

Case Report

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Extramedullary hematopoiesis in case of hemoglobin E Beta-thalassemia: An unusual cause of paraplegia

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Abstract:

Hemoglobin E (HbE) beta-thalassemia is common in Asian countries. Extramedullary hematopoiesis (EMH) is a chronic complication of this condition, which is a rare cause of paraplegia. Here, we discuss an uncommon presentation of HbE beta-thalassemia with EMH. A 32-year-old male patient presented with spastic paraplegia at C7 level. Contrast magnetic resonance imaging showed epidural extramedullary soft-tissue clumps at D2–D7 vertebra. Histology section showed numerous pleomorphic large cells admixed with colonies of small cells having rounded contour. A relook at the history revealed a history of hemolytic anemia diagnosed at the age of 12 years, for which he was on 1–2 transfusions/year. HbE beta-thalassemia had been diagnosed 20 years before. Hence, a final diagnosis of EMH was made. Although such case reports have been documented, the amount of available data is limited. A high index of suspicion for EMH should be held in patients with hematological disease who present with neurological disorders.

Keywords:

Anemia, epidural, high-performance liquid chromatography, paraspinal mass

Introduction

Hemoglobin E (HbE) beta-thalassemia is relatively frequent in certain parts of the world. It is known to present with varied phenotypic manifestation.^[1] HbE beta-thalassemia is very common in India and Southeast Asia.^[2] This existence of both entities together is due to codominance. It is attributed to the high prevalence of both the diseases. The clinical phenotype of the disease is largely decided by the severity of the beta-thalassemia and can manifest as a major-, minor-, or intermedia-type phenotype.^[2] A watchful history taking, pedigree analysis, and clinicoradiological correlation can help in timely diagnosis and management. Here, we discuss an uncommon presentation of HbE beta-thalassemia with extramedullary hematopoiesis (EMH).

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Case Report

A 32-year-old male presented to the neurosurgery department with weakness in both lower limbs and inability to walk which was progressive over 2 months. On examination, he was conscious and oriented with stable vitals. There was pallor along with mild icterus. He had spastic paraplegia with the motor and sensory level at C7. Contrast magnetic resonance imaging showed a T1 isointense and T2 hypointense mildly enhancing clumped soft-tissue mass in the extramedullary epidural plane compressing the cord from D2 to D9 on the dorsal aspect [Figure 1]. The rest of the vertebral bodies, intervertebral discs, spinal ligaments, and posterior elements showed normal signal intensity. Other laboratory investigations revealed hemoglobin of 6.86 g/dL, red cell count $3.9 \times 10^9/L$, total leukocyte count $7.3 \times 10^9/L$, and platelet

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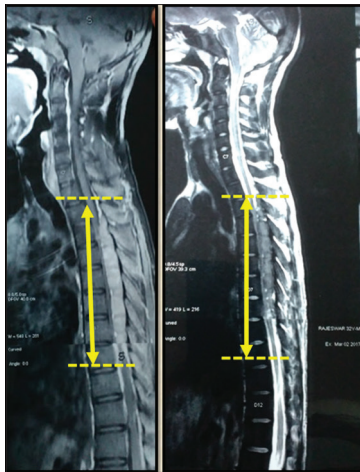


Figure 1: Contrast magnetic resonance imaging of the spine showing epidural extramedullary soft tissue clumps at D2–D7 vertebra

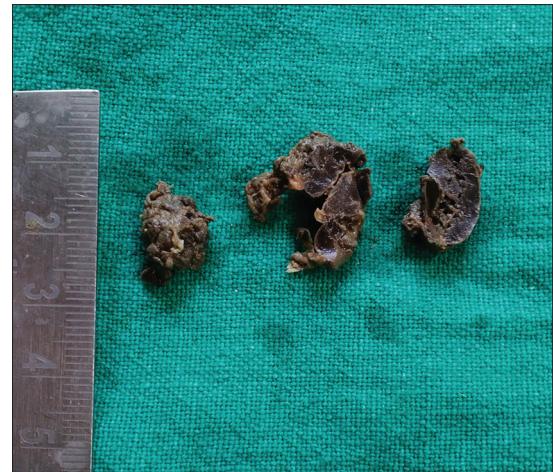


Figure 2: Gross appearance of the mass submitted as epidural mass showing a reddish cut surface

