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Letters to Blood

TO THE EDITOR:

Heparin-induced thrombocytopenia and thrombosis during high dose melphalan and autologous stem cell transplantation

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In patients with complex medical conditions, determining the etiology of thrombocytopenia can be challenging. This is particularly true in patients undergoing treatment with high-dose melphalan and autologous stem cell transplantation (HDM/SCT). Virtually all patients receiving this therapy will develop thrombocytopenia, with potential mechanisms including stem cell collection, administration of high-dose melphalan, prior myelosuppressive therapy, infection, or concomitant medications. Because of the expectation of significant thrombocytopenia during the peritransplant period, the diagnosis of heparin-induced thrombocytopenia (HIT) may not be considered.

HIT is a life-threatening disorder characterized by low platelets and transient hypercoagulability related to the development of antibodies against the heparin-PF4 complex in patients with recent exposure to heparin.[1,2] Rapid and accurate diagnosis is important to prevent morbidity and mortality associated with both thrombocytopenia and the increased risk of venous or arterial thrombosis that can persist for many weeks after diagnosis.[3] In patients with suspected HIT, the rapid and sensitive PF4-dependent enzyme immunoassay can assist with risk prediction.[4] Because of high sensitivity and specificity, confirmatory testing with the serotonin release assay (SRA) is typically performed.[5]

Despite the multitude of reasons for thrombocytopenia in patients being treated with HDM/SCT, it is important to consider the possibility of HIT and perform diagnostic testing if suspicion arises. Here, we highlight the existence of HIT in this population by describing 5 patients who developed clinically apparent and laboratory-confirmed HIT during treatment with high-dose melphalan and autologous SCT.

From June 2012 to May 2017, 121 patients underwent treatment with HDM/SCT at our institution; 5 (4%) were diagnosed with HIT. Four patients (80%) were male and the median patient age was 64 years (range, 59 to 69). One patient had a diagnosis of multiple myeloma; the remaining 4 patients had systemic light chain amyloidosis. Platelet levels were within the normal range for all patients before stem cell collection and at the time of central venous access placement (Table 1). Subsequently, all patients underwent stem cell mobilization using granulocyte colony-stimulating factor at a dose of 16 mcg/kg daily until adequate stem cells were collected.

HIT was diagnosed in all patients after completion of stem cell collection. Only 1 patient received high-dose melphalan before the diagnosis of HIT. Each patient received a 14.5 Fr double lumen tunneled catheter with 5000 units of heparin placed in each catheter port at the time of line placement. Daily central line flushes were performed using 5000 units/mL of heparin to yield the total volume indicated for each port depending on catheter length. For the initial 3 patients, the stem cell collection procedure incorporated heparin into the citrate anticoagulant (3000 units of heparin per 750 mL of anticoagulant citrate dextrose solution A). One patient was receiving prophylactic doses of enoxaparin because of a history of line-associated deep vein thrombosis, but no other patients had received prophylactic or treatment doses of heparin within 100 days before central line placement. No patient had a prior diagnosis of HIT.

In all cases, the patients had delayed platelet recovery or unexpectedly severe thrombocytopenia after stem cell collection. The average platelet nadir after stem cell collection was 29 $\times 10^9$/L (range, 10-69). The degree or duration of thrombocytopenia prompted testing for HIT in 3 patients, whereas the development of thrombosis led to HIT testing in the remaining 2 patients. One of those patients developed an internal jugular vein thrombosis. The other presented on day −2, after completing high-dose melphalan, with severe lower extremity pain because of a limb-threatening aortoiliac thrombosis requiring aortoiliac and femoral artery embolectomy with fasciotomy. All 5 patients had confirmation of HIT diagnosis with heparin-PF4 IgG enzyme immunoassay (optical density range, 0.5-3.3) and a positive SRA (Table 1). Four patients were started on anticoagulation with fondaparinux or argatroban; the remaining patient continued treatment with Lovenox, although this practice is not recommended in patients with HIT (Figure 1). Three patients proceeded with HDM/SCT after diagnosis of HIT. The patient that developed a life-threatening arterial thrombosis received his autologous stem cell infusion on day −1 (the day after HIT was diagnosed and fasciotomy had been performed) without complication; 2 additional patients had uneventful stem cell infusions after platelet recovery. For the remaining 2 patients, the decision was made not to reinfuse the patients' stem cells because the stem cells had been processed with heparin. All patients completed at least 3 months of anticoagulation and the platelets returned to a normal level. No additional complications with bleeding or thrombosis were

