Journal of Community Hospital Internal Medicine Perspectives

Volume 13 | Issue 2 Article 4

2023

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Recommended Citation

Aiken, Arielle; Kania, Brooke; Amin, Riddhi; Ghrewati, Moutaz; and Michael, Patrick (2023) "A Challenging Situation: Empirical Treatment with Therapeutic Plasma Exchange in a Patient with Sickle Cell Disease," *Journal of Community Hospital Internal Medicine Perspectives*: Vol. 13: Iss. 2, Article 4.
DOI: 10.55729/2000-9666.1152
Available at: https://scholarlycommons.gbmc.org/jchimp/vol13/iss2/4

CASE REPORT

A Challenging Situation: Empirical Treatment with Therapeutic Plasma Exchange in a Patient with Sickle Cell Disease

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Abstract

Sickle Cell Disease (SSD) can present with acute painful crises, most commonly manifesting as diffuse bony pain; however, rare presentations of acute coronary syndrome, acute papillary necrosis, or multi-organ failure may also present in these patients. TTP has been rarely described in conjunction with sickle cell pain crisis (SS crisis). In both TTP and sickle cell crises, widespread platelet activation is present with thrombocytopenia as a result. Thrombocytopenia can be utilized as a poor prognostic indicator in patients with SS crisis. Multi-organ failure may appear similar to TTP and patients may benefit from similar therapy. Here, we present a 27-year-old female with a history of SSD who presented with a painful crisis who was found to have worsening renal failure and thrombocytopenia and was treated empirically with therapeutic plasma exchange (TPE), later discovered to have SS crisis with multi-organ failure with unremarkable ADAMSTS13 values. Given the high fatality risk of TTP, the benefits outweighed the risks for empiric TPE therapy, and our patient benefited from the treatment, as patients with both TTP and/or SS crisis multi-organ failure have demonstrated improvement following this treatment. Given the severity of multi-organ failure in SSD patients, additional research is warranted for improvement in the diagnosis and management of these patients.

Keywords: Thrombotic thrombocytopenic purpura, Sickle cell disease, Sickle cell crisis, Plasma exchange, Autosplenectomy

1. Introduction

Patients with sickle cell crises tend to have limited events managed via supportive care. However, in rare instances, patients can develop acute multi-organ failure syndrome, which is defined as a sickle pain event accompanied by rapid dysfunction of approximately 2–3 organ systems.[1] The decline in organ function in this setting is proposed to be secondary to occlusion of microvasculature leading to ischemia of tissue.[2] This life-threatening complication may achieve reversal of organ damage following transfusion exchange therapy, which mimics another phenomenon labeled, "thrombotic thrombocytopenic purpura (TTP)".[1] Here, we present a young patient with a history of sickle cell disease (SSD) who presented with painful crises and was found to have multi-organ failure (that initially impersonated TTP).

2. Case presentation

A 27-year-old female with a past medical history significant for sickle cell disease (SSD) with autosplenectomy and Crigler-Najjar syndrome status post cholecystectomy presented to the Emergency Department (ED) for acute sickle cell pain crisis. The patient endorsed bilateral arm, back, and leg pain and new-onset dyspnea on exertion for a 1-day duration. She denied chest pain.

As for her SSD history, the patient was previously treated with hydroxyurea; however, this medication was discontinued approximately 1-year prior

Received 21 September 2022; revised 8 November 2022; accepted 17 November 2022.
Available online 10 March 2023

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https://doi.org/10.55729/2000-9666.1152

secondary to the development of a right lower extremity ulcer. The patient was started on Voxelotor due to a chronic complaint of fatigue related to her anemia and has been compliant with Voxelotor 1.5 g oral daily. She develops sickle cell pain crises approximately twice yearly. Her baseline hemoglobin levels range from 9.0 to 10.0 g/dL.

In the ED, the patient was hemodynamically stable. She received hydromorphone, and intravenous fluids with normal saline, and was placed on supplemental oxygen. Laboratory studies were remarkable for anemia with levels consistent with the patient's baseline range [Table 1]. Chest X-ray (CXR) was negative for cardiopulmonary infiltrates. She was admitted to the medical floor for further management of her sickle cell crisis.

