-PF4/heparin complex antibodies (HIT antibodies) is presumably detected by sensitive ELISA, the diagnosis should be confirmed, whenever possible, using a functional assay. Immediately after the clinical suspicion of HIT, all sources of heparin should be discontinued including heparin used to flush or lock catheters. Alternative non-heparin anticoagulants, preferentially a direct thrombin inhibitor, should be restarted for dialysis. Early treatment is important as thrombus formation including a clotting circuit may complicate at a high rate within 30 days after the cessation of heparin. Argatroban, a synthetic direct thrombin inhibitor, as an alternative to heparin, must contribute to the rapid recovery of the platelet count and disappearance of visible circuit clotting. A steady decreasing of the ELISA titers can be expected after heparin discontinuation. A negative seroconversion of HIT antibodies is usually observed by ~30 to more than 100 days after discontinuation. Re-exposure to heparin can be selected at the same dose of heparin as used before the onset of HIT. A small peak of HIT antibodies may often appear after exposure, but a follow-up of the antibody titers shows that they not reach a threshold to induce the recurrence of HIT. When HD-HIT patients exhibit a high index of thrombotic formation or worsening thrombosis, the same alternative anticoagulant therapy may be needed on non-session days.

Keywords: Heparin-induced thrombocytopenia; Hemodialysis

Introduction

Unfractionated heparin (heparin) is the most commonly used anticoagulant for hemodialysis (HD) [1]. It is well-known that heparin can cause immune-mediated thrombocytopenia due to immunoglobulin antibody formation against the complex of platelet factor 4 (PF4) and heparin (HIT antibodies). Heparin may also contribute to HD-associated platelet activation, thrombocytopenia, and increased PF4 release from platelets during a heparin dialytic session [2]. Typically, IgG isotype HIT antibodies develop after 5-14 days of heparin exposure. The incidence of heparin-induced thrombocytopenia (HIT) was estimated at 3.9% in newly treated dialysis patients [3]. Also, dialysis is often complicated by clotting of the dialysis lines and/or dialyzer due to hypercoagulation regardless of the etiology. When a diagnosis of HIT based on clinical symptoms of thrombocytopenia and immunoassay for PF4/heparin complex antibodies is employed, it remains unclear why a few patients develop HIT. An antigen-based immunoassay to detect the presence of antibodies in a patient's circulation that binds to the PF4/heparin complex is highly sensitive but less specific. Thus, the serological diagnosis of HIT needs to be confirmed by employing a functional assay such as the ¹⁴C-serotonin release assay and heparin-induced platelet aggregation test. The enzyme-linked immunosorbent assay (ELISA) usually detects antibodies of three classes of isotype (IgG, IgA, and IgM) regardless of the capability of these antibodies to activate platelets. There is a way to improve the specificity based on only IgG class antibodies having the capability of inducing platelet activation by heparin [4].

There are two kinds of dialysis-related complication: unexpected clotting in the circuit, and abrupt fistula thrombosis. The former seems to be more frequent in HIT than that in non-HIT patients. Visible clotting in the extracorporeal circulation may provide a clue to suspect HIT. AVF thrombosis is also observed in both HIT and non-HIT

patients. After starting heparin, the sudden onset of fistula closure is rare in HIT-complicated thrombosis [5,6].

HD patients who develop HIT require not only the discontinuation of heparin, but essentially also the introduction of alternative anticoagulant therapy. An alternative anticoagulant, such as citric acid, and some therapeutic methods, such as heparin-free dialysis and peritoneal dialysis, has been selected for patients who require dialysis. However, these therapeutic modalities are unlikely to be beneficial because of the absence of evidence supporting long-term management.

