J Breast Cancer. 2026 Apr;29(2):192-201
https://doi.org/10.4048/jbc.2025.0278
pISSN 1738-6756·eISSN 2092-9900

Journal of Breast Cancer JBC

Case Report

Delayed Bleeding With Variable Presentations in Implant-Based Breast Reconstruction During Adjuvant Ado-Trastuzumab Emtansine (Kadcyla) Therapy: Two Case Reports

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Received: Nov 12, 2025
Revised: Jan 13, 2026
Accepted: Mar 29, 2026
Published online: Apr 20, 2026

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ABSTRACT

Ado-trastuzumab emtansine (T-DM1) is an effective adjuvant therapy for human epidermal growth factor receptor 2-positive breast cancer; however, its surgical safety profile remains unclear. We observed delayed bleeding with variable and often subtle clinical manifestations during implant-based breast reconstruction (IBBR). Two patients who received adjuvant T-DM1 therapy after IBBR were retrospectively reviewed. The patient in Case 1 developed a recurrent seroma and liquefied hematoma requiring repeated aspirations, with platelet counts decreasing from 218 × 10^9/L to 33 × 10^9/L before expander removal. The patient in Case 2 experienced an acute massive hematoma on postoperative day (POD) 2, prior to T-DM1 initiation, which resolved after re-exploration; a temporally distinct delayed hemorrhagic event occurred on POD 175 during T-DM1 therapy after radiotherapy, accompanied by a platelet nadir of 34 × 10^9/L. Both patients required plateletpheresis and prolonged drainage. Delayed bleeding during T-DM1 therapy may reflect a combination of hematological suppression and vascular vulnerability. Therefore, vigilant surveillance and cautious postoperative rehabilitation are warranted.

Keywords: Ado-Trastuzumab Emtansine; Breast Implants; Hemorrhage; Mammaplasty

INTRODUCTION

Ado-trastuzumab emtansine (T-DM1; Genentech, San Francisco, USA), an antibody–drug conjugate that combines trastuzumab with the microtubule inhibitor emtansine (DM1), has proven to be effective in treating human epidermal growth factor receptor 2 (HER2)-positive breast cancer in both metastatic and adjuvant settings [1-3]. Thrombocytopenia is a well-recognized adverse effect, reported in up to 30%–40% of patients, of whom 8%–13% have

Conflict of Interest
The authors declare that they have no competing interests.

Data Availability
In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon request.

Author Contributions
Conceptualization: Roh TS; Data curation: Min K; Formal analysis: Ryu SJ; Investigation: Kim YS; Methodology: Ryu SJ; Project administration: Roh TS; Resources: Jeong J; Supervision: Roh TS; Validation: Ryu SJ; Visualization: Yun IS; Writing - original draft: Ryu SJ.

grade ≥ three thrombocytopenia. Its pathophysiology is believed to involve DM1-mediated impairment of megakaryocyte maturation and increased platelet clearance [4].

Although the hematologic safety profile of T-DM1 has been described in oncology literature [1,3], its implications for surgical patients, particularly those undergoing implant-based breast reconstruction (IBBR), remain underexplored [5]. Existing studies on chemotherapy and breast reconstruction have focused largely on wound healing and infection, with minimal discussion of bleeding risk beyond the immediate perioperative period [5,6].

We present two cases of delayed bleeding after IBBR, characterized by variable and often subtle clinical manifestations, in patients receiving T-DM1. These events likely arose from a multifactorial process involving not only T-DM1-associated platelet suppression, but also radiation-induced vascular injury and postoperative mechanical stress from rehabilitation [7-9]. This report emphasizes the importance of patient education, postoperative activity modification, and vigilant surveillance in this clinical context.

CASE REPORT

Case identification and data extraction

Two consecutive patients with HER2-positive breast cancer treated with adjuvant T-DM1, who underwent IBBR-related surgery and experienced significant perioperative bleeding, were identified retrospectively. We extracted the following information from the hospital electronic medical records: demographics, cancer stage, systemic therapy timeline, T-DM1 dosing schedule, preoperative platelet counts relative to baseline, operative details, estimated blood loss (EBL), drain output, reoperation, and transfusion. Written informed consent for the publication of the case details and accompanying images was obtained from both patients. This study was approved by the Institutional Review Board of Gangnam Severance Hospital (approval No. 3-2025-0293) and conducted according to the tenets of the Declaration of Helsinki.

