Spontaneous Hemarthrosis following Prophylactic Enoxaparin Therapy in a Patient with Chronic Kidney Disease and COVID-19: A Case Report

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ABSTRACT

Knee pain is a common clinical complaint with a broad differential diagnosis. In critically ill patients, acute monoarticular pain and swelling typically raise concern for septic arthritis. However, alternative etiologies such as crystal-induced arthritis, trauma, and hemarthrosis must also be considered.

This report presents a rare case of spontaneous hemarthrosis in a patient receiving prophylactic enoxaparin. Although uncommon, spontaneous hemarthrosis is a significant complication of anticoagulation therapy, particularly with low molecular weight heparins (LMWH) like enoxaparin.

Keywords: hemarthrosis, CKD, COVID-19, enoxaparin, case report

INTRODUCTION

Knee pain is a common clinical complaint with various underlying etiologies. In critically ill patients, acute monoarticular pain and swelling often prompt consideration of septic arthritis. However, other differential diagnoses such as crystal-induced arthritis, trauma, inflammatory arthritis, and hemarthrosis should also be considered. Hemarthrosis refers to the accumulation of blood within the joint, which may occur following trauma, in patients with bleeding disorders like hemophilia, or, in rare instances, as a spontaneous event.[1] Spontaneous hemarthrosis associated with anticoagulation therapy, particularly low molecular weight heparin (LMWH) like enoxaparin, is an uncommon but recognized complication.[2] Ozdemir et al. reported a case of hemarthrosis after enoxaparin use in an elderly patient, but only after higher doses were administered.[3] To our knowledge, no prior cases of hemarthrosis following prophylactic-dose enoxaparin have been published. Here, we describe a case of spontaneous hemarthrosis in a patient receiving enoxaparin 40 mg subcutaneously every 24 hours for venous thromboembolism (VTE) prophylaxis.

CASE PRESENTATION

This is a case of a 66-year-old Filipino male with a history of chronic respiratory failure secondary to COVID-19 pneumonia, chronic kidney disease on maintenance hemo-

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dialysis for the past six months, and recent tracheostomy, who was transferred to the Philippine General Hospital (PGH) for further management due to failure of ventilator weaning at the previous institution. The patient was initially admitted to a private hospital and later referred to PGH, a government hospital offering subsidized care, for continued multidisciplinary management.

His past medical history is notable for a 20-year history of uncontrolled hypertension, maintained with losartan 50 mg daily, type 2 diabetes mellitus on metformin 500 mg daily, and a history of chronic cerebrovascular infarct in 2020. He had no prior history of gout or osteoarthritis. He was a non-smoker, non-alcoholic, and had previously held a sedentary, office-based job before retirement. Family history was significant for hypertension and cardiovascular disease on both maternal and paternal sides.

During his initial hospitalization, the patient developed critical COVID-19 pneumonia, for which he received a full course of remdesivir 100 mg intravenously once daily for seven days and dexamethasone 6 mg intravenously for 10 days and underwent two sessions of hemoperfusion. A tracheostomy was performed after three weeks of intubation due to prolonged ventilatory support. Multiple weaning attempts failed due to recurrent episodes of desaturation. Throughout his hospitalization, the patient was administered various antibiotics, including ceftriaxone, azithromycin, cefepime, levofloxacin, vancomycin, amikacin, and fluconazole.

Upon transfer to PGH, he was started on meropenem 500 mg IV every 24 hours and ciprofloxacin 400 mg IV every 24 hours. Additional medications included amlodipine 10 mg daily, carvedilol 6.25 mg twice daily, acetylcysteine 600 mg twice daily, atorvastatin 20 mg daily, omeprazole 40 mg IV daily, and salbutamol nebulization. Due to prolonged immobilization and elevated thrombotic risk, he was started on enoxaparin 40 mg subcutaneously once daily for VTE prophylaxis.

