JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

How to cite this article :
FAKHER RAHIM, BIJAN KEIKHAEI, KHODAMORAD ZANDIAN, AHMAD SOLTANI. DIAGNOSIS AND TREATMENT OF CORD COMPRESSION SECONDARY TO EXTRAMEDULLARY HEMATOPOIESIS IN PATIENTS WITH BETA-THALASSEMIA INTERMEDIA Journal of Clinical and Diagnostic Research [serial online] 2008 February[cited: 2008 February 4]; 2:643-647.
Available from
http://www.jcdr.net/back_issues.asp?issn=0973-709x&year=2008&month= February &volume=2&issue=1&page=643-647 &id=117

CASE REPORT

Diagnosis And Treatment Of Cord Compression Secondary To Extramedullary Hematopoiesis In Patients With Beta-Thalassemia Intermedia

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ABSTRACT

Background: Thalassemia is an inherited autosomal recessive hematological disorder due to genetic defect in synthesis of one of the globin chains. This results in reduced rate of hemoglobin formation and presents as anemia. Depending on whether alpha or beta globin chain is affected they are classified respectively as α thalassemia and ß thalassemia. If only *one* ß globin allele bears a mutation, the disease is called ß thalassemia minor and if *both* alleles have thalassemia mutations, the disease is called ß thalassemia major. Thalassemia intermedia(TI) is a condition intermediate between the major and minor forms. Patients with TI do not receive regular blood transfusions unlike thalassemia major patients. Extramedullary hematopoiesis (EMH) is a compensatory mechanism that occurs in patients with hematological dysfunctions such as Thalassemia Major or Thalassemia Intermedia and Sickle Cell Anemia as a result of continuous erythropoietic stress.

Materials and Methods: We report two cases of TI with EMH. One is a 17 year old girl who presented with back pain and leg weakness and a 25 year old man who was referred to the hospital with back pain, paresthesia, urine frequency and impairment of gait.

Results: Both the patients were successfully treated with low dose radiotherapy and Hydroxyurea (HU). At the end of the therapy, both the patients had recovered well and were ambulatory.

Discussion: Surgical decompression has been the method of choice for the management of the disease. The disadvantages of surgical intervention include risk of excessive bleeding due to high vascularity of the mass. Low dose radiotherapy and hydroxyurea offer better outcomes with reduced morbidity and mortality.

Key words: Extramedullary Hematopoiesis ; Thalassemia Intermedia ; Radiotherapy; Hydroxyurea

Abbreviations: EMH (Extramedullary hematopoiesis),TI (Thalassemia intermedia),HU(Hydroxyurea),MRI (Magnetic Resonance Imaging), cGY(centi Gray),Hb(Hemoglobin), HbF(Fetal hemoglobin)

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Introduction

Thalassemia is common in Iran particularly in south west of Iran. It is estimated, 7-10 percent of

population in Khuzestan province are affected by beta thalassemia minor [1].This syndrome is due to an imbalance of globin chain synthesis. In the case of beta Thalasemia intermedia(TI) , the imbalance is greater than that seen in beta thalassemia trait and less than that of beta thalassemia major[2].TI encompasses clinically and genetically heterogeneous patients [3],[4]. Some patients are able to maintain high hemoglobin levels as a result of huge hematopoietic expansion resulting in bony abnormalities[5].Masses of heterotopic marrow often develop in patients as a result of continuous erythropoietic stress.

Extramedullary hematopoiesis (EMH) is a compensatory mechanism that occurs in patients with hematological dysfunction such as Thalassemia Major or Thalassemia Intermedia and Sickle Cell Anemia [6], [7],[8]. EMH most commonly occurs in organs those have physiological hematopoiesis during embryonic life, especially the liver, spleen and lymph nodes. Other less frequent locations of diffuse compensatory EMH are the kidney, adrenal glands, breasts, spinal cord, pleura, pericardium, duramater, adipose tissue and skin [6], [7] Intra-thoracic EMH is a rare condition that is usually asymptomatic and treatment is unnecessary, except in the presence of complications [6], [9]. Massive hemothorax[9], [10], symptomatic pleural effusion [6],[11], and spinal cord compression [12] are complications of intra-thoracic EMH. Here we present two cases of β-TI with intra-thoracic EMH, who responded to radiotherapy and Hydroxy Urea (HU) therapy.

