

Rehabilitation in the Setting of Untreated Cancer-Associated Acute Deep Vein Thrombosis

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Abstract

Objective: Research is needed to guide the timing and safety of rehabilitation (physical and occupational therapy) in patients with acute deep venous thrombosis (DVT) that is untreated due to contraindications. **Case Description:** A 21-year-old man with Hodgkin lymphoma was admitted to the hospital for neutropenic fever. He developed gastrointestinal bleeding, diffuse alveolar hemorrhage, and bilateral lower-extremity DVT. He was not a candidate for chemical anticoagulation or placement of an inferior vena cava filter owing to thrombocytopenia. Rehabilitation was initially deferred because of concern that the thrombus could travel to the lungs, causing a pulmonary embolism. Rehabilitation was, however, started 4 days after the initial diagnosis of lower-extremity DVT to assess functional mobility and activities of daily living skills to prepare for discharge from the hospital. **Results:** The patient experienced no bleeding events during rehabilitation, and his acute, untreated DVT did not propagate based on clinical assessment. His Activity Measure for Post-Acute Care (AM-PAC) “6 Clicks” Basic Mobility score improved from 30.25 to 35.55 over the period of 11 days while he received rehabilitation. **Conclusion:** Despite having an acute bilateral lower-extremity DVT that was untreatable owing to thrombocytopenia, the patient successfully participated in rehabilitation and improved his physical functional status without an adverse event. Untreated acute venous thromboembolism in the setting of recent history of major bleeding raise concerns about physical activity restrictions. It is critical to consider both the risks and benefits of mobilizing patients and prescribing exercises in patients with these conditions.

Keywords

venous thrombosis, exercise, early ambulation, rehabilitation

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Background and Purpose

Patients with cancer are at risk for both thrombosis and hemorrhage.¹ Thrombosis is a significant source of morbidity and mortality and cancer increases the risk of venous thromboembolism (VTE) 4- to sevenfold.¹ Unfortunately, in the United States, it is estimated that VTE may be responsible for 100 000 deaths each year.² VTE, which encompasses deep venous thrombosis (DVT) and pulmonary embolism (PE), is treatable with oral or parenteral anticoagulation, inferior vena cava (IVC) filter placement, and/or thrombolytic therapy.³ In patients with cancer, thrombocytopenia caused by the disease itself and/or its treatment is common⁴ and makes treating VTE challenging, especially in patients who have experienced recent major bleeding complications. Furthermore, both recent history of major bleeding and acute untreated DVT raise concerns about the safety of physical activity and exercise.

Some evidence supports early ambulation rather than bed rest for patients with VTE that are being treated.^{5–8} In patients with thrombocytopenia, multiple rehabilitation guidelines exist to direct types of physical activity and exercises depending on the level of thrombocytopenia.^{9,10} However, no consensus guideline exists to inform clinicians about physical activity recommendations for patients with acute VTE and thrombocytopenia, when treatment options for VTE may be limited. Here, we present a case in which a patient with acute bilateral lower-extremity DVT was deemed ineligible for pharmacologic or procedural

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interventions due to thrombocytopenia and major bleeding complications. Rehabilitation efforts were initially deferred to prevent potential PE. They were ultimately restarted, and no subsequent complications were noted during the patient's rehabilitation course despite his untreated acute DVT.

Case Description

The patient, a 21-year old man with stage IV Hodgkin lymphoma, adrenal insufficiency, gastric ulcerative disease, and history of cerebellar and occipital infarction, was admitted for neutropenic fever. His hospital course was complicated by an episode of gastrointestinal bleeding and diffuse alveolar hemorrhage in the setting of thrombocytopenia. He was also found to also have bilateral lower-extremity DVT.

The patient had initially presented to his local physician 1 year prior to the index presentation with recurrent episodes of fever and cough. Bone marrow biopsy demonstrated hypercellular marrow, increased eosinophils mixed with plasma cells, lymphocytes, and marrow fibrosis. At that time, hydrocortisone and dexamethasone with hydroxyurea were initiated for the treatment of hypereosinophilic syndrome. Three months later, he presented to the emergency department with abdominal pain. Esophagogastroduodenoscopy demonstrated gastric ulcerative disease, and he was started on sucralfate at that time.