While on the hospital floors, the patient was managed with hydromorphone which was later transitioned to Oxycontin, maintenance fluids, and bedside incentive spirometry. Voxelotor was discontinued. On day 2 of admission, the patient had a significant decrease in her blood counts, with laboratory studies significant for bicytopenia (anemia and thrombocytopenia), worsening hemolysis, hyperkalemia, and worsening renal function [Table 1]. She was noted to have hypoxia with an oxygen saturation of 70% and therefore was initiated on oxygen supplementation with Venturi-Mask. Due to the aforementioned lab changes, clinical suspicion for thrombotic thrombocytopenic purpura (TTP) was suspected for which additional laboratory studies were sent which revealed an LDH of 2646 U/L. Over 4 schistocytes/HPF were visualized on peripheral blood smear [Fig. 1]. The calculated PLASMIC score was 4, consistent with an intermediate risk for severe ADAMTS13 deficiency. Critical care was consulted, the patient was transferred to the Medical Intensive Care Unit (MICU), a double-lumen Shiley central venous catheter (SCVC) was placed, and the patient received total plasma exchange therapy (TPE) with a few units of RBCs transfusion. The patient received high-dose intravenous methylprednisolone. Following TPE, ADAMTS13 level activity resulted at 64.9% (reference range: normal low >66.8%). Meanwhile, the patient responded well to plasma exchange transfusion, and platelets, creatinine and LDH improved and remained stable after 2 days of plasma exchange. The patient continued to improve and was subsequently discharged home. Home voxelotor was restarted however at a lower dose.

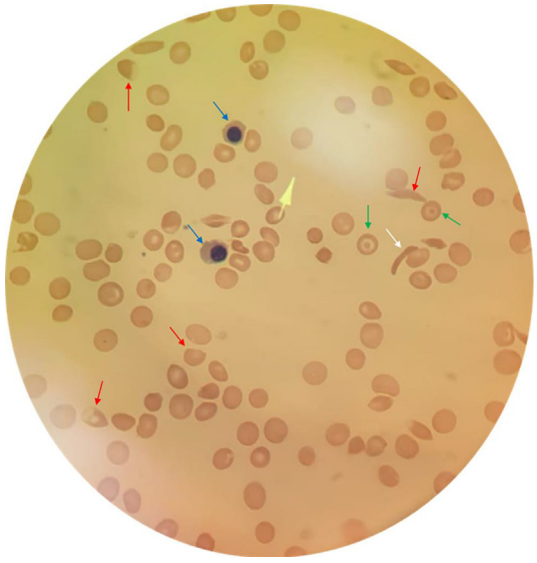

Fig. 1. Peripheral blood smear demonstrating sickle cells (white) in the setting of the history of SSD and current sickle cell pain crisis, orthochromatic erythrocytes (blue) indicative of erythropoiesis, >4 schistocytes (red) on HPF concerning for intravascular hemolysis, target cells identified (green).

Table 1. Laboratory studies indicative of worsening bicytopenia, worsening hemolysis and worsening renal function and improvement after plasma exchange.

Laboratory Studies	Values on Admission	Values on Day 2	After Plasma Exchange	Reference Ranges
Hemoglobin	10.4 g/dL	6.3 g/dL	9.3 g/dL	12.0–16.0
Hematocrit	28.3%	16%	24.9%	36.0–46.0
Platelet Count	510 K/mm3	91 K/mm3	156 K/mm3	140–440
LDH	527 U/L	2646 U/L	1415 U/L	140–271
Haptoglobin	N/A	<10 mg/dL	N/A	33–278
Fibrinogen level	N/A	417 mg/dL	N/A	183–503
Fibrinogen degradation products (FDP)	N/A	≥20mcg/mL	N/A	Normal high≤5 Critical high >20
PT	14.9 s	20.3 s	14.9 s	12.2–14.9
INR	1.2	1.8	1.2	Critical high >4.0
PTT	N/A	48.3 s	28.4 s	21.3–35.1
BUN	7 mg/dL	24 mg/dL	35 mg/dL	7–23
Creatinine	0.77 mg/dL	1.4 mg/dL	1.08 mg/dL	0.6–1.3
Potassium	4.7 mEq/L	5.9 mEq/L	4.6 mEq/L	3.5–5.0

3. Discussion

Acute painful crisis is one of the most common clinical manifestations of sickle cell disease. The average rate of yearly painful crises is 0.8 episodes per patient per year in SSD.[3] As highlighted in our clinical case, patients typically present with functionally impairing diffuse bone pain; however, on occasion, the clinical course can be complicated by acute coronary syndrome, acute papillary necrosis, and multiorgan failure stemming from widespread vaso-occlusive crisis.[2,4] Several differentials must be considered in such scenarios to ensure timely intervention and escalation of care if necessary.