History of Patients

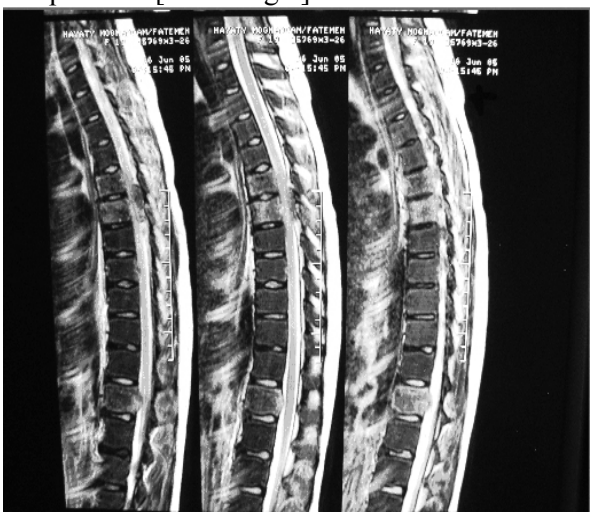
Case 1:

A 17-year-old girl diagnosed with β-TI presented with back pain and leg weakness which started 1 month ago. She had received blood transfusion at, monthly interval between the age of 3 and 4. The patient had received 750 ml of blood each time.The formula used for calculating the blood volume was: (14-Patient_Hb)*3.5*Bodyweight)). Subsequently she has been taking only folic acid tablet.

On admission, she had wide based gait, she was not able to climb stair and could not run. On examination upper extremities did not show any abnormality. However there was sensory level deficit below T5-T6, deep tendon reflexes had decreased, lower limb muscles strength was 3/5. No fecal or urinary incontinency was present. Her liver and spleen were palpable 3 cm below subcostal margin.

The hemoglobin concentration was 10g/dl, hematocrit: 32.2, reticulocyte count: 6%, mean corpuscular volume: 71.6 fl, mean corpuscular hemoglobin: 21.8 pg, mean corpuscular hemoglobin concentration: 30.69g/dl. Red Blood Cell count was 4.49 $\times 10^{12}$ cell/liter, total billirubin- 4.2 mg/dl, direct billirubin: 0.5 mg/dl, serum ferritin: 760ng/ml Hemoglobin Electrophoresis on the alkaline media of acetate cellulose showed Hb A1:0% Hb F: 95% Hb A2:5%.

MRI of thoracic spine with and without contrast were performed and on T2 weighted images demonstrated abnormal bright signal intensity of thoracic vertebrae bodies of T5 , T6 and T12 with bony expansion, retropulsion and epidural soft tissue component due to extramedullary hematopoises which caused thecal sac and cord compression [Table/Fig 1] .



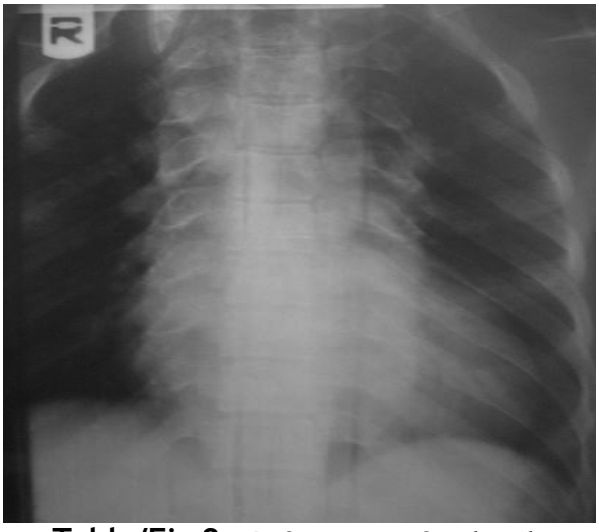
Table/Fig 1: Refer to text for details

Case 2:

A 25 year old man was referred to hospital with back pain, paresthesia, urinary frequency and impairment of gait since last 3 weeks .He was not able to walk without a stick. He had no history of blood transfusion; however, he had splenectomy at the age of 9 years and occasionally took folic acid.