Literature review

Targeted searches were performed for T-DM1-associated thrombocytopenia/hemorrhage, label warnings, and IBBR chemotherapy hematomas. The inclusion criteria were primary data, regulatory/labelling documents, systematic reviews, and high-quality cohort studies.

Case presentation

Case 1

A 49-year-old woman with no significant medical history was diagnosed with right breast cancer (cT3N1M0, stage IIIA) and received neoadjuvant chemotherapy. She subsequently underwent total mastectomy with sentinel lymph node biopsy and immediate tissue expander insertion using acellular dermal matrix (ADM) coverage. Preoperative intravenous cefazolin (1 g) was administered, and the implant pocket was irrigated with a triple antibiotic solution (cefazolin 1 g, metronidazole 500 mg, and gentamicin 80 mg). A 450-mL expander (Mentor Worldwide LLC, Irvine, USA) was placed in the prepectoral plane, and a drain was inserted. The patient was discharged on postoperative day (POD) 7.

On POD 17, the patient was readmitted with fever and localized erythema. Drain culture revealed the presence of *Corynebacterium*, and intravenous teicoplanin (400 mg daily) was

administered for five days, with subsequent discharge. On POD 20, the drain was removed; however, seroma formation required drain reinsertion on POD 29, which was maintained for 47 days. During this period, the oral antibiotics included linezolid (600 mg twice daily for five days), amoxicillin–clavulanate (twice daily for 24 days), and levofloxacin (500 mg daily for 36 days).

Following drain removal, the patient continued to visit the outpatient clinic two to three times a week, where 30–50 mL of seroma and liquefied hematoma were repeatedly aspirated. Adjuvant T-DM1 therapy was initiated on POD 36. Platelet counts, which had been within the normal range before T-DM1 initiation (218×10^9/L), progressively declined thereafter, persisting between 30×10^9/L and 70×10^9/L and necessitating repeated platelet transfusions (6–12 packs per cycle). After five cycles, T-DM1 was discontinued because of persistent grade 3 thrombocytopenia. Despite the cessation of T-DM1, platelet recovery remained incomplete for several months and gradually improved only after transitioning to trastuzumab therapy.

Postmastectomy radiotherapy (PMRT) was delivered to the right chest wall and regional lymph nodes, including level IV, axillary levels II–III, and the internal mammary nodes, at a total dose of 4,005 cGy in 15 fractions over three weeks, beginning on POD 90. No grade II or higher radiation-related complications were observed.

After PMRT, recurrent hematoma collection persisted, with thinning of the overlying skin. On POD 168, the patient underwent expander removal. Intraoperatively, diffuse oozing from the raw tissue surfaces was observed without discrete bleeding vessels. The patient recovered uneventfully after expander removal (**Figure 1**).

Case 2

A 56-year-old woman with a history of hypertension and diabetes mellitus was diagnosed with left-sided breast cancer (cT2N2M0, stage IIIA) and received neoadjuvant chemotherapy. She underwent nipple-sparing mastectomy with axillary lymph node dissection and immediate direct-to-implant reconstruction with ADM coverage via a radial incision. The specimen weighed 388 g, and a 340-mL implant (MemoryGel® Breast Implants Smooth Round Moderate Classic; Mentor Worldwide LLC) was placed in the prepectoral plane with two drains inserted.

On POD 2, the patient developed massive bleeding with a tense hematoma requiring urgent reexploration. The EBL was approximately 2,000 mL, and hemostasis was achieved by ligating

