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Case Report

Middle meningeal artery embolization for symptomatic chronic subdural hematoma in the setting of severe transfusion-refractory thrombocytopenia: A case study and review of literature

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ABSTRACT

Background: Surgical decompression for the treatment of chronic subdural hematomas (cSDHs) is irrefutably effective; however, its utility in managing cSDH in patients with comorbid coagulopathy remains controversial. The optimal threshold for platelet transfusion in cSDH management is <100,000/mm³, according to guidelines from the American Association of Blood Banks GRADE framework. This threshold may be unachievable in refractory thrombocytopenia, though surgical intervention may still be warranted. We present a patient with symptomatic cSDH and transfusion-refractory thrombocytopenia successfully treated with middle meningeal artery embolization (eMMA). We also review the literature to identify management approaches for cSDH with severe thrombocytopenia.

Case Description: A 74-year-old male with acute myeloid leukemia presented to the emergency department with persistent headache and emesis following fall without head trauma. Computed tomography (CT) revealed a 12 mm right-sided, mixed density SDH. Platelets were <2000/mm³ initially, which stabilized to 20,000 following platelet transfusions. He then underwent right eMMA without surgical evacuation. He received intermittent platelet transfusions with platelet goal >20,000 and was discharged on hospital day 24 with resolving SDH on CT.

Conclusion: High-risk surgical patients with refractory thrombocytopenia and symptomatic cSDH may be successfully treated with eMMA without surgical evacuation. A platelet goal of 20,000/mm³ before and following surgical intervention proved beneficial for our patient. Similarly, a literature review of seven cases of cSDH with comorbid thrombocytopenia revealed five patients undergoing surgical evacuation following initial medical management. Three cases reported a platelet goal of 20,000. All seven cases resulted in stable or resolving SDH with platelets >20,000 at discharge.

Keywords: Chronic subdural hematoma, Middle meningeal artery embolization, Platelet goal, Platelet transfusion, Thrombocytopenia

INTRODUCTION

Chronic subdural hematoma (cSDH) is a common complication of acute myeloid leukemia (AML).^[20] The incidence of cSDH is estimated to be 1.7–20.6 patients/100,000 patients/year

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and commonly presents with cognitive and behavioral symptoms.^[3,30,35] The most common treatment for cSDH for patients is surgical drainage with burr hole trephination, craniotomy, and decompressive craniectomy.^[6] However, 5–30% of cases will experience recurrence of their hematoma,^[7] and one of the factors that increase the risk of recurrence is comorbid coagulopathy, such as in patients with leukemia.^[23]

Treatments for acute myeloid leukemia (AML) like chemotherapy and hypomethylating agents put patients at increased risk for thrombocytopenia and intracranial hemorrhage,^[15] and, the mainstay of treatment for thrombocytopenia continues to be platelet transfusions.^[11] Increased risk for spontaneous bleeding occurs with platelet counts <20,000/µL, and a threshold platelet count of >10,000/ µL is recommended for prophylactic platelet transfusion in patients receiving therapy for hematologic malignancies.^[26,36] Higher platelet counts of >20,000/µL are recommended in the setting of hemorrhage as well as in settings of expectant invasive procedures.[36] Threshold platelet counts 40-50,000/µL are recommended before performing any major invasive procedure and platelet counts >100,000/µL before neurosurgery.^[36] According to the World Health Organization, nonfatal cerebral bleeding with neurological signs and symptoms is considered Grade 4 bleeding with a recommended maintenance platelet goal of 100,000/µL.[11] However, there are limited evidence-based

recommendations in cases of transfusion-refractory thrombocytopenia and case reports have shown patient survival at much lower platelet levels.^[2,11,43]