On general examination, he was mildly icteric, his blood pressure was 100/60 mmHg, had an apical 2/6 systolic murmur. Neurological examination of upper extremities showed no abnormality but lower extremities showed muscle atrophy. He had

ankle clonus, exaggerated deep tendon reflexes and sensory deficit below T5-T6 level. Strength in lower extremity muscles were 2/5. The hemoglobin concentration was 10.2g/dl, hematocrit: 32.7, reticulocyte count: 4%, mean corpuscular volume:80.5fl, mean corpuscular hemoglobin: 25.1pg, mean corpuscular hemoglobin concentration: 31.2g/dl , Red Blood Cell count:$4.06*10^{12}$ cell/liter, total bilirubin: 3.2mg/dl, direct bilirubin:0.5 mg/dl , serum ferritin:1519ng/ml Hemoglobin Electrophoresis on the alkaline acetate cellulose showed Hb A1:0% Hb F:98% Hb A2:2% .Uric acid 8.5 mg/dl,calcium:8.5, ,phosphore:5 mg/dl, AST:74U/L, ALT:81 U/L NRBC:320/100WBC. Chest X-ray showed normal sized heart and multiple para-vertebral masses due to EMH and coarsening of trabecular pattern of thoracic bone [Table/Fig 2].



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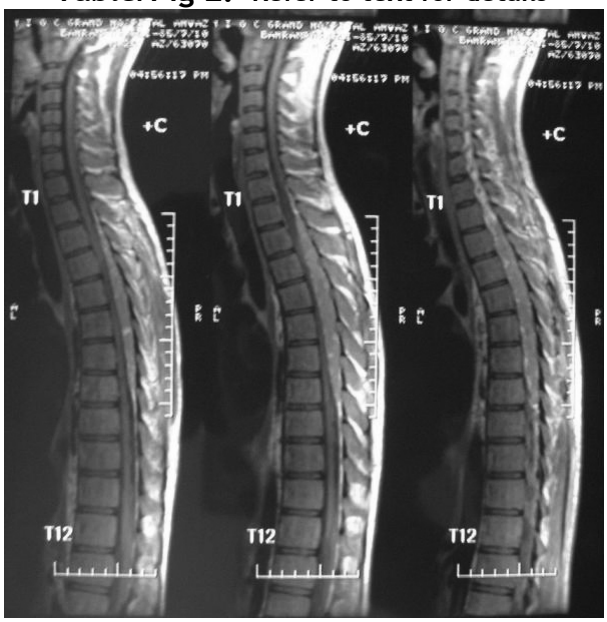

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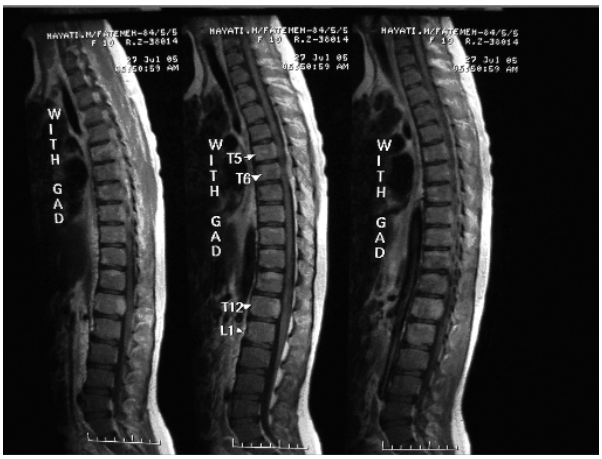
MRI demonstrated extramedullary hematopoitic deposits as posterior epidural disease causing spinal cord compression in the thoracic region[Table/Fig 3].