On the 12th day of hospitalization at PGH, while showing signs of resolving sepsis and maintained on mechanical ventilation with 30% fraction of inspired oxygen (FiO_2) and stable vital signs, the patient developed acute, spontaneous left knee pain and swelling. He remained bedridden with no history of trauma preceding symptom onset. Physical examination revealed erythema, swelling, warmth, and tenderness of the left knee joint, with pain on both active and passive movement. Initial differential diagnosis included crystal-induced arthritis and septic arthritis. Laboratory findings revealed leukocytosis (24,000 cells/L), anemia (hemoglobin 82 g/L), and a normal platelet count (252,000 cells/L). Coagulation studies were unremarkable, with an INR of 1.12 (normal range of 0.8-1.1) and an APTT of 29 seconds (normal range 21-29 seconds).

Prior to arthrocentesis, the primary service initiated empiric intravenous methylprednisolone as coverage for possible inflammatory arthritis and subsequently referred the patient to the Rheumatology service for further evaluation.

Figure 1. Aspirated viscous, hemorrhagic synovial fluid from the left knee joint, consistent with hemarthrosis.

Arthrocentesis was performed, yielding 25 mL of viscous hemorrhagic fluid (Figure 1). Synovial fluid analysis revealed a predominance of red blood cells (680,000 RBCs), 7,200 white blood cells, and no crystals on polarizing microscopy. Aerobic bacterial culture showed no growth after five days of incubation, and both fungal and tuberculosis cultures were negative. These findings were consistent with hemarthrosis.

Treatment for this case involved two key interventions: first, arthrocentesis to evacuate the intra-articular hemorrhagic fluid, thereby relieving joint pressure, reducing inflammation, and improving mobility, and second, the administration of intravenous methylprednisolone to address the inflammatory response and further aid in symptom control. Although hemarthrosis is primarily a bleeding event, inflammation may contribute to ongoing joint symptoms. In this context, corticosteroid therapy may have played a role in hastening symptom resolution by mitigating local synovial inflammation and irritation.[4] Enoxaparin was continued despite the presence of hemarthrosis, due to the patient's high thrombotic risk. Methylprednisolone at 20 mg IV daily was discontinued after two doses, as the patient experienced complete resolution of symptoms.

Following treatment, the patient regained full active range of motion in the left knee without difficulty. No recurrence of joint swelling was observed, and physical examination revealed resolution of tenderness, warmth, and

erythema. Physical therapy was not required, as the patient independently recovered full knee mobility.

The patient reported marked relief of knee pain within 24 hours of arthrocentesis, with complete resolution by the following day. This rapid improvement suggests that both aspiration and corticosteroid therapy significantly contributed to symptom relief. No recurrence of knee pain or swelling during the remainder of the hospital stay. Given the sustained absence of symptoms, no further diagnostic work-up was pursued. Arthrocentesis was well-tolerated, with no immediate complications. Unfortunately, the patient expired on the 26th hospital day due to septic shock secondary to hospital-acquired pneumonia, *an event deemed unrelated* to the hemarthrosis or its management.

DISCUSSION

Enoxaparin, a LMWH, is widely used for the prevention and treatment of VTE, particularly in hospitalized patients at risk for deep vein thrombosis (DVT) or pulmonary embolism (PE). Compared to unfractionated heparin (UFH), enoxaparin offers several advantages, including better bioavailability, a longer half-life allowing for less frequent dosing, a more predictable dose-response, and a reduced risk of heparin-induced thrombocytopenia.[5-8]

Despite its favorable safety profile, bleeding remains the primary adverse effect associated with LMWH therapy. Known risk factors include advanced age, renal insufficiency, high doses of enoxaparin, and concomitant use of antiplatelet or anticoagulant agents.[9] In this case, the patient was an elderly male with multiple comorbidities, including chronic kidney disease on maintenance hemodialysis, long-standing hypertension, diabetes mellitus, and a recent history of critical COVID-19 pneumonia requiring prolonged mechanical ventilation. Despite receiving the standard prophylactic dose of enoxaparin (40 mg subcutaneously every 24 hours), he developed spontaneous hemarthrosis in the absence of overt coagulopathy or concurrent anticoagulant use.