Middle meningeal artery embolization (eMMA) for cSDH is an emerging treatment modality.^[9,19,21,27,28,33,38] The efficacy of eMMA is centered around the theory that cSDHs are, in part, caused by repeated membranous vessel rupture that is supplied by the MMA, so eMMA works by devascularizing these ruptured membranes.^[13] It decreases the likelihood of hematoma recurrence and can be used as the sole treatment for patients with high surgical risk. In a recent meta-analysis of nine case series, Srivatsan et al. demonstrated a robust effect of eMMA as a sole therapy or as an adjunct to prevent rebleeding with eMMA having significantly lower rates of hematoma recurrence compared to the conventional surgery group (2.1% vs. 27.7%; P < 0.001).^[39] Moreover, this meta-analysis found the procedural complication rates to be similar between eMMA and conventional surgery (2.1% vs. 4.4%; P = 0.497).^[39] Two of the largest case series using eMMA for the management of cSDH (Link et al.[28] and Ban et al.^[4]) found no complications related to eMMA. In addition, a recent meta-analysis of 54,083 cerebral angiography cases found a procedural complication rate of 3.60%.^[16] These complications include transient ischemic attack, ischemic stroke, contrast-induced nephropathy, and contrast-induced allergic reaction.^[16,32,37] Several large prospective randomized trials are underway investigating

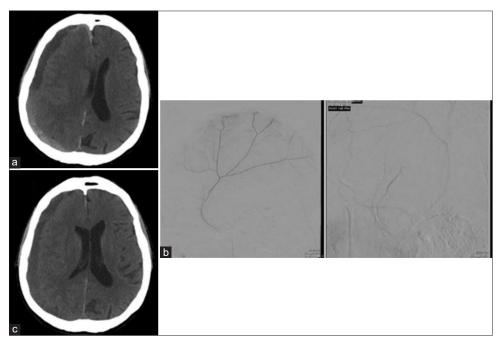


Figure 1: Evolution of subdural hematoma (SDH) from presentation to 45 days later via head computed tomography (CT). (a) Head CT at initial presentation revealed a right-sided, mixed density 12 mm SDH with 12 mm midline shift to the left. (b) Cerebral angiogram visualizing middle meningeal artery. (c) Repeat head CT on hospital day 17 showing stable right SDH with resolving midline shift (5 mm to left).

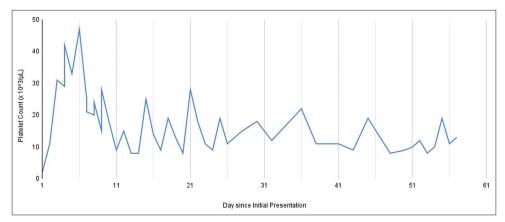


Figure 2: Graphical depiction of patient's platelet counts following initial presentation. The patient's platelet count ranged from <2000/mm³ at initial presentation up to 48,000 5 days after presentation following multiple platelet transfusions. He underwent eMMA 7 days after presentation with platelet count of 20,000. He was discharged on 23 days after presentation and received outpatient platelet transfusions 3 times a week with a platelet goal of 20,000. His average platelet count was 14,000.

patient selection and the combination of surgery and embolization. $^{\left[8,13\right] }$

To the best of our knowledge, there has been no report of a patient with AML, symptomatic cSDH, and transfusionrefractory thrombocytopenia treated with eMMA. We present a case of improving chronic SDH in the setting of AML-related thrombocytopenia by eMMA without surgical evacuation. We also performed a systematic review of the literature to identify management strategies for cSDH with severe thrombocytopenia.

CASE PRESENTATION

A 74-year-old man with a history of AML presented to the emergency department (ED) for a complaint of nonresolving throbbing headache with nausea and vomiting after a witnessed fall without head trauma. He was on his second cycle of therapy with venetoclax and a hypomethylating agent.

