Case Report

Spinal Cord Compression Due to Intradural Extramedullary Hematopoiesis in a Young Adult with Cooley's Anemia

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ABSTRACT

Cooley's anemia, also known as beta thalassemia major, is an inherited multisystemic disorder characterized by skeletal and non-skeletal complications resulting from hemoglobinopathies. Extramedullary Hematopoiesis (EMH) is a complication of thalassemia major due to insufficient erythropoiesis expansion. The incidence rate of paraspinal EMH in beta-thalassemia is rare but tends to be on the rise. We present a case of spinal cord compression due to intradural EMH in a 21-year-old man with Beta Thalassemia major, who exhibited acute lower motor, sensory, and autonomic disorder, along with severe anemia, and electrolyte imbalance. Patients were treated with corticosteroids, blood transfusions, electrolyte correction and pain medications. Several days later, the patient experienced clinical improvement in reduced pain and motor improvement. The patient was planned to undergo elective surgery and radiotherapy after reaching the stabilized condition. Management options of spinal cord compression due to EMH include corticosteroids, adequate blood transfusion, hydroxyurea, radiotherapy, surgical decompression, exchange transfusion, or a combination of these approaches. The choice of therapy should be based on the patient's clinical condition, diagnostic evaluations, and the size of the mass exerting pressure on the spinal cord. The optimal management of EMH remains uncertain. We need further research to establish effective treatment strategies of spinal cord compression due to EMH in Cooley's Anemia.

Keywords: spinal cord compression; hematopoiesis ; thalassemia beta major

INTRODUCTION

Thalassemia is a group of blood disorders characterized by a reduced or absent synthesis of one or more normal globin chains, which are hemoglobinopathies.[1] Beta thalassemia major is an inherited multisystemic disorder with both skeletal and non-skeletal manifestations, resulting from the disruption of beta globin chains. It spreads across the rest of the tropical belt country at varying frequencies.

Indonesia has around 3.0-10.0% of the population carrying beta thalassaemia.[2]

Hematopoietic tissue may develop in almost all body sites as a physiological response to chronic anemia or deficient erythropoiesis. These sites include the spleen, liver, lymph nodes, thymus, heart, breasts, prostate, broad ligaments, kidneys, adrenal glands, pleura, retro-peritoneal tissue, peripheral and cranial nerves, and the spinal canal. Extramedullary Hematopoiesis (EMH) is a complication of thalassemia major resulting from insufficient erythropoiesis. The incidence of EMH in thalassemia major is estimated to be less than 1%.[3] A paraspinal location for hematopoietic tissue occurs in 11–15% of EMH cases. [4] In this report, we present a case of spinal cord compression due to intradural EMH in a young adult with beta thalassemia major. We discuss the clinical syndrome, radiographic findings, pathophysiology, and treatment options.

CASE REPORT

A 21-year-old man (weight 49kg, height 153 cm) presented to the emergency room with bilateral lower limb paraplegia that had started one day prior. The patient reported a tingling sensation in the abdomen and increased back pain upon attempting leg movement. The day before admission, he experienced abdominal constriction extending to his back, accompanied by tingling and numbness from the abdomen down to the toes. Additionally, the patient reported a complete inability to urinate and an absence of bowel movement.

Three days before admission, the patient narrowly avoided a collision while riding a motorcycle, requiring a sharp turn to evade other vehicles. Despite not falling or sustaining injuries, his body twisted to the right during this maneuver. Following the incident, he suffered intense, non-referred middle back pain, described as stabbing and rated at 9 on the Numeric Rating Scale (NRS). Although he could still walk, he did so more slowly due to the pain, with no initial complaints of tingling or numbness in his feet.

However, the symptoms progressed, resulting in bilateral lower limb paraplegia upon admission.

One and a half months prior to admission, the patient experienced sudden middle back pain when bending over. The pain was described as resembling an electric shock and was not radiating, with a pain intensity rating of 6 on the Numeric Rating Scale (NRS). The pain subsided when the body was in an upright position or when lying down. The discomfort persisted for about a week and notably improved after the patient performed back pain stretching exercises discovered on the internet.

The patient had a medical history of beta thalassemia major TDT (Transfusion-Dependent Thalassemia) diagnosed since the age of 7 months old. His hemoglobin level before transfusion ranged from 5.5 to 8 mg/dL. He had been receiving regular transfusions every two weeks and has been taking folic acid and deferasirox, an iron-chelating agent, at a daily dose of 1250 mg for the past 7 years. The patient has no history of hypertension, diabetes mellitus, stroke, or lung disease and does not smoke or consume alcohol.