count $160 \times 10^9/L$. The differential leukocyte count was neutrophils 53%, lymphocyte 40%, monocyte 5%, and eosinophil 2%. The red cell indices showed a microcytic hypochromic anemia (mean corpuscular volume: 69.8 fL, mean corpuscular hemoglobin: 21.08 pg, and mean corpuscular hemoglobin concentration: 30.18 g/dL). Bilirubin was raised with total serum bilirubin of 42.8 $\mu\text{mol/L}$, direct serum bilirubin 10.3 $\mu\text{mol/L}$, aspartate aminotransferase 31 U/L, and alanine aminotransferase 18 U/L. Based on the clinicoradiological findings, a diagnosis of spontaneous thoracic epidural hematoma was made.

Laminectomy and decompression were done with a surgical excision of the mass. Tissue sent as epidural mass was in multiple gray-brown pieces ranging in size from 0.3 cm \times 0.3 cm \times 0.3 cm to 1.2 cm \times 2.4 cm \times 2.6 cm [Figure 2]. The separately sent lamina of thoracic vertebrae comprised bony tissue bits ranging in size from 5 cm \times 3.8 cm \times 1.1 cm to 6 cm \times 4 cm \times 1.2 cm.

Microscopically, the tissue sent as epidural mass showed fibrocollagenous capsule with high cellularity, revealing large pleomorphic cells having lobulated nuclei. These cells were admixed with colonies of small cells having rounded nuclear contour and a clearing around the nuclei, reminiscent of erythroid colonies. Also seen were identifiable myeloid cells [Figure 3]. Tissue sent as vertebral lamina showed hypercellular marrow spaces with active trilineage hematopoiesis [Figure 4]. In view of the hypercellularity, numerous identifiable erythroid colonies, myeloid cells, and megakaryocytes, a diagnosis of EMH was made.

To identify a cause for the same, the history was relooked. He was apparently asymptomatic until the age of 12 years when he developed progressive pallor

and weakness for 2 months. As per the records, he then had moderate pallor, icterus, and hepatosplenomegaly. His hemoglobin was 5.6 g/dL, and the peripheral smear examination showed microcytic hypochromic anemia, moderate anisopoikilocytosis, numerous target cells, and nucleated red cells (10/100 white blood cells). Hemoglobin electrophoresis revealed an E band. Sickling test was negative, and osmotic fragility test was within normal range. Fetal hemoglobin (HbF) was 9%, and a diagnosis of HbE beta-thalassemia was made. The details of the technique used were not available in the records. A three-generation pedigree chart was made, and there was a similar history and findings in the elder brother [Figure 5].

The patient was managed with 1–2 transfusions/year. After 20 years of the primary diagnosis, he had developed paraplegia secondary to EMH. He had an uneventful postoperative period. Currently, he can walk and is maintaining adequate hemoglobin with transfusions. On a follow-up visit, with informed consent, the diagnosis was reconfirmed by high-performance liquid chromatography (HPLC) performed by Bio-Rad D-10™ dual mode. The patient had a history of blood transfusion 3 weeks before the HPLC. Hemoglobin A2, A0, and F were 63.8%, 21.6%, and 12.1%, respectively [Figure 6].

Discussion

HbE beta-thalassemia is attributed to the phenomenon of codominance, which is due to the high prevalence of both the diseases in these endemic areas. The clinical phenotype of the disease is largely decided by the severity of the beta-thalassemia and can manifest as a major, minor, or intermedia phenotype.^[2] Hematopoiesis starts *in utero* in the yolk sac at 2 weeks. Later, the liver and subsequently the bone marrow establish the