At presentation to the ED, he had left upper extremity and left lower extremity drift with 4/5 left upper and lower extremity weakness, and scattered ecchymoses with a petechial rash. Laboratory studies were significant for severe thrombocytopenia of <2000/ μ L in the ED. Computed tomography of the head (hCT) revealed a right sided, mixed density 12 mm SDH with a 12 mm leftward midline shift and patchy acute subarachnoid hemorrhages [Figure 1a]. The patient received an initial infusion of 2 units of platelets with an increase to 11,000/ μ L. Neurosurgery was consulted and patient was subsequently admitted to the intensive care unit (ICU) with a platelet goal of 100,000/ μ L. Patient received regular platelet transfusions; however, platelet levels remained <50,000/ μ L [Table 1]. Given his refractory thrombocytopenia, neurologically intact status,

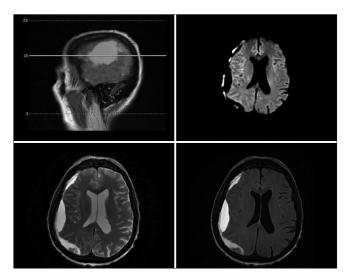


Figure 3: Head magnetic resonance imaging 54 days after initial presentation of subdural hematoma (SDH). Sagittal and axial views of the right-sided hyperintense with patchy hypointense areas consistent with acute on chronic SDH.

and stable SDH on repeat hCT; conservative management was chosen over neurosurgical intervention. On hospital day 4, he was transferred out of the ICU and liberalized to a platelet goal of $50,000/\mu$ L and transfusion threshold of $40,000/\mu$ L. After receiving a total of 17 units of platelets, the patient underwent right eMMA with 150 µm of polyvinyl alcohol particles on hospital day 8 [Figure 1b]. Repeat hCT on hospital day 17 demonstrated a decreasing SDH [Figure 1c]. Patient received an additional 6 units of platelets for refractory thrombocytopenia, a course of levetiracetam for seizure prophylaxis and was discharged 24 days after admission with a platelet count of 19,200/µL. Discharge plans included a systolic blood pressure goal of <140 mmHg

Hospital day	Platelet count (×10 ³ /µL)	Units of platelets transfused	Comments			
l	<2	2	Initial head CT with 12 mm R SDH and 12 mm R to L midline shift; admitted to ICU			
2 (AM)	11		Platelet goal 100,000/µL			
2 (PM)	24	1	Repeat head CT with stable R SDH			
3 (AM)	28	2	Levetiracetam started			
3 (PM)	31	2				
4 (AM)	29	2	Repeat head CT with 10 mm R SDH and 8 mm R to L midline shift. Platelet goal >50,000/µL			
4 (PM)	42		Transferred out of ICU			
5	33	2				
6	47	2				
7 (AM)	25	1				
7 (PM)	21	1				
8 (AM)	20	1				
8 (PM)	24	1	R MMA embolization with 150 μ m of PVA			
9 (AM)	15	1				
9 (PM)	28					
10	18					
11	9	2				
12	15					
13	8	2				
14	8	2				
15	25					
16	14					
17	9	2	Repeat head CT with 12 mm R SDH and 5 mm R to L midline shift. IV dexamethasone and IVIG started.			
18	19					
19	13					
20	8	2				
21	28					
22	18					
23	11	2	Underwent bone marrow biopsy			
24	9	2				
25	19		Discharged with home health			

CT: Computed tomography, SDH: Subdural hematoma, ICU: Intensive care unit, PVA: Polyvinyl alcohol, IV: Intravenous, IG: Immunoglobulins, L: Left, R: Right, mm: Millimeter, MMA: Middle meningeal artery

and a platelet count goal >10,000/ μ L. He continued to have platelet transfusions 3 times a week with an average platelet count of 14,000/ μ L [Figure 2]. A hCT 30 days after discharge demonstrated a stable, panhemispheric acute on chronic SDH that was 15 mm in size with a 5 mm leftward midline shift [Figure 3].

Fifty days after his initial presentation, the patient was readmitted for acute kidney injury secondary to severe tumor lysis syndrome, acute colitis, acute left pyelonephritis, anemia with hemoglobin of 7.8 g/dL, and thrombocytopenia with platelet count of 9000/ μ L. On hospital day 2, hCT showed a grossly stable SDH. He was considered a poor candidate for hemodialysis due to AML, discharged to hospice on hospital day 7, and passed 4 days later.