Regarding clinical evidence to support HIT, a non-heparin anticoagulant should be employed with an alternative to heparin. Argatroban rather than lepirudin is recommended as elimination is not via the kidneys, but mainly via the biliary system. As the elimination of lepirudin primarily depends on the renal function, it is not easy to monitor the optimal dose of lepirudin in each session. However, the dose of argatroban in hepato-renal failure is recognized variably to reduce while avoiding major bleeding in a critical setting [7]. Nafamostat mesilate, a polyvalent protease inhibitor, is sometimes used as an alternative to heparin in Japan. Although a few patients showed the effective resolution of clotting and a slow increase of the platelet count to the baseline level in a subsequent session receiving nafamostat mesilate, no clinical trial has ever been carried out to evaluate the efficacy in the management of HIT [8]. Although dialysis-related HIT

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tends to appear in an early session after starting HD with heparin, some patients with the PF4/heparin complex antibody may have a risk of delayed-onset HIT.

Frequency of HIT in dialysis patients

The frequency of HIT is suggested to be from 1 to 5% of patients exposed to heparin, and significantly lower in patients exposed to low-molecular-weight heparin. As one of the reasons for the various frequencies of HIT, assays used to detect HIT antibodies vary in their specificity and sensitivity. An assay for HIT antibody usually detects both non-pathogenic and pathogenic antibodies irrespective of the presence of thrombocytopenia. The clinical significance without thrombocytopenia in which a patient exhibits a stable, high titer of long-term HIT antibodies remains unclear, but there is an ongoing survey on whether or not subjects have a risk of thrombosis [9].

Few reports on the frequency of HIT in dialysis patients are known, although heparin is employed as the most useful anticoagulant during dialysis. It was believed that the frequency of HIT would be low in a survey targeting all dialytic patients including both acute and chronic stages [10]. Two surveys involving different subjects show quite different figures on the frequency of HIT. A relatively high frequency of 3.2% was reported for newly treated subjects receiving dialysis in three months [3], and a low frequency of 0.6% is described in chronic dialysis patients treated for over 3 months [11]. Thus, the frequency of HIT in a dialysis population is different between newly treated and chronic maintained dialytic groups. HIT in the former shows a similar incidence to the heparin-sensitive group, and HIT in the later group is rarely identified as HIT recurrence when a patient experiences changes in immunological tolerance brought about by cardiovascular surgery, orthopedic surgery, and the high-dose administration of erythropoietin with an adverse platelet-stimulating reaction.

Clinical manifestations and laboratory testing in HD-HIT patients

Major clinical manifestations are primary thrombocytopenia and new thrombosis. The complication of thrombosis sometimes develops before thrombocytopenia emerges 5-10 days after starting heparin. Although thrombocytopenia is ordinarily defined as a >50% fall in the platelet count and below $100 \times 10^9 /L$, the definition of HD-HIT is less strict, in the range of a >30% fall in the platelet count and below $150 \times 10^9 /L$ due to the intermittent use of heparin. Timing of the fall of platelet counts is likely to delay due to intermittent heparin use. Thus, no dialytic session day may give a chance of recovering the platelet count, and the timing is usually delayed over 10 days. However, heparin flushing to maintain the patency of the inserted catheter on non-session days sometimes leads to the conventional formation of HIT antibodies.

HIT symptoms may occur more rapidly within 24 hr or less in patients who have had a previous exposure to heparin within the prior 3 months. However, a dialytic patient can experience the onset of an acute systemic reaction associated with circuit clotting and a marked drop in the platelet count immediately after a bolus heparin injection at the start of the session. In chronic intermittent dialysis, HIT is unlikely to occur after several weeks of heparin exposure. A few patients have suffered from delayed-onset HIT a few weeks after the cessation of heparin.

Firstly, a newly treated dialytic patient with primary thrombocytopenia ($<150 \times 10^9 /L$, fall rate of > 30%) and no other cause of circuit clotting may be suspected of having HD-HIT. In HIT with thrombosis including circuit clotting, AVF occlusion should be

confirmed with no other causes except a heparin immune-mediated reaction.