Table 1. Patient characteristics

Patient	Exposure to heparin during central line placement and daily flushes	Stem cell collection performed with heparin	Heparin-PF4 antibody (OD)	SRA (% release with 0.1 IU/mL UFH)	Platelet level at time of central line placement ($\times 10^9$/L)	Platelet level at completion of stem cell collection ($\times 10^9$/L)	Platelet nadir after stem cell collection and before melphalan ($\times 10^9$/L)	Thrombosis detected on imaging	HDM/SCT treatment completed
1	Yes	Yes	3.1	Positive (100)	198	14	10	Internal jugular	No*
2	Yes	Yes	0.5	Positive (82)	298	36	35	No	Yes
3	Yes	Yes	3.3	Positive (100)	213	27	24	No	No*
4	Yes	No	1.95	Positive (99)	309	84	69	Aortoiliac and femoral artery	Yes
5	Yes	No	2.7	Positive (96)	248	51	51	No	Yes

*Stem cells were not reinfused.
OD, optical density; UFH, unfractionated heparin.

noted after anticoagulation was initiated and no mortalities occurred.

As a result of a multitude of factors that affect platelet counts and thrombosis risk, the diagnosis of HIT may evade clinicians during the process of stem cell collection and high-dose chemotherapy. Careful attention should be given to the onset, severity, and recovery of thrombocytopenia after stem cell collection because these patients are at risk for HIT. Because of the paucity of data the true incidence of HIT in this population is unknown, although at least 7 cases have been reported in the literature.[6-8]

In all of our cases, there was no history of HIT and it seems that the development of heparin-PF4 antibodies was related to heparin use during the placement or daily flushing of the tunneled catheter. This suggests the development of autoimmune HIT, as previously reported in this population,[7] because the small doses of heparin administered to these patients with catheter flushes would likely not be sufficient for continued development of heparin-PF4 complexes.

Since the diagnosis of HIT in the first 3 patients, we have instituted practice changes to decrease the incidence of HIT. After the first 3 patients, heparin was removed from the stem cell collection process. We have since removed heparin from all central line flushes, although the policy to do so went into effect after all 5 cases were identified. Since this change, there have been no additional cases of HIT identified at our institution. We are also diligently monitoring all transplant patients for unexpected or prolonged thrombocytopenia and we maintain a low threshold for PF4 antibody testing, as well as confirmatory SRA testing.

In conclusion, these cases highlight the existence of HIT resulting from minimal heparin exposure during central line placement and daily catheter flushes. We recommend close monitoring for unexpectedly severe thrombocytopenia or sluggish platelet recovery, particularly following stem cell collection, with a low threshold to send diagnostic testing and remove heparin exposure. It is prudent to consider removing unnecessary heparin exposures, such as heparin used during central line flushes or stem cell collection. Removal of heparin from these processes is feasible, may be associated with significant reduction in the risk of HIT, and may allow for safe infusion of stem cells in patients who develop HIT during treatment with HDM/SCT.

Authorship

Contribution: S.S. and V.S. reviewed the cases and analyzed the laboratory results; all authors were involved in the clinical care and practice changes referenced in this manuscript; and S.S. and V.S. coauthored the original manuscript, which was reviewed and approved by all other authors.