Systematic review

The optimal management of cSDHs in patients with concurrent thrombocytopenia remains obscure. In this review, we sought to find case reports or series similar to our patient to identify management strategies and treatment efficacy for cSDH with severe thrombocytopenia currently documented in the literature.

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) reporting guideline were implemented for this review. A systematic search of PubMed and Web of Science data was conducted on October 13, 2021. The following search terms were utilized: *thrombocytopenia* OR *pancytopenia; subdural; hematoma* OR *hemorrhage* OR *bleed**. Inclusion criteria required detection of isodense or

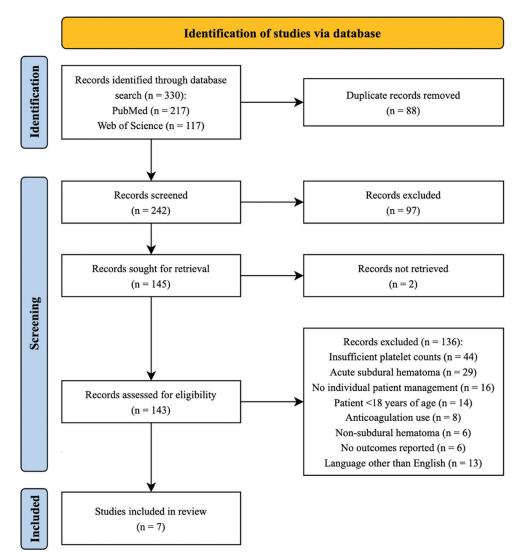


Figure 4: Preferred reporting items for systematic reviews and meta-analyses flow chart of systematic review conducted in October 2021. A total of 242 unique records were identified using PubMed and Web of Science databases. Initial title and abstract screening excluded 97 articles. Full-text screening found seven articles meeting inclusion criteria, n: Number.

hypodense areas in the subdural space on CT and report of individual patient data on platelet counts at intracranial cSDH confirmation, management of cSDH, platelet count following management, and outcome. Patients <18 years old and patients taking anticoagulants before cSDH presentation were excluded from the study. Reviews, editorials, and non-English articles were also excluded from the study. Two independent authors assessed the articles for inclusion and exclusion criteria.

Individual patient data on the following were collected: age, sex, risk factors/etiology of thrombocytopenia, location of SDH, size of SDH, presence of midline shift, platelet counts at the time of SDH confirmation and after management, management of SDH and thrombocytopenia, platelet goal for management, complications, recurrence of SDH, and outcome at last follow-up. These data were collected by one author and reviewed by another author.

Seven out of 242 studies met inclusion criteria.^[2,17,24,25,29,40,43] The PRISMA flow chart for the search strategy is depicted in [Figure 4]. There was a total of seven patients whose data were extracted. A summary of these data is shown in [Tables 2 and 3]. The most common etiology of thrombocytopenia was immune thrombocytopenic purpura (ITP; 71.4%). Other etiologies included human immunodeficiency virus (14.3%) and acute lymphoblastic leukemia (ALL) (14.3%). Location of SDH was in the frontoparietal region in 4 patients (57.1%), frontotemporal in 1 (14.3%), and hemispheric in 2 (28.6%). Four patients