HIT testing is grouped into two types: 1) Detection of immunoglobulin antibody against PF4/heparin complexes by ELISA as a standard technique according to high sensitivity and low specificity. ELISA is simple to perform, can be done in a few hours, is highly sensitive, and is less specific for antibody detection. Owing in part to its high sensitivity, ELISA often detects non-pathogenic antibodies that would not be positive for ^{14}C serotonin release and may be clinically non-significant. ELISA provides as much information as possible about the likelihood that a patient has HIT [12,13]. 2) Functional assays for the detection of platelet-activating immunoglobulin G by ^{14}C serotonin release assay.

ELISA permits the identification of three subclasses of immunoglobulin: IgG, IgA, and IgM, reacting with PF4/heparin complexes in a solid-phase plate. To avoid the overdiagnosis of HIT, the pathogenic impact of HIT antibodies should be considered if the optical density is ≥ 0.4 [14]. Therefore, a negative result always excludes the diagnosis of HIT. ELISA detects IgA and IgM antibodies that do not react on FcγIIA-receptor-mediated platelet activation. Specific IgG-HIT antibodies can contribute to the interaction of the HIT antibody/PF4/heparin complexes with the FcγIIA receptor, and subsequently induce platelet activation and the release of microparticles. A high-titer of IgG antibodies is accountable for HIT as well [15,16].

The ^{14}C serotonin release assay is the gold standard because of its high sensitivity and specificity. Thus, the ^{14}C serotonin release assay should be performed to confirm the diagnosis if a weak positive result is obtained using ELISA [17,18] (Table 1). For the assessment of HD-HIT, the pretest probability of the diagnosis of HIT (4T's test) has not clarified regarding whether clot formation in the extracorporeal circulation is the first sign of HIT [19]. Sudden unexpected visible clotting in the circuit often provides an important clue for HIT diagnosis despite there being many causes of clotting during dialysis. After changing the clotted dialyzer and circuit to new ones, the subsequent dialytic session must be restarted with an alternative to heparin, and the planned treatment modality can be uneventfully completed. Subsequent sessions will never affect re-clotting or the recurrence of thrombocytopenia under adequate switching to non-heparin anticoagulation. Furthermore, the patient is more likely to have HIT in the presence of a comparable HIT antibody seroconversion. Clotting of the extracorporeal circuit seems to be a manifestation of HIT in the context of primary thrombocytopenia, the resolution of clotting with an alternative anticoagulant, HIT antibody seroconversion, and an onset within 3 months of starting HD.

The clinical features of HIT in dialysis patients often include acute thrombocytopenia [20], repeated clotting of the extracorporeal

Step	Clinical and Lab. assessment	Action plan
1	suspicion of HIT	thrombocytopenia ($<150 \times 10^9 /L$, unexplained decrease of > 30%), timing of over 5 days, no other cause of thrombocytopenia or thrombosis
2	ELISA (IgG, A, M)	no likelihood of HIT due to a negative qualitative assay
3	specific IgG-ELISA	high specificity for platelet-activating antibodies
4	^{14}C serotonin release assay (platelet aggregation test)	confirmation of HIT as a gold standard test (not preferable due to being less sensitive)
5	reassessment of HIT if necessary	recheck other causes of thrombocytopenia and thrombosis, assess with alternative therapy

Table 1: Diagnostic approach to HIT.

circulation undergoing heparin administration [21], the clear disappearance of clots on using an alternative anticoagulant to heparin, and/or, rarely, thrombotic occlusion in AV fistula/grafting [5,6]. Circuit clotting occasionally occurs in a routine dialysis procedure, caused by non-HIT factors. The causes of clotting are slow blood flow, a high hematocrit, high ultrafiltration rate, intradialytic blood and blood product transfusion, and intradialytic lipid transfusion. In clinical settings, it is difficult to decide whether or not the clotted circuit is derived from HIT. Differences in the platelet count's fall and timing between clotting-circuit and non-clotting patient groups have been found in clinical settings. However, a high level of optical density in ELISA is noted in the clotting group. This suggests that HIT antibody formation may be activated in the clotting rather than non-clotting patient group (Table 2).