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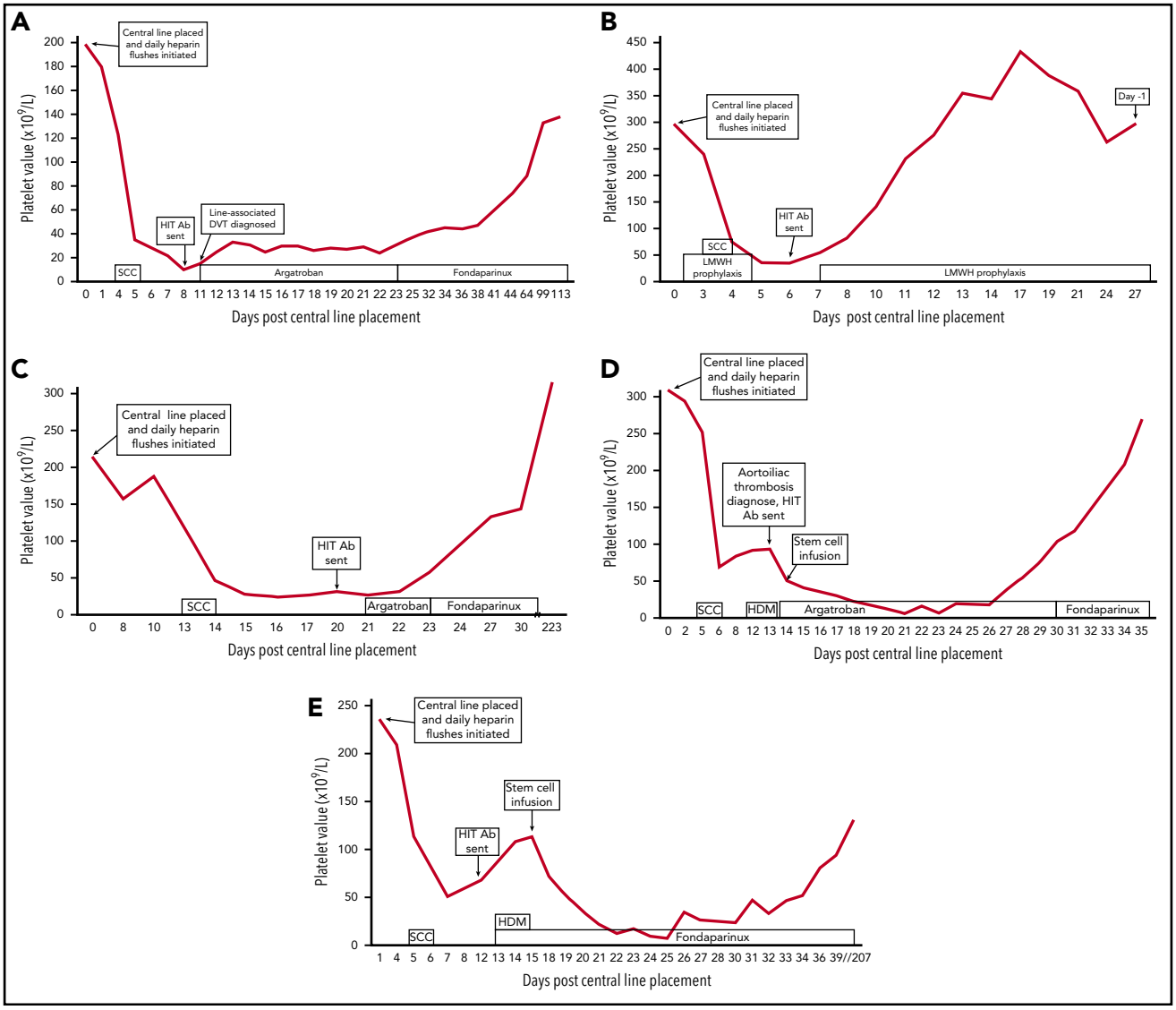

Figure 1. Platelet trends in patients after central line placement. (A) Patient 1 (multiple myeloma). (B) Patient 2 (AL amyloidosis). (C) Patient 3 (AL amyloidosis). (D) Patient 4 (AL amyloidosis). (E) Patient 5 (AL amyloidosis). Ab, antibody; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; SCC, stem cell collection.

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