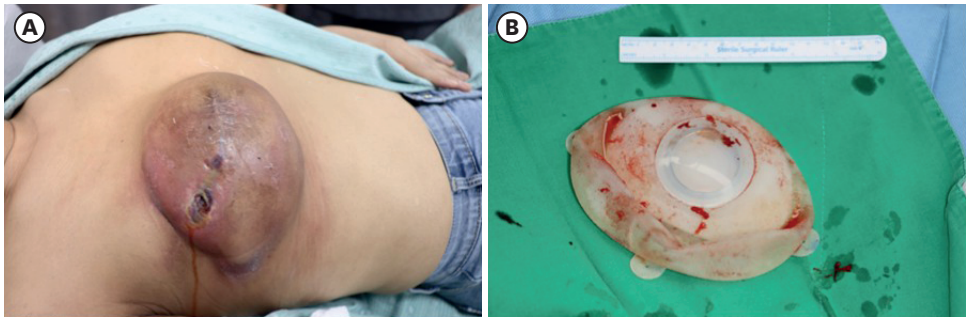

Figure 1. Removal of the tissue expander revealed severe skin flap color change, fragility, and expander exposure in Case 1. (A) Clinical photograph showing dark discoloration and thinning of the overlying skin flap with exposed tissue expander, consistent with delayed bleeding and hematoma-related compromise during ado-trastuzumab emtansine therapy. (B) The removed expander, which had been associated with recurrent seroma and liquefied hematoma formation prior to explantation.

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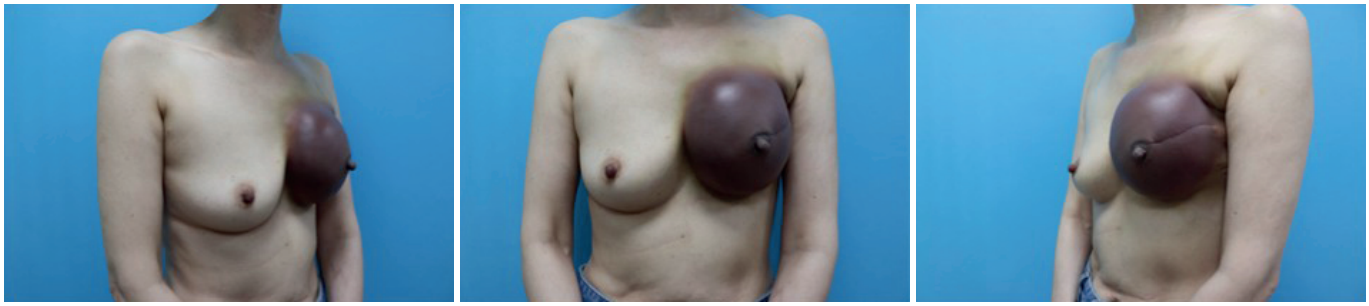

Figure 2. Preoperative photograph showing chocolate-colored discoloration of the left breast skin in Case 2. The clinical findings indicated insidious bleeding that progressed without acute clinical signs until discoloration became evident.

the bleeding vessel. She received six units (~1,900 mL) of platelet concentrate and 1,400 mL of packed red blood cells. The drains were maintained for 29 days. PMRT (4,005 cGy) was initiated on POD 52 over three weeks, and adjuvant T-DM1 therapy was initiated on POD 44.

On POD 175, the patient presented with chocolate-colored skin discoloration over the reconstructed breast (**Figure 2**). On POD 192, surgical exploration revealed an old hematoma consistent with delayed hemorrhage, which was likely exacerbated by radiation-induced vascular injury (**Figures 3** and **4**). Nipple perfusion remained intact on indocyanine green angiography (**Figure 5**). Capsulectomy and implant removal were performed simultaneously. Preoperatively, her platelet count decreased from 251 × 10^9/L to 34 × 10^9/L, requiring two plateletpheresis sessions.

Negative pressure wound therapy was applied until POD 219, after which the drain was maintained for an additional 12 days. Following drain removal, the patient continued weekly outpatient visits, during which 20–30 mL of liquefied old hematoma was consistently aspirated.