Diagnostic approach to HD-HIT patients

An HD patient associated with HIT is recognized by stepwise assessment. The first step is evaluation of the platelet count with the definition ($<150 \times 10^9/L$ and $>30\%$). If the patient shows circuit clotting with no other causes, the next step would be to evaluate the timing of thrombocytopenia over days 7-30. The timing of HD-HIT is generally applied over a wider range than usual due to the use of heparin being limited in dialysis of 4-6 hours per day. Positive ELISA added to define platelet reduction, the presence of a clotting circuit, and reasonable timing, should be considered as revealing HIT. As level-one assessment, HD-HIT patients with four-factor combinations of thrombocytopenia, clotting circuit, optimal timing of platelet fall, and positive ELISA are expected to show a high rate of positive ^{14}C serotonin release assays. In the case of no circuit clotting, HD patients with thrombocytopenia, reasonable timing, and positive ELISA show a moderate rate of positive ^{14}C serotonin release assays. Thus, four diagnostic levels can be identified: HD-HIT is most likely due to a high positive rate of ^{14}C serotonin release assays, 'HD-HIT most likely'; HD-HIT is likely to show a moderate rate on a functional assay, 'HD-HIT likely'; timing outside the range and a negative ELISA despite the presence of a clotting circuit should be identified as 'unlikely'; the level of 'HIT less likely' without any clotting/thrombosis is rare even though ELISA is positive.

The sudden occurrence of clots in the dialyzer and/or circuit with an unexpected fall in the platelet count between 7 and 30 days are marked symptoms of HIT in HD patients undergoing appropriate anticoagulation with heparin. In an HD patient with suspected HIT, the clinical implication of clotting in the circuit as HIT diagnosis can be supported in combination with thrombocytopenia, timing of the platelet fall, and result of ELISA.

Management of HD-HIT patients

Visible clotting in the circuit, including blood chambers, tubes, and

<p>Step 1. Recognition of HIT is most important:</p> <ol style="list-style-type: none"> 1. Unexpected clotting of dialyzer/circuit, and thrombotic occlusion of arterio-venous fistula/grafting despite optimal dose of heparin infusion 2. Absence of other cause of clotting: slow blood flow, high hematocrit, high ultrafiltration rate, intradialytic blood and blood product transfusion, intradialytic lipid transfusion 3. Check primary thrombocytopenia <p>Step 2. Emergent protocol for suspected HIT patient:</p> <ol style="list-style-type: none"> 1. Stop dialysis immediately, and replace whole extracorporeal circuit with a new one 2. Restart dialysis with argatroban (lepirudin) 3. Confirm by visible inspection that there is no clot in the circuit once starting an alternative to heparin 4. Avoid heparin flush on non-session days
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Table 2: Management strategy for HIT in dialytic patients.

dialyzer, are easily recognized by medical staff in the session, so HIT management can be initiated immediately when clotting is likely to arise from HD-HIT. Once the HIT diagnosis has been established based on a high clinical suspicion alone before laboratory confirmation, it is essential that all sources of heparin, including low-molecular-weight-heparin, heparin flushing, and heparin-coated catheters or devices, are discontinued. The early recognition of HIT in the presence of clot formation in the extracorporeal circuit is critical, and any additional infusion of heparin on the misunderstanding of heparin shortage must be contraindicated to resolve the clot. When the dialytic procedure cannot be continued with circuit clotting, a new dialyzer and devices of the extracorporeal circuit must be set up, and the session must be immediately restarted with an alternative anticoagulant. Then, the diagnosis of HIT can be verified using the assessment in Table 3.

Established alternative anticoagulation in HD patients with HIT is conducted with danaparoid, lepirudin, and argatroban. Danaparoid is a low-molecular-weight heparinoid. Although danaparoid is the most widely used for HD-HIT patients, it does not exhibit proper anticoagulation for HD-HIT due to clinically relevant cross-reactivity. Lepirudin is a recombinant hirudin derivative thrombin inhibitor. Adequate dose adjustment is very difficult for HD-HIT patients, in which it is cleared mainly by the kidneys and its half-life is markedly long in uremic patients.