During the index admission with neutropenic fever, the patient suffered hematemesis resulting in hypovolemic shock necessitating intensive care unit admission and frequent transfusions to treat coagulopathy. At this time, esophagogastroduodenoscopy revealed lower curvature deep ulcerations as well as smaller ulcers. The larger ulcers were clipped, and the patient also underwent empiric embolization of the left gastric artery by the interventional radiology service. He was subsequently noted to have frank rectal bleeding and underwent additional embolization. While in the intensive care unit, he was briefly intubated for diffuse alveolar hemorrhage.

These bleeding episodes ultimately resolved with the administration of vitamin K, aminocaproic acid, intravenous pantoprazole, and numerous blood products. Upon transfer to the medical floor, bilateral lower-extremity edema was noted, and Doppler ultrasound showed new bilateral DVT within the left mid femoral, left posterior tibial, right common femoral, right posterior tibial, and peroneal veins. A core posterior mediastinal biopsy demonstrated a mixed lymphohistiocytic infiltrate suggestive of classic Hodgkin lymphoma.

Consequent to these findings, physical and occupational therapies were temporarily stopped owing to concern that a thrombus could move to the pulmonary artery, resulting in a potentially fatal PE. The benign hematology service advised deferring initiation of chemical anticoagulation in light of the patient's ongoing thrombocytopenia and clinical risk for

recurrent bleeding episodes. While it was deemed that placement of an IVC filter would attenuate the patient's risk of PE and allow him to initiate physical and occupational therapies, the patient was not a candidate for IVC filter placement due to his history of recent gastrointestinal bleeding and thrombocytopenia. The following transfusion parameters were used: transfuse if hemoglobin is <7.5 g/dL (or if symptomatic) and if platelets are <50 K/ μ L (due to plans for inferior vena cava filter placement).

The physical medicine and rehabilitation service was consulted by the oncology team to assist in a formal evaluation of the patient's candidacy for acute inpatient rehabilitation. The physical examination was notable for bilateral upper- and lower-extremity muscular atrophy and bilateral lower-extremity edema. On manual muscle strength testing, he had right upper extremity: 3/5 throughout; left upper extremity: 4/5 throughout, with the exception of 3-/5 for shoulder abduction; bilateral hip flexors: 3-/5; bilateral knee flexors: 3/5; right knee extensors: 3-/5; left knee extensors: 4/5; bilateral ankle dorsiflexors: 3/5; and bilateral plantar flexors: 5/5. Functional independence measure (FIM), which has been shown to be reliable across a wide variety of settings and raters,¹¹ noted that the patient required total assistance for activities of daily living and for ambulation of 80 feet. Upon discussion, the patient and his mother voiced their preference for outpatient rehabilitation services upon discharge. In order to be safe for hospital discharge, the patient needed to reach a goal of minimal assistance level on the FIM for bed mobility, transfers, basic activities of daily living, and household ambulation of 50 feet. The focus was on therapeutic exercises (including strengthening exercises) and basic activities of daily living. He did not have any stairs at home to negotiate and thus steps training was not included. It is routine for the physical and occupational therapist to review the following as part of the treatment sessions: vital signs and patient-reported symptoms such as pain, fatigue, and dyspnea level on a numeric rating scale from 0-10.

Ethics Approval

The patient provided written consent for publication of the case study and a copy of the consent is held within the institutional records.

Outcomes

Rehabilitation was resumed to help the patient reach his functional goal of discharge to home with family. The Table 1 outlines the patient's rehabilitation course and progress along with relevant clinical characteristics including hemoglobin, platelet, and international normalized ratio. Post-transfusion platelet counts were not measured and were not relevant since exercise restrictions would

Table 1. Clinical Characteristics and Physical Activity Scores of a Patient with Untreated Deep Venous Thrombosis (DVT).