Treatment:

Both cases were successfully treated with low-dose radiotherapy and HU. Radiotherapy was begun with 200 cGY fractions and escalated to a total dose of 1600 cGY. HU was given at 10mg/kg/day. Both patients received 1600 cGy radiation with cobalt 60 to the thoracic cord in 8 fractions (five fractions per week). Also blood transfusion was given on two occasions in order to increase the hemoglobin level up to14 gm/dl. Hydroxyurea was given 10 mg/kg body weight daily. Duration of treatment was 43 days in case 1 and 30days for case 2. MRI of the thoracic *spine* 43 days after treatment [Table/Fig 4], revealed almost complete resolution of the mass. She was recommended for periodic follow up.



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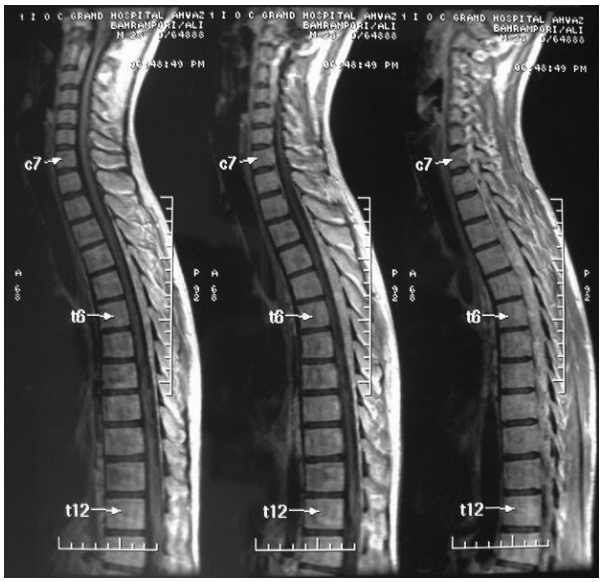
Results

At the end of radiotherapy, both the patients were ambulatory with mild residual weakness. 43 days after therapy MRI of first case showed *significant* resolution [Table/Fig 4]. She was regularly followed up for two years, at present she is active and asymptomatic. Case No 2 was regularly followed up for 6 months, in his last visit, he was able to walk without a stick and he could climb stairs. One month later MRI of second case showed partial resolution of the epidural soft tissue component and improvement in the degree of spinal cord compression [Table/Fig 5].

Discussion:

Spinal cord compression due to EMH is a well described but rare syndrome encountered in several hematological disorders, including Thalassemia, sickle cell anemia, and hereditary



Table/Fig 5: **Refer to text for details**

spherocytosis [7], [9], [10], [13]. EMH is secondary to the production of blood cells outside the bone marrow and is a compensatory mechanism for bonemarrow dysfunction [6]. The common sites of EMH are the liver, spleen and lymph nodes. It has also been seen in the adrenal glands, kidneys, breast, dura mater, adipose tissue, abdomen, chest, and epidural space and skin. [14,15]**.** .There are two forms of EMH namely "paraosseous"-in which the normal medullary tissue of the bone marrow ruptures through the bone to present as a paraosseous mass, and "extra osseous"-in which EMH occurs within soft tissue. Paraosseous EMH occurs more frequently in hemoglobinopathies whereas extra osseous EMH is predominantly seen in myeloproliferative disorders [16]. Involvement of the epidural space by extramedullary hematopoiesis is commonly seen in patients with Thalassemia. It may occur by direct extension from the bone marrow, stimulation of embryonic multipotential hematopoietic stem cells, or via hematogenous emboli. Patients may present with complaints of back pain or spinal cord compression symptoms. Extramedullary hematopoiesis usually forms a soft, red mass resembling a hematoma on its cut surface. On histopathologic analysis, all hematopoietic elements are found in extramedullary hematopoiesis [17]. Recognition of spinal cord EMH requires through physical examination and MRI for accurate diagnosis [18].