Argatroban (formerly called MD805), a synthetic direct thrombin inhibitor, is non-immunogenic and does not show cross-reactivity with HIT antibodies. In contrast to lepirudin, argatroban is primarily hepatically metabolized, and its half-life is moderately extended in HD patients [22,23]. Argatroban as an alternative anticoagulant is predominantly used for the prevention of extracorporeal circuit clotting in HD-HIT patients at the initial dose of $250 \mu\text{g}/\text{kg}$ at the start of dialysis, and followed by a continuous infusion of $2 \mu\text{g}/\text{kg}/\text{min}$ while the hepatic function is normal. Dose adjustment is conducted for an empirical target of a 1.5-3.0-fold prolongation of the activated partial thromboplastin time (APTT), as an equivalent to the prolongation of heparin therapy. This dose can be reduced to $<2 \mu\text{g}/\text{kg}/\text{min}$ with a 1.5-2.5-fold prolongation of the APTT after the acute phase of HIT has subsided. The dose should also be reduced to $<2 \mu\text{g}/\text{kg}/\text{min}$ depending on the severity hepatic dysfunction to avoid unexpected hemorrhagic complications. Only the replacement of heparin with argatroban in dialysis can lead to recovery from symptoms of HIT [24-26]. Despite there being no apparent evidence to support the systemic administration of argatroban on non-session days, argatroban anticoagulation may prevent the risk of new and worsening thrombotic events. When an HD-HIT patient is in a hypercoagulable state, such as with an elevated

Level	Diagnosis of HIT	Platelet fall ($\leq 150 \times 10^9/L$, $\geq 30\%$)	Clotting circuit	Timing of fall (7-30 day)	ELISA (IgG, IgA, IgM)	Estimates of positive SRA
1	most likely	+	+	+	pos.	high (~95%)
2	likely	+	-	+	pos.	moderate (~75%)
3	less likely	+	-	-	pos.	less moderate (~70%)
4	unlikely	+	+	+/-	neg.	neg. (0%)

+, clinical factor present, -, not present, SRA, ^{14}C serotonin release assay

Table 3: Evaluating patients with three clinical factors and ELISA.

level of plasma D-dimer, argatroban therapy seems to be essential. The empirical dose of the drug is estimated to be 0.7µg/kg/min in patients with a normal liver function and 0.2µg/kg/min in those with hepatic dysfunction or a risk of bleeding.

Nafamostat mesilate, a polyvalent synthetic protease inhibitor, is employed as a regional anticoagulant in dialysis patients with bleeding risks as an alternative to heparin in Japan. The drug has no effect on the systemic blood coagulation cascade due to its very short half-life, within 10 min, about 40% of the drug is removed from the dialyzer, and there is no cross-reactivity with HIT antibodies. Despite the fact that the HD-HIT session is uneventfully completed using nafamostat mesilate, it remains unknown why the drug has a therapeutic benefit regarding the resolution of HIT over the effect of heparin cessation [8,27].

Cardiovascular surgery in patients with chronic hemodialysis

Chronic dialysis patients who are repeatedly exposed to heparin are rarely at risk of developing heparin-induced thrombocytopenia, and show high-level mortality due to atherosclerotic cardiovascular events [28]. Sometimes they have indications for cardiovascular surgery on non-dialysis sessions. There are few data available on whether long-term heparin usage accelerates post-operative seroconversion, and the development of HIT. Surgical procedures usually stimulate the release of PF4 from platelets and the endothelium. PF4 will certainly facilitate complex formation in the presence of a dynamic equilibrium with external heparin. Macromolecular PF4/heparin complexes stimulate the

immunomediated production of anti-PF4/heparin complex antibodies. Increased levels of immunomediated HIT-antibody production are occasionally recognized in the post-operative period. Although a high rate of seroconversion appears to be involved in the development of HIT, most seroconversion shows a lack of thrombocytopenia, and very few patients with seroconversion develop HIT.