Renal dosing considerations are crucial when using enoxaparin in patients with CKD. Because enoxaparin is primarily cleared by the kidneys, reduced renal function leads to decreased drug clearance and a prolonged half-life, which increases the risk of bleeding. Moreover, CKD itself is associated with increased bleeding tendency due to multiple mechanisms, including platelet dysfunction, altered platelet-vessel wall interactions, and uremia-related inhibition of platelet aggregation and adhesion. These intrinsic hemostatic defects compound the pharmacologic effects of anticoagulation.[10]

Current guidelines recommend dose adjustment or consideration of alternative anticoagulation strategies like the use of unfractionated heparin in patients with severe renal impairment (creatinine clearance <30 mL/min).[11] In this case, the patient received the recommended prophylactic dose. Although no pharmacokinetic interactions directly increasing enoxaparin's potency were identified, impaired renal clearance likely contributed to increased anticoagulant exposure. Anti-factor Xa monitoring, which can guide dosing in patients with significant renal dysfunction,[11] was not performed in this case, but could have provided additional safety insights.[11]

The patient's concurrent use of potentially nephrotoxic medications—including meropenem, vancomycin, amikacin, levofloxacin, and fluconazole—may have contributed to worsening renal function, thereby further impairing enoxaparin clearance and enhancing bleeding risk. While none of these drugs are known to directly interact with enoxaparin, which generally has a low potential for drug-drug interactions, the combination of comorbidities, nephrotoxic agents, and polypharmacy may have amplified the pharmacodynamic response to LMWH.[12]

Although hemarthrosis is more commonly reported in patients receiving therapeutic doses of enoxaparin, this case illustrates that even prophylactic dosing can result in clinically significant bleeding in high-risk individuals.[1] Additionally, COVID-19 may have contributed to the patient's coagulopathy. While COVID-19 infection is classically associated with a hypercoagulable state, evidence highlights the dual risk of thrombosis and bleeding. Endothelial injury, cytokine-mediated inflammation, and immune dysregulation may impair hemostasis and promote paradoxical bleeding.[13] The patient's normal coagulation profile at the time of hemarthrosis underscores the unpredictable and multifactorial nature of coagulopathy in the context of COVID-19 and CKD.

Prompt joint aspiration in suspected hemarthrosis is essential for diagnosis and symptom relief. In this case, the patient experienced rapid improvement following arthrocentesis, which confirmed the diagnosis and helped avert further complications. Although the exact role of COVID-19 in contributing to bleeding remains uncertain, clinicians should maintain a high index of suspicion for hemarthrosis in patients on anticoagulation, especially those with CKD or a history of recent COVID-19 infection.

A key strength of this case is the clear temporal association between enoxaparin administration and the onset of spontaneous hemarthrosis, in the absence of any history of trauma or joint injury that could otherwise explain the bleeding. Additionally, the patient was not on any other anticoagulant or antiplatelet medications, and there were no overt coagulation abnormalities, strengthening the association with enoxaparin use. However, this report is limited by its single-case nature, which restricts the generalizability of the findings. Additionally, while the role of COVID-19 in promoting bleeding remains plausible, causality cannot be definitively established. Further studies are needed to better understand the mechanisms underlying bleeding tendencies in patients with COVID-19 receiving anticoagulation therapy.

CONCLUSION

This case highlights a rare occurrence of spontaneous hemarthrosis in a patient on prophylactic-dose enoxaparin, suggesting the need for vigilance in at-risk populations, particularly those with chronic kidney disease. Early recognition and management, including joint aspiration, may be important for symptom relief and the prevention of complications.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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