During the general physical examination, the patient demonstrated full awareness and responsiveness to the environment. He could follow commands, open his eyes spontaneously, and track objects. Vital signs were normal. Both eyes exhibited anemic conjunctiva and subicteric sclera. Neurological examination revealed no cranial nerve palsy and showed reactive pupils.

In the lower extremities, the patient had motor strength graded as 1111|1111, and there were signs of positive pathological reflexes. Sensory examination indicated hypoesthesia extending up to the Th7 level and below, along with proprioceptive dysfunction. Additionally, there was retention of both urinary and bowel functions.

The laboratory examinations revealed several significant findings, including severe anemia with a hemoglobin level of 7.9 g/dL, thrombocytopenia (platelet

count of 133,000/uL), hyponatremia with a sodium level of 127 mEq/L, hyperkalemia with kalium level of 5,9mEq/L, prolonged activated partial thromboplastin time (APTT) with a value of 49.9 (reference range: 31.5), and elevated D-dimer levels (700).

The MRI of the thoracolumbar region (Fig.1) displayed hypointensity in the thoracolumbar vertebral corpus, lesions in the intradural extramedullary canal at the Th6 to Th7 levels, and splenomegaly.

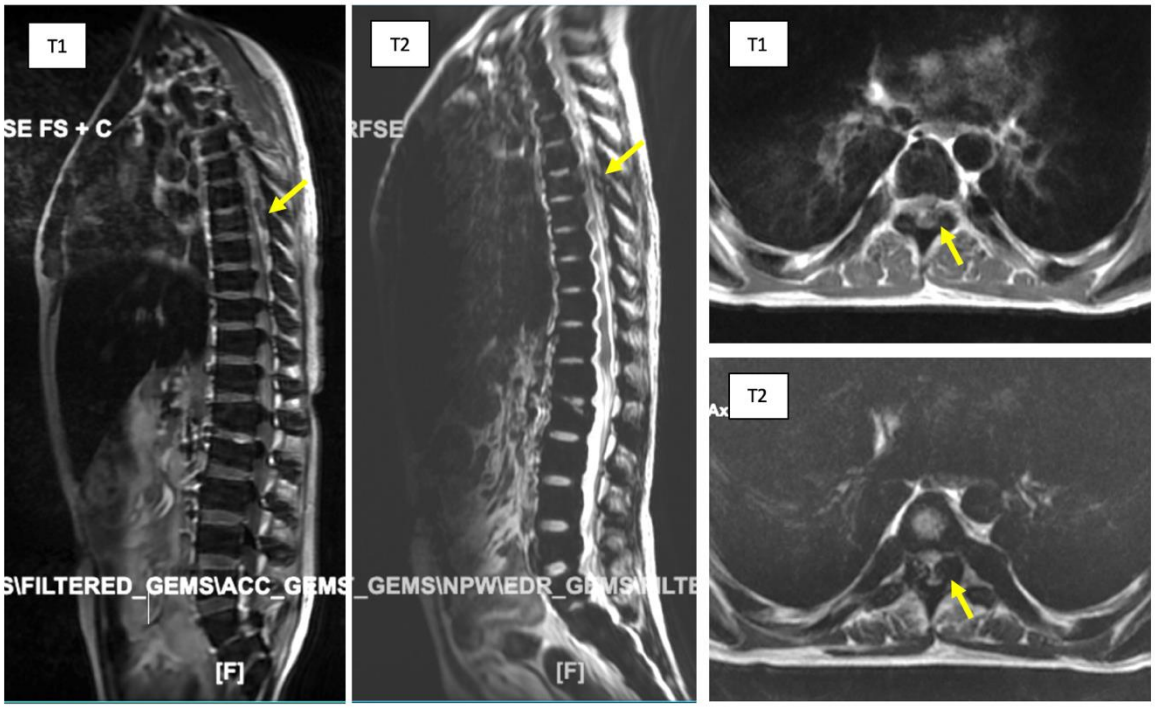

Figure 1. Spine MRI. Intradural extramedullary hypointense lesions at Th 6 and Th 7 levels (yellow arrow).

Based on the clinical findings and ancillary test, the patient was diagnosed with paraplegia of the upper motor neuron (UMN) resulting from spinal cord compression at the Th6-Th7 level, attributed to intradural extramedullary hematopoiesis in patient with beta thalassemia major. The initial treatment plan involved performing evacuation laminectomy surgery after an overall improvement in the patient's condition to ensure stabilization. In cases where surgery was not feasible or posed a risk

of bleeding, the second option considered was radiotherapy.