In cardiovascular patients receiving regular dialysis, the risk of HIT is presumed to increase in certain situations, such as cardiac intervention, through the modification of immunological tolerance to PF4/heparin complexes. Eight out of 79 patients undergoing cardiovascular surgery were treated with dialysis (Table 4). Two patients with neither thrombocytopenia nor thrombosis experienced seroconversion with positive ELISA and SRA. One patient was negative in the pre-operative state despite receiving heparin dialysis for 3.5 years. He may have undergone a resetting of the immunologic response to PF4/heparin complexes due to the influence of perioperative surgical procedures (#1). The other patient (#8) had pre-existing HIT antibodies on ELISA and a negative serotonin release assay, and both would be induced by accelerating the production of HIT antibodies. No ‘true HIT’ patient could be found in the series despite two patients experiencing sufficient seroconversion to induce HIT. This suggests that reactivation of the immune system could be functioning in the perioperative period, and the risk of developing HIT may be continuing until the subsidence of HIT antibody production. Any thrombocytopenia corresponding to HIT criteria could not be detected with the monitoring of platelet counts for post-operation, despite a marked fall within 4 postoperative

	Age/sex	Type of surgery	Thrombocytopenia (50%fall, 5-10 days from pre-op. level)	Immunoassay ELISA (>0.4)			Functional SRA (>20%) assay		
				Pre	7days	14days	Pre	7days	14days
1	58/M	vas-grafting	-*	-**	1.82	2.39	-***	-	96
2	67/M	vas-grafting	+ (56.6%)	-	-	-	-	-	-
3	63/M	CABG	-	-	-	-	-	-	-
4	69/M	CABG	+ (69.6%)	-	-	-	-	-	-
5	55/M	CABG	-	-	-	-	-	-	-
6	60/F	CABG	+ (73.5%)	-	-	-	-	-	-
7	63/M	valve op.	-	-	-	-	-	-	-
8	70/M	CABG	-	1.28	1.87	2.01	-	65	68

* not consistent with platelet criteria
 **optical density under 0.4 by ELISA
 ***radioactive serotonin release under 20% SRA, ¹⁴C serotonin release assay

Table 4: Seroconversion in cardiac surgery patients with chronic hemodialysis.

	Symptoms of acute systemic reaction	Circuit clotting	AVF thrombus	Platelet count (×10 ⁹ /L) at ASR	Maximum fall (%) in platelet count	Timing of platelet fall (days)
1	Dyspnea, chills, fever	+**	-	53	85	14
2	Nausea, vomiting	-	+	25	88	12
3*	Dyspnea, flushing, chills, fever,	-	-	16	90	13
4	Dyspnea, chest pain	+	-	28	94	7
5	Dyspnea, chest pain, hypotension, nausea, vomiting	-	+	84	72	13
6*	Dyspnea, fever	+	-	57	67	8
7***	Dyspnea, chills, nausea	+	-	92	80	11
8	Dyspnea, chills, fever, chest pain, nausea	+	-	74	73	11

*diagnosed with pseudo-pulmonary embolism, ** unexpected closure of hollow fibers of dialyzer with fibrin-platelet aggregates in two consecutive sessions, ***heparin flushing on non-session day.

Table 5: Eight patients with HIT-induced acute systemic reaction from twenty-seven dialytic patients who experienced some acute systemic reaction.

days, and steeply increasing platelet counts in the following days were observed regardless of whether or not the patients experienced seroconversion.

Post-operative thrombocytosis, in contrast to HIT-evoked thrombocytopenia, can influence the results of platelet counts, because marked thrombocytosis may compensate for thrombocytopenia derived from immune-mediated platelet destruction. When the recovery of platelet counts remains low over the 5th post-operative day and an abrupt platelet fall is induced by the reuse of heparin, HIT should be considered in patients with no other causes of thrombocytopenia.