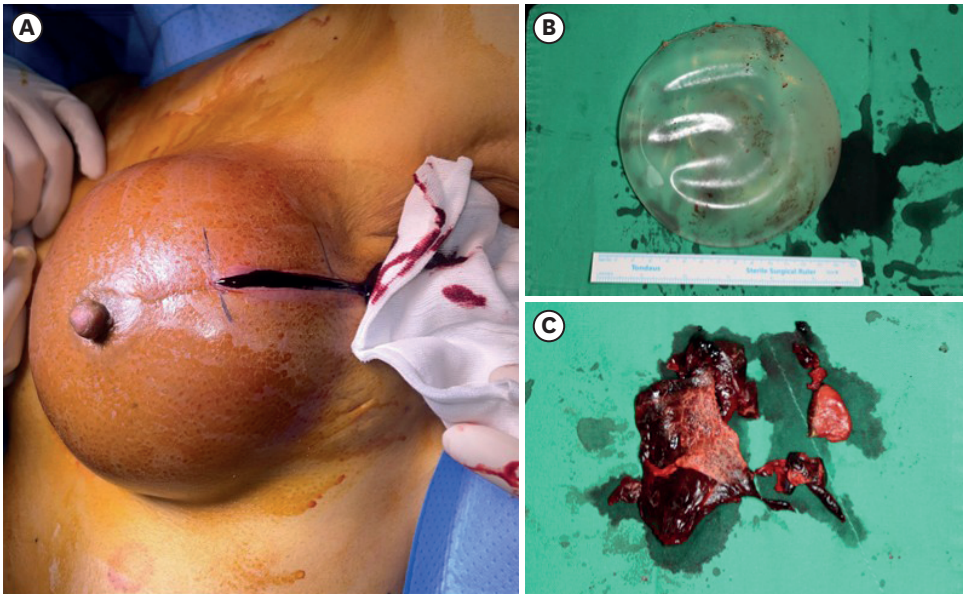

Figure 3. Intraoperative findings and surgical specimens demonstrating massive hematoma within the implant pocket. (A) Intraoperative findings reveal massive hematoma within the implant pocket. The explanted implant is shown in the (B), and the organized hematoma specimens are displayed in the (C).

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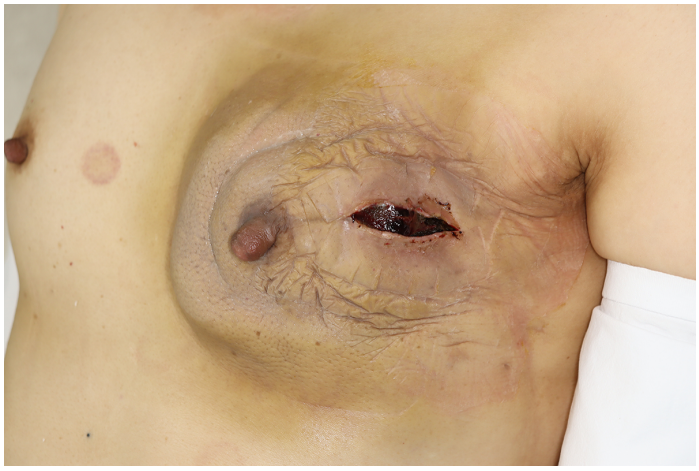

Figure 4. Postoperative day 5 photograph showing improvement in skin discoloration in Case 2. Evacuation of surgical hematoma led to the recovery of flap viability and improved skin tone.

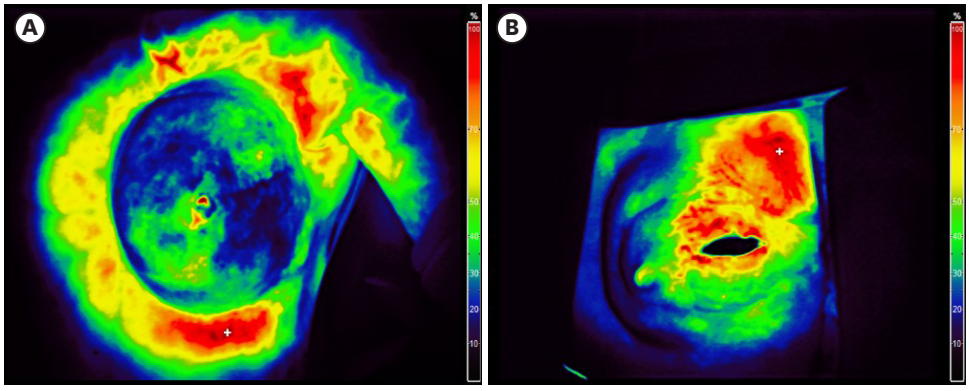

Figure 5. Indocyanine green angiography showing perfusion changes before and after the surgery in Case 2. (A) Preoperative ICG angiography showing markedly impaired circulation in the inferolateral and superomedial portions of the skin flap. (B) Postoperative ICG angiography showing improved perfusion following hematoma evacuation and implant removal.
ICG = indocyanine green.