Day	AM-PAC “6-Clicks” Basic Mobility Score	AM-PAC “6-Clicks” Daily Activity Score	Platelets ^a (K/ μ L)	INR ^b	Hemoglobin ^c (g/dL)	Transfusions ^d
1 ^e	No physical therapy due to procedure	No rehabilitation due to procedure	31	1.36	8.1	1 U platelets
2	No physical therapy due to DVT	No occupational therapy due to DVT	42	1.35	8.4	1 U platelets
3	No physical therapy on weekend	No occupational therapy on weekend	39	1.41	7.8	1 U platelets
4	No physical therapy on weekend	No occupational therapy on weekend	38	1.43	7.5	1 U platelets 1 U PRBCs
5	30.25	No occupational therapy due to DVT	37	1.37	8.4	1 U platelets
6	25.80	No occupational therapy due to DVT	35	1.33	8.3	1 U platelets
7	25.80	No occupational therapy due to DVT	32	1.24	8.1	2 U platelets
8	No physical therapy; patient was busy with another provider	17.07	60	1.33	8.1	-
9	25.80	No occupational therapy due to procedure	46	1.24	8.1	1 U platelets
10	No physical therapy on weekend	No occupational therapy on weekend	45	1.31	7.2	1 U PRBCs
11	No physical therapy on weekend	No occupational therapy on weekend	52	1.25	8.0	-
12	33.99	No AM-PAC score was assessed	63	1.34	7.8	-
13	33.99	No occupational therapy	90	1.37	7.8	-
14	33.99	No occupational therapy	120	1.30	7.5	-
15 ^f	35.55	25.33	152	1.33	7.6	-

Abbreviations: AM-PAC, Activity Measure for Post-Acute Care; INR, international normalized ratio; PRBCs, packed red blood cells; U, unit.

^a Reference range: 140–440 K/ μ L.

^b Reference range: 0.90–1.10.

^c Reference range: 14.0–18.0 g/dL.

^dThe following transfusion parameters were used: transfuse if hemoglobin is < 7.5 g/dL (or if symptomatic) and if platelets are < 50 K/ μ L (due to plans for inferior vena cava filter placement).

^eBilateral lower extremity DVT diagnosed.

^fApixaban started because the platelet level had improved.

only be applicable if platelet count was <20 000 cells/ μ L.¹⁰ His Activity Measure for Post-Acute Care “6 Clicks” Basic Mobility score¹² improved from 30.25 (limited movement) to 35.55 (limited mobility indoors) over the period of 11 days while he received rehabilitation. Ultimately, following the improvement of his thrombocytopenia, it was recommended that the patient begin apixaban 5 mg orally twice daily and undergo repeat esophagogastroduodenoscopy in 8 to 12 weeks to confirm healing of his ulcers. The patient was started on anticoagulation the day before discharge. We coordinated and provided prescriptions for external outpatient physical and occupational rehabilitation and for follow-up with our Physical Medicine and Rehabilitation clinic.

Discussion

Rehabilitation is critical for identifying the overall functional goals, disposition needs, and mobility safety concerns of patients with cancer. Because cancer rehabilitation

involves comprehensive evaluations of medical status, mobility, performance of activities of daily living, need for durable medical equipment, and family training, daily assessment over time is essential. An individual patient’s rehabilitation program should account for the type of cancer and the involved structures and should aim to prevent functional decline and the sequelae of immobility.⁹ The consequences of immobility, including muscle atrophy, accelerated bone loss, skin breakdown, and poor cardiovascular endurance, coupled with cancer related frailty and fatigue, are significant and can lead to poor functional outcomes.¹³

This case demonstrates an interesting confluence of factors involving multiple and simultaneous cancer-associated medical complications—acute thrombosis, thrombocytopenia, and major bleeding events—that resulted in a dilemma for the safe timing of physical and occupational rehabilitation. Specifically, the patient was ineligible for immediate pharmacologic or procedural intervention for his acute bilateral lower-extremity DVT because of concurrent thrombocytopenia and recent major bleeding.

Recommendations regarding physical activity and exercise in this setting are not well established. Such situations are particularly common in patients with cancer, in whom thrombocytopenia is often coupled with a hypercoagulable state.¹⁴

Broadly, clinical decisions are based upon an intrinsic risk-benefit analysis; here, the primary considerations were the risk of bleeding with anticoagulation therapy or IVC filter placement versus the potential mobilization of an existing thrombus resulting in a fatal PE.³ Active cancer, particularly in the first 3 months following cancer diagnosis and in patients with metastatic disease, is a major risk factor for VTE.^{1,15} Additionally, a history of prior VTE is one of the strongest risk factors for VTE, even in patients being treated with anticoagulation therapy.¹⁵ Concern for a fatal PE from dislodgment of thrombi originating from deep veins of the lower extremities—particularly the iliac, femoral, and popliteal veins—is significant.¹⁵ It is estimated that lower extremity central DVTs can cause PE 15% to 32% of the time due to embolization.¹⁶ Along with the risk-benefit analysis regarding overall bleeding risk versus potential development of fatal PE, clinicians should weigh important considerations regarding mobility management. Although not evidenced-based, strict bed rest has been considered the cornerstone for management for DVT.⁷ A meta-analysis found that early ambulation of patients with acute DVT with anticoagulation was not associated with a higher incidence of progression of DVT, new PE, or death.⁷ No robust criteria exist for determining a mobilization timeframe following VTE events,¹⁷ in the setting of untreated VTE in a patient with cancer-associated thrombosis and thrombocytopenia. Similarly, although methods are available to assist with bleeding risk assessment before initiating anticoagulation, no formal risk stratification regarding mobility management for those unable to receive pharmacologic or procedural intervention currently exists.³ Interestingly, early mobilization, thrombus location, and duration of symptoms did not correlate with the incidence of symptomatic PE in patients with acute DVT undergoing anticoagulation therapy.¹⁸ However, it is unclear whether this is also the case for early mobilization in patients with DVT that is untreated and who are unable to undergo pharmacologic or procedural intervention.