Patient number	Title	Author(s)	Year	Age	Sex	Risk factors/ Etiology	Location of SDH	Size of SDH	Midline shift
1	Emergency Surgical Intervention to Treat a Wide Septated Subdural Hematoma in a Patient with ITP: A Case Report. ^[2]	Asan, Z; Kilitci, A	2019	54	F	ITP	L frontoparietal	60 mm	R 20 mm
2	Successful treatment of idiopathic thrombocytopenic purpura by Chinese herbal medicine EK-49 and ascorbic acid in an elderly patient developing chronic subdural hematoma. ^[17]	Hirano, A; Ueoka, H	2007	88	F	ITP	R hemispheric	NR	NR
3	Conservative Treatment of Chronic Subdural Hematoma in HIV-Associated Thrombocytopenia with Tranexamic Acid. ^[25]	Kutty RK; Peethambaran AK; Sunilkumar; Anilkumar M	2017	42	F	HIV	L frontotemporal parietal	8.5 mm	R 12 mn
4	Bilateral subdural hemorrhage as a serious adverse event of dasatinib in a patient with Philadelphia chromosome-positive acute lymphoblastic leukemia. ^[43]	Yhim HY; Kim HS; Lee NR; Song EK; Kwak JY; Yim CY	2012	58	F	Ph(+) ALL w/imatinib and dastinib therapy	L frontoparietal and R frontal	NR	NR
5	Subdural hematoma secondary to immune thrombocytopenic purpura: case report. ^[24]	Kolluri VR; Reddy DR; Reddy PK; Naidu MR; Kumari CS	1986	18	М	ITP	R hemispheric	NR	NR
6	Spontaneous subdural hematoma in the setting of immune thrombocytopenia complicated by ischemic infarcts. ^[29]	Mathews MS; Yu W; Chappell ET	2007	38	F	ITP	R frontoparietal	11 mm	L 8 mm
7	Therapeutic Suggestions for Chronic Subdural Hematoma Associated with Idiopathic Thrombocytopenic Purpura: A Case Report and Literature Review. ^[40]	Takase H; Tatezuki J; Ikegaya N; Yamamoto D; Hashimoto M; Takagi M; Mochimatsu Y; Kawahara N	2015	66	F	ITP	L frontoparietal	NR	R

cSDH: Chronic subdural hematoma, SDH: Subdural hematoma, ITP: Immune thrombocytopenic purpura, HIV: Human immunodeficiency virus, Ph(+) ALL: Philadelphia positive acute lymphoblastic leukemia, L: Left, R: Right, NR: Not reported, mm: Millimeter

also had a midline shift on imaging (57.1%), with the majority having a shift to the right (75%). All seven patients had severe thrombocytopenia with a platelet count <5000/ μ L at cSDH discovery. Five patients received medical management followed by surgical evacuation (71.4%), while one patient was managed conservatively (14.3%). Surgical evacuation included partial craniotomy (1; 20%) and craniotomy evacuation (4; 80%). Three cases reported a platelet goal of 2000/ μ L for management (42.9%). The final

platelet counts were all above $20,000/\mu$ L, and all cSDHs were stable or completely resolved following treatment.

DISCUSSION

Previous studies on safe platelet ranges for surgical management of SDHs focused on platelet transfusions for achieving platelet goals.^[1,11,12] However, a small subset of patients remains thrombocytopenic despite platelet

Patient number	PC at confirmed SDH	Initial management	PC after initial management	Other management	Platelet goal	Complications	Recurrence	Outcome
1	5	IV methylprednisolone, IVIG, L frontoparietal craniotomy	18	Levetiracetam	20	Recurrence	Yes	Resolution
2	5	Prednisolone (50 mg/day) + azathioprine (50 mg/day)	20	Methylprednisolone, Chinese herbal medicine EK-49 + ascorbic acid	20	Severe thrombocytopenia on readmission; bronchopneumonia	No	Resolution
3	17	Platelet transfusion, HAART, TXA and mannitol	68	Twist drill craniostomy and evacuation under local anesthesia, 6 week course of TXA + HAART	NR	Intraoperative seizure	No	Resolution
4	42	Discontinued dasatinib + trephination of L parietal bone	38	Intermittent platelet infusions	>20	Recurrence	Yes	Improved headache
5	30	Surgical evacuation under local anesthesia + perioperative platelet transfusions	Normal	Steroids	NR	None	No	Resolution
6	7	Platelets, FFP, packed RBCs, steroids, IVIG, mannitol	205	Bedside twist drill drainage and subsequent burr hole evacuation after worsening neurological symptoms	NR	Expansion of SDH; R PCA infarct 5 days following burr hole	No	Resolution except L homonymous hemianopia
7	3	15 units of platelets and IV prednisolone, IVIG	210	NA	NR	None	No	Resolution