During hospitalization, the patient received a single intravenous dose of Dexamethasone (10 mg), however, no clinical improvement was observed and then discontinued. He received red blood cell transfusion (Packed Red Cells Leukodepleted) to achieve a target hemoglobin level greater than 13 mg/dL. Additionally, the patient received electrolyte correction therapy in the form of Calcium Gluconas and Calcium Polystrene Sulphonate administration, 500 mg NaCl capsules to be taken three times a day, and 1500 mg of deferasirox daily. For pain management, the patient was administered Gabapentin at a dose of 100 mg orally twice daily, and intravenous Paracetamol at a dosage of 1000 mg three times daily.

A few days into hospitalization, the patient experienced a worsening of the condition, with a drop in hemoglobin, low platelets, and decreased leukocytes due to thalassemia. and were treated in multidisciplinary approach. As the patient's condition began to stabilize, notable clinical improvements were observed. The back pain had subsided, and there was an increase in motor skills. The motor strength of lower extremities improved and was graded as 2211|1122 with the presence of positive pathological reflexes. Sensory examination revealed hypoesthesia extending up to Th8 level and below, along with proprioceptive dysfunction. Laboratory and ancillary tests were needed to reassess the patient's condition and treatment plan. However, neither surgery nor radiotherapy was performed on this patient due to the clinical outcomes and other factors influencing the decision.

DISCUSSION

Beta (β) thalassemia major is an autosomal recessive hereditary disorder that impacts the structure or function of beta-globin chains. Clinically and in terms of severity, beta thalassemia can be categorized into three groups: Transfusion-dependent β-thalassemia (TDT) or major, non-transfusion-dependent β-thalassemia (NDT) or intermedia, and Thalassemia minor or β-thalassemia trait. [5] The term "Beta

thalassemia major" was first defined by Cooley and Lee in 1925 and commonly known as Cooley's Anemia or Mediterranean Anemia. [6]

In thalassemia major, patients experience severe anemia with hemoglobin levels below 7 g/dL, leading to symptoms such as weakness, fatigue, and the potential development of heart failure. To compensate for the loss of red blood cells, the body responds by expanding the bone marrow's erythropoiesis process.[7] Ineffective erythropoiesis is a characteristic feature of thalassemia, setting off a cascade of compensatory mechanisms, including Extramedullary Hematopoiesis (EMH), expansion of the erythroid marrow, hepatosplenomegaly, and increased iron accumulation.[4,8] In thalassemia, anemia and the resulting hypoxia lead to an elevation in serum erythropoietin levels, which activate the EPOR/JAK2 (Erythropoietin Receptor/Janus kinase-2) pathway. The sustained phosphorylation of JAK2 subsequently triggers excessive erythroid proliferation and the formation of EMH. [8]

The patient presented to the emergency room with complaints of weakness in both legs, a tingling sensation, and progressively worsening low back pain, in the context of Cooley's anemia. Upon neurological examination, findings indicated a decrease in lower motor strength, along with sensory and autonomic dysfunction. The primary suspicion was the presence of spinal cord lesions, often referred to as myelopathy. Classic "red flags" for myelopathy encompass the rapid onset of muscle weakness, sensory deficits, and loss of bowel and bladder sphincter control. Acute compressive myelopathy, not stemming from trauma, is considered a medical emergency, necessitating early intervention within 24 hours to preserve nerve function. Compressive myelopathy results from external compression on the spinal cord and can be further categorized into extradural, intradural extramedullary, or intramedullary, depending on the location of the lesion within the cord.[9]

The treatment provided to this patient included the administration of corticosteroids and blood transfusions, as described earlier. During several days of hospitalization, the patient showed noticeable clinical improvement. It is important to note that this improvement may be temporary, as corticosteroids and blood transfusions can have a short-term effect in improving the patient's condition by downregulating hematopoiesis.[10]

In another study, a thalassemia patient presented complaints of progressive weakness in both limbs. An MRI examination revealed a spinal cord mass causing compression. Subsequently, the patient underwent a neurosurgical decompression procedure, specifically an evacuation laminectomy. Following the procedure, the patient experienced hypotension and required intensive management to stabilize circulation and enhance spinal cord perfusion. It is crucial to recognize that invasive treatment of EMH should be approached cautiously, with full consideration of the potential risks that may exacerbate the patient's condition.[11]

Another study has also explored conservative treatment options for EMH. The combination of hydroxyurea, low-dose radiotherapy, and regular blood transfusions can be an effective therapeutic approach for patients with EMH. This study demonstrated that a hydroxyurea regimen of 1500 mg/day (22 mg/kg), in conjunction with blood transfusions and a total of ten fractions of low-dose radiotherapy (200 Gy per fraction), led to improvements in patient complaints. After six months of therapy, the EMH mass disappeared. The hydroxyurea dose was then continued at 15 mg/kg/day, along with deferasirox. No complications were reported during nine months of follow-up after achieving complete remission.[12]