The baseline platelet count before adjuvant T-DM1 administration was normal. During continued T-DM1 exposure, platelet levels demonstrated a chronic downward trend, frequently remaining below 100×10^9/L without full recovery. Delayed hemorrhagic presentation occurred in the setting of persistent thrombocytopenia during the ongoing T-DM1 therapy.

PMRT was administered to the left chest wall and regional lymphatics, including the supraclavicular field, according to the ESTRO/RTOG guidelines, axillary levels I–III, and internal mammary nodes at a total dose of 4,005 cGy in 15 fractions, beginning on POD 52.

The temporal association between progressive thrombocytopenia, clustered transfusion support, and delayed hemorrhagic complications during T-DM1 therapy is illustrated in **Figures 6** and **7**.

The key clinical characteristics, treatment timelines, platelet nadirs, and bleeding-related outcomes of the patients are summarized in **Table 1**.

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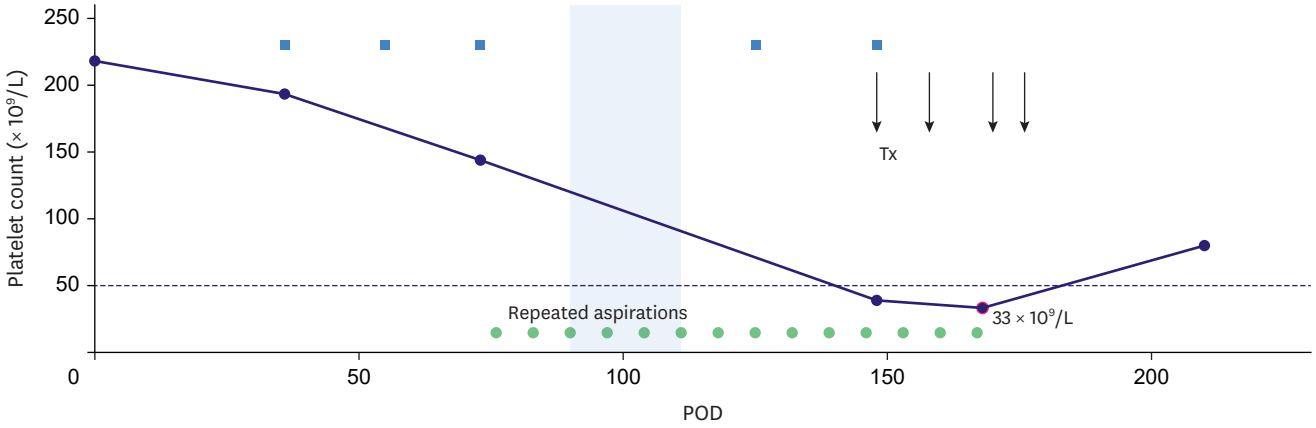

Figure 6. Temporal relationship between platelet nadirs, transfusion support, and delayed bleeding in Case 1. The timeline illustrates postoperative platelet trends in relation to T-DM1 administration and postmastectomy radiotherapy (shaded intervals). The platelet nadir of 33 × 10^9/L is annotated at the time of expander removal for persistent hematoma and skin compromise. Black arrows indicate clustered platelet transfusion support during periods of severe thrombocytopenia. The green dots along the lower margin represent repeated outpatient aspirations for seroma and liquefied hematoma, reflecting gradual and ongoing microbleeding rather than an acute hemorrhagic event. The dashed horizontal line indicates a platelet threshold of 50 × 10^9/L. Blue squares indicate T-DM1 administration cycles.
T-DM1 = ado-trastuzumab emtansine; POD = postoperative day.