Platelet level=*n*/mm³. cSDH: Chronic subdural hematoma, PC: Platelet count, IV: intravenous, IVIG: Intravenous immunoglobulins, HAART: Highly active antiretroviral therapy, TXA: Tranexamic acid, FFP: Fresh frozen plasma, RBCs: Red blood cells, PCA: Posterior cerebral artery, L: Left, R: Right, NR: Not reported, NA: Not applicable, mg: Milligram

transfusions. There is limited knowledge on contingent management options for these patients. This case report demonstrated the usefulness of eMMA as a minimally invasive treatment for cSDH in the setting of refractory thrombocytopenia. Each of the seven patients reported in this systematic review had final platelet counts >20,000/ μ L, and all cSDHs were stable or completely resolved following medical or surgical treatment. While current guidelines suggest a platelet count >100,000/ μ L before performing neurosurgery (level 1C evidence), there are no current platelet thresholds for patients needing surgery complicated by platelet refractoriness.^[11,22,34] The medical and surgical management varied widely among cases. Complications varied with two of the seven cases (Patient 1 and 4) having recurrence of the SDH after treatment. Patient 1 was diagnosed with concurrent ITP with the left-sided SDH and underwent left frontoparietal craniotomy with IV methylprednisolone and IVIG. Patient 4 had philadelphia chromosome positive ALL with bilateral SDH while receiving imatinib and dasatinib therapy and underwent trephination. Thrombocytopenia induced by hematologic disorders, such as ITP and ALL predisposed these patients to higher risk of recurrence after initial surgical management for SDH. Circulating autoantibodies due to the ITP present in Patient 1 led to a diminished recovery rate in endogenous platelet counts. ALL is known to lead to marrow failure contributing to decreased platelet count, making it difficult to recover adequate platelet numbers to prevent recurrent bleeding. This is the first report of eMMA for stabilization of cSDH without recurrence in the setting of refractory thrombocytopenia.

Once thought to be due to a singular event, the central pathology of SDHs is now being recognized as a cerebrovascular event with a cycle of hemorrhage, fibrosis, and angiogenesis.^[5] While the shearing of bridging veins may remain an inciting factor to the formation of a SDH, it is the inflammatory response to the extravasation of blood into the subdural space that accounts for the chronic and remittent nature of the hemorrhage.^[5] Mild head injury causes an insidious bleed that activates fibroblasts to migrate toward the site of the clot.^[10,18] Once activated, these fibroblasts initiate fibrosis and neovascularization through the release of vascular endothelial growth factor and other proinflammatory signaling molecules.[5,10,18] These newly formed vessels are frail and prone to rebleeding, causing the cycle to repeat. While resorption of extravasated fluid may initially be maintained, eventually the rate of hemorrhage overwhelms the rate of resorption leading to increased intracranial pressure and focal neurological deficits.^[5,10,18]

The MMA is believed to supply the outer membrane of a SDH,^[41,42] and a more recent study by Mureb *et al.* proposed that the MMA contributes to not only the outer membrane but the entire hematoma complex.^[31] Therefore, eMMA is proposed to occlude the distal branches of the MMA decreasing the neovascularization of the hematoma. This is thought to prevent fluid leakage and shift the balance back toward resorption.^[14]

Although the exact mechanism of eMMA remains unclear, our findings support its use in populations with persistent refractory thrombocytopenia to prevent further bleeding. In this case, the patient's cSDH was stable enough to be managed outside the hospital, so he spent his last moments with his loved ones as per his advanced directive. The overall treatment benefit among patients with substantial disease burden should also be emphasized in the management of cSDH.

CONCLUSION

Our case has shown the success of eMMA without surgical evacuation in successfully treating symptomatic cSDH in a high-risk surgical patient with refractory thrombocytopenia. Based on this case and a systematic review of seven cases of cSDH with comorbid thrombocytopenia, a platelet goal of 20,000/mm³ prior to any surgical intervention may be sufficient and more attainable than current platelet goals of

40,000-50,000/mm³. Though all patients included in this review had stable or resolving cSDH, further investigations are required to determine the utility of lowering the platelet threshold prior to neurosurgical intervention.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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