It is not known how HIT occurs even after years of uneventful chronic intermittent hemodialysis due to resetting of the immune mechanism triggered in cardiovascular surgery.

Characteristics of acute systemic reaction in dialytic patients

Infrequently, an acute systemic reaction (ASR) as a manifestation of HIT occurs 5-30 min after heparin bolus administration at the start of dialysis. The symptoms are fever, chills, and flushing as acute inflammatory reactions, and hypertension, tachycardia, dyspnea, chest pain, and cardiopulmonary arrest. Although hypertension is usually associated with ASR [29], in contrast, acute hypotension often occurs as a sign of cardiovascular collapse during dialysis. When dyspnea as the cardiorespiratory reaction in ASR is prominent, it is considered to be a pseudo-pulmonary embolism [30-32]. However, the signs and symptoms are very similar to those in dialyzer reactions, dialytic complications as disequilibrium syndrome, and circuit clotting during the procedure. Except for platelet reduction by heparin, it is difficult to determine whether symptoms of ASR are most likely to be due to HIT in clinical settings. There are two causes of hypotension: HIT-induced hypotension may associate with cardiorespiratory collapse due to pseudo-pulmonary embolism, and HD-induced hypotension often with nausea and vomiting, and occasionally with back pain and syncope.

As the clinical features of eight patients defined with HIT-induced ASR from twenty-seven patients who experienced some ASR, seven of the eight patients suffered from dyspnea, and two ASR patients (case #3, #6) showing hypoxia, no radiological evidence, and the rapid recovery of symptoms after the cessation of heparin were defined as pseudo-pulmonary embolism patients. Hypotension was implicated when pulmonary collapse was noted in a patient (case #5). Thus, hypotension was not a primary feature of the HIT-induced acute systemic reaction. However, no hypertension appeared in eight HIT-induced ASR patients. Either complications of circuit clotting or AVF thrombus formation appeared in seven patients excluding a case (#3) of pseudo-pulmonary embolism. The platelet fall rate and timing in HIT-induced ASR cannot be differentiated from those of HD-induced ASR (Table 5). Complications during dialysis including dialyzer reactions, a clotting circuit, anticoagulation failure, and hypotension may mimic the signs and symptoms of HIT-induced ASR except hypotension. Thus, a platelet count and assays for HIT antibodies should be considered for diagnosing acute HIT when HD patients show an abrupt fall in platelet counts and clinical symptoms of ASR with an unknown cause during dialysis. The results of the HIT-antibody assay showed that the differential diagnosis would be straightforward regarding whether HD patients with thrombocytopenia suffered from HIT-induced or HD-complicated ASR.

Re-exposure to heparin

The principal of heparin re-exposure is based on a characteristic

immune response in T-cell-independent B-cell activation because of the lack of a memory response, perhaps explaining transience and a lack of anamnesis of the anti-PF4/heparin immune response [34]. The re-exposure can be effectively performed due to a lack of immune memory for the PF4/heparin complex antigen in patients with previous episodes of HIT when their HIT antibodies are ablated in circulation. However, there is no clinical consensus regarding re-exposure to heparin for acute HIT. The re-exposure is necessary at least 100 days after no detection of HIT antibodies by ELISA. Reductions in the optical density of ELISA are quite variable after the cessation of heparin. While a positive ELISA continues long-term over years, a short span type is also recognizable. Since the various half-lives of HIT antibodies may reveal the presence of different properties of HIT antibodies, each patient should be followed by ELISA until there is no longer a detection of HIT antibodies. Re-exposure to heparin should be introduced under negative ELISA where adequate emergent measures are adopted, including platelet-counting tests [35-37]. A majority of heparin-re-exposure patients show no recurrence of HIT unless they undergo cardiovascular surgery, catheter intervention, and, rarely, receive platelet-stimulating drugs. Re-exposure to heparin in HD patients showing a stable titer with an optical density over 0.4 may not be allowed because the risk of HIT-recurrence is likely to rise on heparin reuse.

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