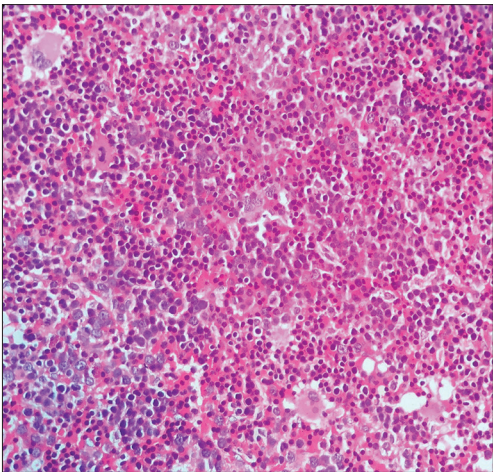


Figure 3: Microscopy of the tissue sent as epidural mass showing extramedullary hematopoiesis (H and E, x400)

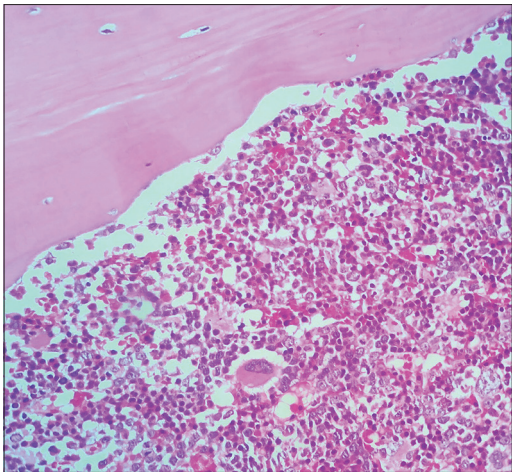


Figure 4: Section from the vertebral bone showing hypercellular marrow spaces with active trilineage hematopoiesis (H and E, x400)

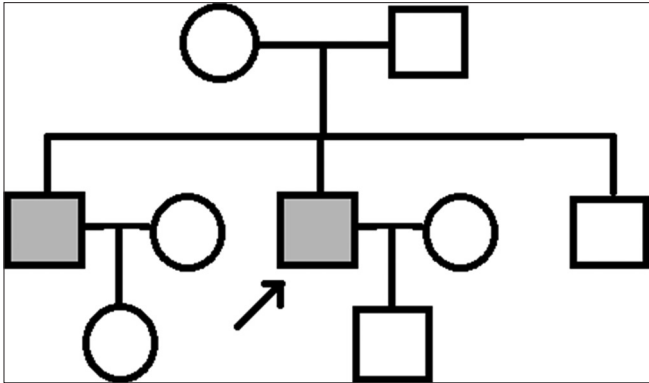


Figure 5: A three-generation pedigree chart of the index case showing a worked up index case and one affected sibling (The affected index case is indicated by arrow and gray square. The empty squares and circles indicate unscreened members. The elder brother is also affected and is depicted by shaded by gray square)

required microenvironment. Hematopoiesis that occurs in organs other than bone marrow is called as EMH. In thalassemia, there is a chronic, moderate-to-severe anemia, due to ineffective erythropoiesis, leading to hyperplastic marrow. Along with the usual sites of EMH in spleen, liver, and lymph node, the “nonhepatosplenic EMH” includes vertebral column, lung, abdomen, and pelvis.^[3] The incidence of EMH in thalassemia intermedia is much higher (~20%) as compared to thalassemia major (~1%). About 11%–15% of cases with EMH occur at a paraspinal location and present with back and lower extremity pain, paresthesia, and paraplegia. Size, location, and the extent of spinal cord involvement determine the acuteness, severity, and signs and symptoms. The pathogenesis may lie either in the extrusion of hematopoietic cells from the vertebral body or proximal ends of ribs, or presence of embryological hematopoietic cell remnants within the epidural space. The reason for thoracic spine predilection is not known. However, as the subarachnoid space and spinal canal