Spinal cord compression resulting from EMH in some cases, can lead to recurrences.[13,14] In one reported case, a patient (18 year old man) presented with bilateral lower limb paresis with beta thalassemia major, then initially underwent a surgical procedure to treat

spinal cord compression. The patient's complaints had improved after the procedure, however, he later experienced a deterioration in his condition. As a result, a second surgical procedure was carried out to achieve complete resection of the mass, and the patient also received local radiotherapy to prevent further recurrence. Two years after these interventions, the patient showed clinical recovery, and subsequent MRI examinations did not reveal any remaining EMH mass. [14] This case demonstrates the importance of thorough and effective management to address the recurrence of EMH-related spinal cord compression.

There are no established guidelines for the treatment of spinal cord compression due to EMH in thalassemia major. Management options encompass corticosteroids, blood transfusions, hydroxyurea, radiotherapy, surgical decompression, exchange transfusion, or a combination of these modalities.[3] The choice of therapy should be determined based on the patient's clinical condition and the outcomes, results of laboratory and imaging examination, and the size of the mass that is compressing the spinal cord. Individualized treatment plans are crucial in addressing this condition effectively.

CONCLUSION

Extramedullary Hematopoiesis (EMH) is a complication that can appear in thalassemia patients because of the body's compensatory response to increase the levels of red blood cells in circulation. It can also manifest in various organs. The incidence of paraspinal EMH in beta thalassemia is relatively rare but tends to be on the rise. Symptoms associated with paraspinal EMH may include motor, sensory, and autonomic disturbances, depending on the innervation of the affected nerves. Therefore, it is crucial to maintain clinical awareness and further evaluations in thalassemia patients, particularly those who present with complaints of pain, lower limb weakness, tingling sensations, or urinary and bowel dysfunction. The management of EMH in thalassemia patients remains unclear, and further

studies are essential to establish effective treatment strategies.

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REFERENCES

1. Farmakis D, Porter J, Taher A, et al. 2021 Thalassaemia International Federation guidelines for the management of transfusion-dependent thalassemia. *Hemasphere*. 2022;6(8).
2. Wahidiyat PA, Sari TT, Rahmartani LD, et al. Thalassemia in Indonesia. *Hemoglobin*. 2022;46(1):39–44.
3. Subahi EA, Ata F, Choudry H, et al. Extramedullary haematopoiesis in patients with transfusion dependent β-thalassaemia (TDT): a systematic review. *Ann Med*. 2022;54(1):764–74.
4. Haidar R, Mhaidli H, Taher AT. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. *European Spine Journal*. 2010;19:871–8.
5. Jhalani M. Regional desk review of haemoglobinopathies with an emphasis on thalassaemia and accessibility and availability of safe blood and blood products as per these patients' requirement in South-East Asia under universal health coverage. 2021;
6. March HW, Schlyen SM, Schwartz SE. Mediterranean hemopathic syndromes (Cooley's anemia) in adults: Study of a family with unusual complications. *Am J Med*. 1952;13(1):46–57.
7. Ali S, Mumtaz S, Shakir HA, et al. Current status of beta-thalassemia and its treatment strategies. *Mol Genet Genomic Med*. 2021;9(12):e1788.
8. Yang X, Chen D, Long H, et al. The mechanisms of pathological extramedullary hematopoiesis in diseases. *Cellular and Molecular Life Sciences*. 2020;77:2723–38.
9. Laur O, Nandu H, Titelbaum DS, et al. Nontraumatic spinal cord compression: MRI primer for emergency department radiologists. *Radiographics*. 2019;39(6):1862–80.
10. Moncef B, Hafedh J. Management of spinal cord compression caused by extramedullary hematopoiesis in beta-thalassemia. *Internal Medicine*. 2008;47(12):1125–8.
11. Amin A, Crenesse-Cozien N, Amardeep K, et al. A Rare Case of Cord Compression From Extra-Medullary Hematopoiesis (EMH) in Beta Thalassemia. *Cureus*. 2023;15(5).
12. Karimi M, Zarei T, Pishdad P. Extramedullary hematopoiesis in a patient with transfusion dependent beta-thalassemia presenting with cord compression. *Iranian Journal of Blood and Cancer*. 2018;10(1):28–30.
13. Abbarh S, Al-Mashdali AF, Abdelrazek M, et al. Recurrent spinal cord compression due to extramedullary hematopoiesis in thalassemia patient: case report. *Medicine*. 2022;101(25).
14. Bukhari SS, Junaid M, Rashid MU. Thalassemia, extramedullary hematopoiesis, and spinal cord compression: a case report. *Surg Neurol Int*. 2016;7(Suppl 5):S148.