Documentation with an imaging technique, such as MRI is mandatory [19]. Bony abnormalities are seen on plain radiographs evidenced by osteoporosis with coarsened trabeculation. With severe involvement, there is expansion of the bony cortex also. Spinal cord involvement may be suggested by the presence of paraosseous masses seen on chest radiographs. Along with the bony abnormalities, CT demonstrates extramedullary hematopoiesis as a soft-tissue mass that is often adjacent to the involved bone. Extramedullary hematopoiesis can be distinguished from the epidural fat because the former has attenuation similar to that of muscle and shows enhancement with intravenous administration of contrast material [20]. MRI is the most effective method of demonstrating extramedullary hematopoiesis in the epidural space and is indicated on an urgent basis when symptoms of spinal cord compression are present. On T1-weighted images, extramedullary hematopoiesis is seen as an extramedullary mass with signal intensity slightly higher than that of the adjacent red marrow of the vertebrae. Similar findings are seen on T2-weighted images, with the signal intensity of extramedullary hematopoiesis being only slightly higher than that of bone marrow. Post-contrast imaging may help better delineate the epidural soft tissue component. T2-weighted sequences may be useful, however, to demonstrate the high signal intensity of an injured spinal cord. This high signal intensity could be from edema, myelo-malacia, or gliosis of the spinal cord due to chronic compression [21]. The most common site of spinal epidural extramedullary hematopoiesis is posterior thoracic spine. The epidural space between the spinal dura mater and the ligaments and periosteum of the posterior spinal elements contains fat, loose connective tissue, and venous plexuses. It is widest in the posterior thoracic spine and is the most common site for extramedullary hematopoiesis when the spinal cord is affected [22]. Management strategies have included radiotherapy, blood transfusion and, occasionally, surgery [23], [24]. Spontaneous recovery with no therapeutic intervention has also been reported, but may take several months to occur and is subject to frequent recurrence and morbidity [25]. Although there is limited experience with HU in thalassemia, some studies have demonstrated successful regression of EMH with HU therapy [26], [27], [28].

Radiation in conservative doses of (750-3500 cGy) is non-invasive, avoids the surgical risks of

potentially severe hemorrhage and incomplete resection, and has a high complete remission rate in the majority of patients. Relapse rates are moderate (37.5%), but re-treatment provides excellent chance for second remission [17]. EMH can be prevented by the institution of regular transfusion therapy, which corrects anemia and thereby, abolishes the stimulus for EMH. Surgical decompression has been the method of choice for the management of the disease because histological diagnosis can be established, and immediate decompression of the mass can be achieved. This is especially important in rapid decompression of spinal cord in patients with epidural mass caused by EMH [29]. The disadvantages of surgical intervention include risk of excessive bleeding due to high vascularity of the mass and higher incidence of recurrence. Furthermore, total resection of the mass can lead to clinical decompensation and deterioration since these masses play a crucial role in maintaining an adequate hemoglobin level. To avoid this, incomplete resection of the mass can be attempted, followed by low dose radiation therapy. Being very sensitive to radiation therapy, low doses of radiation (1000-3000 cGy), bring about a good clinical response. The major disadvantages of radiation therapy are the lack of histological diagnosis and the reduction in the bone marrow activity secondary to the procedure itself. Hydroxyurea, a myelosuppressive agent, has also been successfully employed in the management of EMH[30].The differential diagnosis of the posterior mediastinal locations of EMH includes neurogenic tumours, lymphoma, paravertebral abscess and metastatic carcinoma. In geographic areas where thalassemia is prevalent, EMH should be considered in the differential diagnosis of patients who have chronic anemia with an intrathoracic mediastinal mass.

Acknowledgment

Authors want to thanks patients and their families. This work was supported by Physiology and Thalassemia Research Center, Ahwaz Jondishapur University of Medical Sciences**,** Ahwaz, Iran.

JCDR services were used in improving and redrafting this manuscript.

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