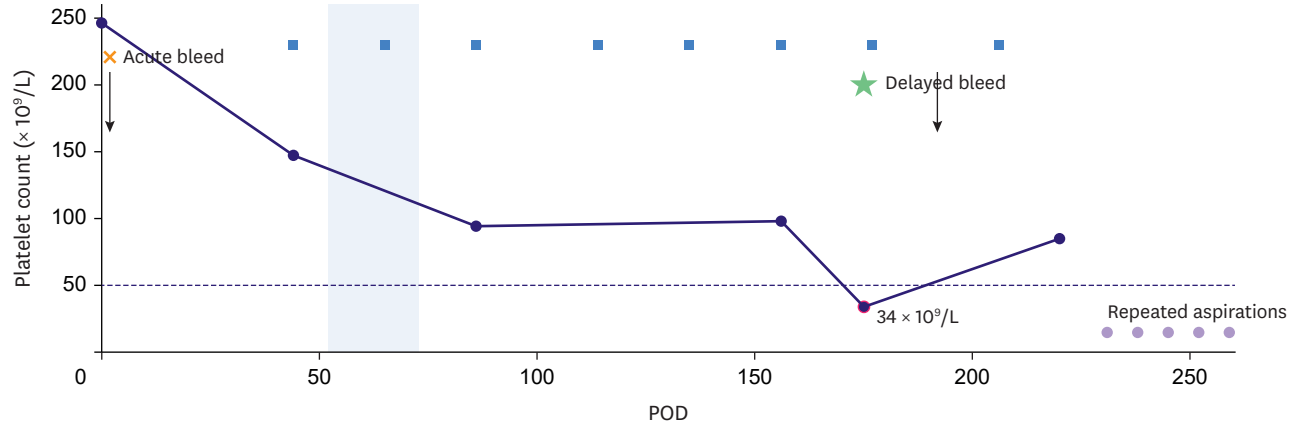

Figure 7. Distinction between early postoperative bleeding and delayed hemorrhage during ado-trastuzumab emtansine therapy in Case 2. The timeline demonstrates an acute postoperative bleeding event on POD 2 (X marker), occurring prior to the initiation of T-DM1 and requiring transfusion support (black arrow). A temporally distinct delayed hemorrhagic event (star) developed on POD 175 during ongoing T-DM1 therapy after postmastectomy radiotherapy, coinciding with a platelet nadir of 34 × 10^9/L. The purple dots indicate repeated outpatient aspirations for liquefied old hematoma in the late postoperative period. The dashed horizontal line denotes a platelet threshold of 50 × 10^9/L. The blue squares indicate T-DM1 administration cycles.
POD = postoperative day; T-DM1 = ado-trastuzumab emtansine.

DISCUSSION

The presented cases illustrate that bleeding complications in patients receiving adjuvant T-DM1 therapy may occur in a delayed and clinically unnoticeable manner and become evident only as secondary complications. In both patients, hematoma developed gradually without clear early warning signs.

In Case 1, postoperative infection was an important potential confounding factor that warrants careful consideration. Although the patient developed fever and erythema on POD 17, with *Corynebacterium* isolated from the drain culture, the infection resolved clinically and biochemically before T-DM1 initiation. C-reactive protein normalized from 73.1 to 0.5 mg/L, and a drain tip culture obtained immediately prior to T-DM1 initiation

https://doi.org/10.4048/jbc.2025.0278

Table 1. Clinical characteristics, treatment timeline, platelet nadirs, and bleeding-related outcomes in two patients receiving ado-trastuzumab emtansine after implant-based breast reconstruction

Variable	Case 1	Case 2
Age (yr)	49	56
Comorbidities	None	Hypertension, diabetes mellitus
Tumor stage	cT3N1M0 (stage IIIA)	cT2N2M0 (stage IIIA)
Neoadjuvant regimen	TCHP	TCHP
Reconstruction type	Prepectoral tissue expander + ADM	Prepectoral DTI + ADM
Surgery date	POD 0	POD 0
Baseline platelet count (× 10^9/L)	218	251
Adjuvant T-DM1 start (POD)	36	44
Postmastectomy radiotherapy (POD)	90–111	52–73
Platelet nadir (× 10^9/L)	33	34
Early postoperative bleeding	No	Yes (POD 2)
Delayed bleeding event (POD)	168	175
Transfusion support	Platelet transfusions ×4 during adjuvant T-DM1 therapy (total platelet concentrate 24 units, plateletpheresis 2 units) plateletpheresis ×2 prior to expander removal	Acute postoperative period (POD 2, pre–T-DM1): platelet concentrate 6 units + packed red blood cells 1,400 mL during re-exploration Delayed period during T-DM1 therapy: plateletpheresis ×2 prior to implant removal
Repeated aspirations	Yes	Yes
Definitive surgical intervention	Expander removal	Implant removal
Outcome	Resolved	Resolved