TTP complicating sickle cell disease has been previously described, though seldomly. Whereas the underlying mechanism still remains a mystery, prior studies have suggested the implication of altered levels of Von Willebrand's Factor (VWF) and ADAMTS13 in the pathological process.[5,6] Primary diagnostic elements include thrombocytopenia, microangiopathic hemolytic anemia (MAHA), and the absence of alternative etiologies for both thrombocytopenia and/or MAHA.[7] Additional criteria to consider include generalized weakness, gastrointestinal upset, neurologic changes most prominently with mentation changes, renal dysfunction, and fever (however exceedingly high fever with chills favors against TTP and more towards sepsis).[7] Given the longevity of the ADAMTS13 result, therapeutic plasma exchange should not be delayed while waiting for this result.

In light of the similar pathogenesis of microangiopathy resulting in widespread non-inflammatory anoxic injury to various organs & the indistinguishable clinical features of both TTP and acute sickle cell crisis complicated by multi-organ failure, a diagnostic conundrum is often faced in the differentiation of the disease processes occurring simultaneously.

Acute multiorgan failure results in the compromise and injury to two of three major organs, specifically lung, liver, and kidney and can ultimately result in fatality. As discussed in Aref et al., SCD crisis as a result of vaso-occlusion and the inflammatory response propagated can affect the aforementioned organs.[8] However, TTP and SCD both have the potential through non-inflammatory processes in causing organ injury, by targeting small vessels via platelet aggregation.[8] Our patient had evidence of acute injury to the renal and hepatic circulation as there was an acute elevation of the corresponding organ markers. In reviewing the rise of these markers and the patient's development of worsening crisis symptoms, we considered a compromise of microvascular circulation as an instigator of these findings. Specifically, in our case, we saw clinical improvement with plasma exchange; however, given the latter review of ADAMTS13 levels, our patient's cause for deterioration was likely SCD with multiorgan failure.

TPE-related complications have been variable as some complications reported have been considered an expected physiologic response to therapy. Studies investigating complications of TPE have reported an incidence of complications in approximately 4–36% of patients, with the majority of reactions mild in nature, and the most common reactions including paresthesia secondary to hypocalcemia from the anticoagulation citrate product.[9] Many of these studies included adverse effects associated with central catheter line access rather than specifically adverse effects of the TPE itself.[9] Alternatively, in another study, 5% of patients expired secondary to complications of TPE (due to bleeding complications from the central catheter as well as catheter-related sepsis) with 26% experiencing major complications of TPE (including thrombosis, hypotension, and systemic infection).[10] Ultimately, in patients with high clinical suspicion of TTP, the benefits of TPE outweigh the risks of potential side effects of TPE.[10] The fatality rate is high in untreated patients, and therefore early diagnosis and treatment are essential.[11] In our patient, although we did not have the ADAMTS13 levels, given her clinical criteria and risk of mortality given high clinical suspicion for TTP, she underwent TPE with the absence of complications, given the benefits of treatment outweighed her risks.

4. Conclusion

Uncommonly patients can develop multi-organ failure with SS crises, which is thought to be secondary to vasoocclusion and organ ischemia, leading to organ failure in at least 2–3 organ systems. This complication can be fatal and oftentimes resembles TTP, given the thrombocytopenia present in SS crises and potential renal dysfunction associated with multi-organ failure. Treatment for SS crisis with multi-organ failure and TTP are similar, with rapid TPE achieving reversal of dysfunction. Our patient presented with a clinical picture mimicking TTP; however, was later diagnosed with SS crisis with multi-organ failure, with subsequent improvement following TPE. Ultimately, additional research is warranted to further understand the relationship between sickle cell crises, thrombocytopenia, and multi-organ failure.

Author contribution

Arielle Aiken and Brooke Kania are the article guarantors. Arielle Aiken, Brooke Kania, and Riddhi Amin performed the literature review and wrote the manuscript. All authors assisted in the collection of the patient's clinical data. All authors took part in the medical management of the patient and edited the final manuscript for submission. All work was performed at St. Joseph's University Medical Center at the following address: St. Joseph's University Medical Center Department(s) of Hematology/Oncology and Internal Medicine 703 Main Street Paterson, NJ USA 07503 (973) 754-2000.

Consent

As this is a case report, consent was obtained for the purpose of this paper.

Conflict of interest

The authors report no conflict of interest. Ethical review is not necessary, because this is a case report. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

The authors would like to thank the patient and their family for allowing us to share this case with our colleagues. We would also like to thank the Hematology-Oncology team for their assistance in diagnosing and managing the patient's disease.

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