General parameters for aerobic, range-of-motion, and resistance training for patients with thrombocytopenia are used in the cancer rehabilitation setting.⁹ These guidelines are based more upon subjective than objective criteria.¹⁹ Notably, these guidelines warn that patients with platelet count lower than 10,000 cells/ μ L are at significant risk for spontaneous hemorrhage and must require prophylactic transfusions when undergoing rehabilitation focused on performing essential activities of daily living, fall precaution training, and short-distance ambulation.⁹ Recently, it was reported that patients with platelet count greater than

20,000 cells/ μ L may participate in rehabilitation with no additional restrictions.¹⁰ Guidelines for patients with platelet counts of 10,000 to 20,000 cells/ μ L recommend avoiding both resistive exercise and standing or ambulation if deemed a high fall risk, while for those with platelet counts of 5,000 to 10,000 cells/ μ L, it is recommended to avoid resistive exercises, with minimal activity and implementation of focused bed or chair exercises.¹⁰ For patients with platelet counts lower than 5,000 cells/ μ L, it is recommended to consider deferring physical therapeutic interventions pending further discussion with the medical team.¹⁰ At our institution, the patients are assessed by the treating physical and occupational therapists during each rehabilitation session for the development of any new (or worsening of) symptoms such as pain, fatigue, and dyspnea along with checking vital signs if indicated, and notifying medical team if needed. Fortunately, a study of the application of these exercise guidelines in severely thrombocytopenic patients found the risk of severe exercise-related major bleeding events to be low, with the majority of bleeding events being minor ones such as bruising, ecchymosis, petechiae, and epistaxis.¹⁰ Development of a definitive method for determining when anticoagulation should be administered in the setting of thrombocytopenia is challenging, as a simple platelet threshold or international normalized ratio value may not necessarily correlate with the degree of coagulopathy that increases overall bleeding risk.²⁰

Following the diagnosis of DVT, our patient received a limited rehabilitation course, undergoing occupational therapy only 3 times and physical therapy 8 times, in part owing to ambiguous expectations regarding acceptable physical activity status amidst other concurrent medical procedures and specialist care in the inpatient setting. In this patient's case, to avoid the potential consequences of immobility and optimize the patient's functional outcome, physical therapy was restarted 4 days after the discovery of bilateral lower-extremity DVT despite no treatment and no significant change in the patient's clinical status. Notably, occupational therapy was delayed for longer, resuming on day 8 despite no other clinical status changes. Thus, this patient's history showcases the inconsistencies that may exist in the management of a single case and the need for physical activity management guidelines within this context so that physical and occupational therapists can have a unified approach.

The patient preferred outpatient rehabilitation instead of a short stay of acute inpatient rehabilitation. Fortunately, this patient was ultimately able to meet his functional goals and to discharge home with his family with no subsequent complications from his clot burden or further bleeding episodes. Nonetheless, a clearer method for risk stratification based on clot burden and risk for fatal PE would help clinicians make more informed determinations regarding treatment approach and timely mobilization in patients with cancer-associated thrombosis and thrombocytopenia who

are not candidates for immediate pharmacologic or procedural intervention. A single successful case does not abrogate the potential for complications if early rehabilitation is widely applied with large numbers of patients in similar situations. Further studies to clarify safe physical activity goals in the setting of untreated DVT would also be warranted to allow for refocusing rehabilitation effort toward patients' functional goals and overall outcomes.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: The abstract of this study has been accepted for poster presentation at the American Academy of Physiatrists Annual Meeting, in New Orleans, Louisiana in May 2022..

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