TCHP = docetaxel, carboplatin, trastuzumab, pertuzumab; ADM = acellular dermal matrix; DTI = direct-to-implant; POD = postoperative day; T-DM1 = ado-trastuzumab emtansine.

was negative. Additionally, baseline hematologic evaluation before T-DM1 showed normal coagulation parameters and platelet counts, with no clinical bleeding events. These findings suggest that persistent or subclinical infection alone is unlikely to account for subsequent recurrent seroma and liquefied hematoma formation observed during adjuvant therapy.

In both cases, platelet counts were within normal ranges prior to mastectomy and before T-DM1 initiation, indicating preserved baseline hemostasis. Progressive thrombocytopenia developed only after T-DM1 exposure with nadirs temporally corresponding to clinically significant delayed bleeding. In Case 1, platelet counts failed to fully recover despite the discontinuation of T-DM1 and improved only gradually after switching to trastuzumab, whereas in Case 2, platelet counts remained chronically suppressed throughout the prolonged T-DM1 therapy. These distinct recovery patterns further support the role of T-DM1-associated hematologic toxicity as a key permissive factor in delayed hemorrhage.

Although T-DM1-induced thrombocytopenia remains a plausible primary mechanism, other factors must be considered given the documented platelet nadirs in both cases. For instance, radiotherapy-induced vascular injuries can cause late-onset endothelial damage and increase vessel fragility [7,10]. Additionally, mechanical stress from early rehabilitation or patient activity can disrupt the fragile neovasculature in the healing breast pocket [9,11]. Importantly, insidious bleeding should not be considered a phenomenon unique to T-DM1. PMRT is independently associated with microvascular injury, endothelial dysfunction, and tissue fragility in reconstructed breasts. In our cases, the platelet counts were within normal limits in the immediate postoperative period and prior to T-DM1 initiation, suggesting preserved baseline hemostasis. Progressive thrombocytopenia developed only after T-DM1 exposure, followed by delayed hemorrhagic manifestations after PMRT. This temporal relationship supports a model in which radiation-induced vascular vulnerability is subsequently unmasked by T-DM1-associated thrombocytopenia, thus facilitating gradual and clinically inapparent bleeding, rather than *de novo* drug-specific hemorrhage.

https://doi.org/10.4048/jbc.2025.0278

In this context, the term "insidious" refers not to the absence of clinical signs but to the gradual evolution and delayed recognition of bleeding without an abrupt sentinel hemorrhage. These heterogeneous presentations underscore that delayed bleeding after IBBR may not follow a uniform clinical pattern, particularly when influenced by combined hematological suppression and radiation-related tissue vulnerability.

In Case 1, repeated aspirations for seroma and liquefied hematoma likely reflected ongoing microvascular bleeding. In Case 2, it was critical to distinguish between two temporally and mechanistically distinct bleeding events. Acute massive hemorrhage on POD 2 occurred prior to T-DM1 initiation and was attributable to a discrete surgical bleeding source, with complete clinical and radiological resolution confirmed during outpatient follow-up. In contrast, delayed hemorrhagic presentation on POD 175 occurred during ongoing T-DM1 therapy after radiotherapy and was accompanied by a marked platelet nadir, suggesting a separate, delayed process likely driven by combined hematologic suppression and radiation-induced vascular fragility rather than the persistence of the initial hematoma. Importantly, the platelet recovery patterns differed between cases. In Case 1, thrombocytopenia persisted despite the cessation of T-DM1 and improved only gradually after switching to trastuzumab, whereas in Case 2, platelet counts remained chronically suppressed throughout prolonged T-DM1 exposure. These observations suggest inter-individual variability in hematologic recovery and further support cautious perioperative decision-making in this population. Accordingly, we did not attribute the early postoperative bleeding events to T-DM1 exposure. Our findings suggest that T-DM1 may act as a potentiating factor for delayed hemorrhage when superimposed on prior surgical insults and radiation-related tissue vulnerability. Collectively, these findings support a multifactorial pathogenesis in which prior surgical complications, T-DM1-associated platelet suppression, radiation-related vascular fragility, and local mechanical stress may synergistically contribute to gradual and often-unnoticed hematoma formation, rather than a single causative mechanism.