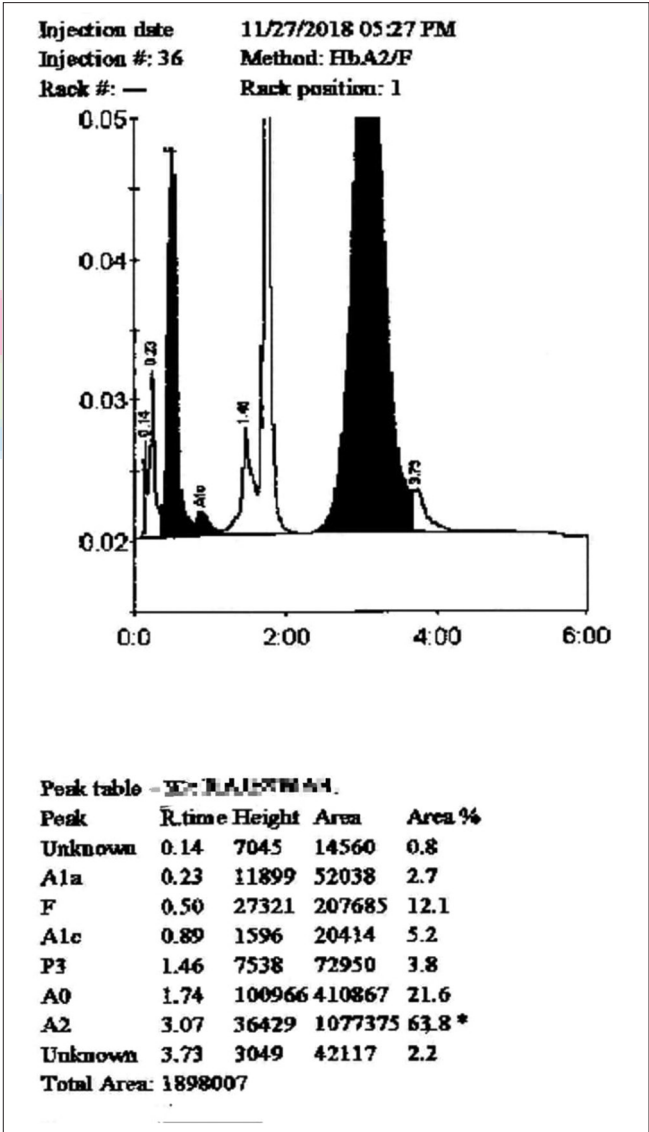


Figure 6: High-performance liquid chromatography showing elevated hemoglobin E and fetal hemoglobin

are narrow in the thoracic region, it results in the early onset of symptoms.^[4-6]

In compound heterozygotes for HbE beta-thalassemia, the HbA0 should either be diminished or absent.^[7] The hemoglobin analysis, in this case, showed a mildly higher value of the same. This was possibly due to the history of blood transfusion. In view of raised HbE and HbF, the diagnosis could still be confirmed.

Although such manifestations have been documented before, there are a certain unusual observations in this case. First, the EMH masses are more common in either nontransfused or under transfused thalassemia patients postsplenectomy.^[1] As this patient was neither, the exact reason for the EMH could exactly not be explained. Second, platelet count, in this case, was higher as compared what is usual in a nonsplenectomized thalassemia intermedia patient. As the splenomegaly was only moderate and there was neither basophilia nor neutrophilic left shift nor any other evidence of myeloinfiltrative disorder in the peripheral blood smear in the form of leukoerythroblastic blood picture, the probability of a myeloproliferative neoplasm was excluded. The extramedullary foci of hematopoiesis showed a good number of megakaryocytes, the thrombopoiesis from which could be responsible for the high platelet counts. Finally, with regard to the location, the mass was completely lacking any obvious link to the bone marrow.

The present case posed a diagnostic challenge to us, because at the time of biopsy interpretation, the history available was incomplete and hence a multitude of morphologic possibilities was considered. However, only after a detailed clinical history, pedigree analysis, meticulous clinical examination, and a careful radiologic as well as histomorphologic assessment, the complete diagnosis was clinched, and differential diagnoses of other epidural masses (metastatic malignant disease, lymphoma, multiple myeloma, vascular anomalies, or epidural abscess) were excluded. Although there is no consensus on the ideal management scheme, the various modalities include transfusion therapy, radiotherapy, use of HbF-inducing agent and surgical management, requiring an individualized approach.^[1,8]

Conclusion

As is highlighted in this case, a detailed clinical history and appropriate imaging techniques with accurate histomorphologic assessment can help in timely diagnosis. A high index of suspicion for EMH should be maintained in patients with chronic anemia and hematological disease who present with neurological disorders.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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