Clinical implications include the need for perioperative coordination around expected platelet nadirs (T-DM1 nadir commonly appears on day 8 approximately) [12], preoperative and early postoperative platelet checks, meticulous hemostasis in ADM-assisted pockets, extended surveillance for late, subtle signs (increasing seroma outputs, recurrent collections initially appearing as seroma but later identified as liquefied hematoma), and structured patient education to encourage early exercise while on T-DM1. From a practical standpoint, both cases developed clinically significant delayed bleeding when platelet counts declined to approximately 30–40 × 10^9/L. Existing transfusion guidelines generally recommend maintaining platelet counts at above 50 × 10^9/L for invasive procedures, with higher thresholds suggested for surgeries involving irradiated or fragile tissues [5]. In this context, we propose that secondary reconstructive procedures in patients receiving T-DM1 be deferred until platelet counts are corrected to at least 70 × 10^9/L, with perioperative platelet transfusion considered when spontaneous recovery is unlikely. In addition, early postoperative upper-extremity exercise has been associated with increased seroma formation [11], which may serve as a surrogate for pocket shear stress and microbleeding [9]. Given the combined effects of T-DM1-associated thrombocytopenia and radiation-induced vascular fragility, we recommend cautious, staged rehabilitation and temporary avoidance of early aggressive arm exercises until platelet counts stabilize and early wound healing is achieved.

T-DM1 is an HER2-targeted antibody–drug conjugate known to cause bleeding-related adverse events; however, severe cases are uncommon [1-3]. Clinical trials have documented

https://doi.org/10.4048/jbc.2025.0278

higher rates of hemorrhagic events in patients receiving T-DM1 than in those receiving alternative HER2-targeted therapies. In the phase III EMILIA trial, the incidence of any-grade bleeding was 29.8% in the T-DM1 arm versus 15.8% in the lapatinib plus capecitabine arm, although rates of grade ≥ three bleeding events were low in both groups [1]. The KATHERINE trial reported a similar trend [13]. Case reports have described intracranial hemorrhage, hemorrhagic cystitis, and telangiectasia-related bleeding [14,15]. Mechanistically, T-DM1-induced thrombocytopenia results from the off-target uptake of the conjugate by megakaryocytes, leading to the disruption of microtubule networks by T-DM1 and impaired proplatelet formation [4]. Thrombocytopenia is the most common dose-limiting toxicity of T-DM1, and is directly associated with the risk of bleeding.

PMRT is linked to higher overall complication and reoperation rates after immediate reconstruction, reflecting the chronic effects of radiation on the skin and microvasculature [5,8]. Radiation-induced endothelial injury via oxidative stress, inflammation, and fibrosis provides a biological substrate for late microhemorrhages [10]. Several randomized and controlled studies have indicated that delaying shoulder exercise for approximately one week can reduce seroma formation (a proxy for pocket shear/microbleeding) without compromising function, thus supporting our recommendation for cautious, staged rehabilitation in T-DM1 recipients [9,11].

These cases underscore the fact that bleeding in patients receiving adjuvant T-DM1 therapy may be gradual, insidious, undetectable, or multifactorial. The combination of T-DM1-induced thrombocytopenia, radiation-related vascular fragility, and early postoperative activity may synergistically increase the risk of delayed hematoma formation.

Hence, surgeons should ensure the following:

- Maintain a heightened vigilance beyond the immediate postoperative period.
- Incorporate routine platelet monitoring and prophylactic measures in high-risk patients.
- Educate patients about the risks of early exercise and encourage cautious rehabilitation.
- Promptly evaluate subtle or prolonged postoperative fluid collection for possible ongoing bleeding.

By adopting these measures, surgeons and patients can better anticipate and mitigate the unique bleeding risks associated with T-DM1 therapy in breast reconstruction.

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