Cord Compression due to Extramedullary Hematopoiesis in an Adolescent with Known Beta Thalassemia Major

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ABSTRACT

We describe a 16 year-old male with ß thalassemia major and gait disturbances that had not been given blood transfusions due to a severe childhood transfusion reaction. Thoracic spine MRI demonstrated hematopoietic marrow throughout the spine and epidural masses causing cord compression consistent with extramedullary hematopoiesis (EMH). After treatment with steroids, radiotherapy and monitored blood transfusions, the patient demonstrated significant improvement of his paraspinal lesions and near complete resolution of his neurological symptoms. While EMH causing cord compression in adolescents is rare in the current era of bone marrow transplantation or chronic transfusions, it should be considered when thalassemia major patients present with neurological deficits. The well defined imaging features of EMH can play a central role in its diagnosis and management, especially because surgical and / or radiotherapeutic intervention are often considered in cases of failed medical treatment.

CASE REPORT

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INTRODUCTION

ß -Thalassemia major is the most severe form of the ß–Thalassemias, a group characterized by a genetic defect in the production of hemoglobin ß-globin chains that causes a relative excess of α-globin chains, ineffective erythropoiesis and peripheral destruction of red blood cells. ß-thalassemia major is distinguished from the rest of its group on the basis of clinical severity, with ß-thalassemia major presenting as a transfusion dependent anemia, ß-thalassemia intermedia as an anemia not requiring transfusion, and ß-thalassemia minor indicating a usually asymptomatic heterozygous state (1). Individuals of Mediterranean descent are among the groups with increased incidence of B-Thalassemia major condition (2). The clinical course is characterized by severe anemia with resultant complications, including the formation of massive deposits of extramedullary hematopoietic tissue. This tissue may occur within the spinal canal, resulting in neurological compromise secondary to the compression of neural structures (2, 3). EMH is reported to be rare in children (4, 5), especially in the current era of commonly treating blood dyscrasia patients with bone marrow transplants, transfusions and with fetal hemoglobin stimulating drugs such as hydroxyurea (HU)

(6, 7). There have been a few reports in the literature describing spinal cord compression by such a disease process in the pediatric population (4, 8, 9). We present an adolescent patient who was not given transfusions throughout the majority of his life due to a severe transfusion reaction he experienced early in his disease course, and who, despite being on HU therapy, developed extramedullary hematopoietic masses causing cord compression and resultant neurological symptoms.

CASE REPORT

16-year-old male of mediterranean and baltic descent with beta thalassemia major presented with a 10-day history of worsening gait. Four months prior to presentation the patient reported a self limited episode of low back pain. Two months after this episode he noted numbness and tingling of his legs that had progressed to his current gait disturbance. An outpatient pediatric neurologist noted clonus on the patient's physical exam and referred him to our emergency department (ED) for further evaluation. Upon presentation to the ED, the patient denied any bowel or bladder symptoms, gave no history of trauma, and had a hemoglobin count of 8.8 g/dl, a hematocrit of 27% MCV of 90.4 fL and a MCH of 29.5 pg. Subsequent hemoglobin electrophoresis revealed 6.7% HbA, 1.0% HbA2 and 92.3% HbF. The patient has a family history of a deceased first degree relative with medulloblastoma, and another who is a living beta thalassemia carrier. While the patient has beta thalassemia major, he has not had a transfusion for over 13 years due to a history of severe transfusion reaction early in his disease course (hemolytic anemia). The patient is status post splenectomy and was on daily regimen of HU and growth hormone (GH). The patient was reported to not have taken GH for 3 weeks prior to presentation.

Physical exam was remarkable for bilateral lower extremity decreased muscle tone, minimal right lower extremity weakness, bilateral ankle clonus, and 3+ patellar reflexes bilaterally. Gait testing demonstrated no truncal ataxia, however some unsteadiness when standing was observed. The cremasteric reflex was also noted to be absent. No spinal tenderness was appreciated. MRI of the brain exhibited marked thickening of the calvarium, skull base and facial bones secondary to marrow hypertrophy (Fig. 1).

MRI of the thoracic spine demonstrated abnormal signal within the marrow with decreased signal on T1-weighted images, most prominent at the T6 level, with thickened adjacent ribs also showing some abnormal marrow signal (Fig. 2, Fig. 6). T6 level posterior enhancing epidural masses were also identified, noting to be causing cord compression. Sagital T2-weighted and STIR images showed focal cord compression and cord signal abnormality consistent with edema. The findings were consistent with multiple foci of EMH, some resulting in focal cord compression.

The patient was admitted for medical evaluation and stabilization, and was started on steroids and blood transfusions preceded by pre-medication. He was also treated with 1500 cGy of radiation therapy targeted to the T5-T7 region, as 300 cGy over five fractions, over seven days, with dose two given on day four and the remaining doses given a day apart respectively. The patient's hemoglobin was elevated from 8.8g/dl to 10.1g/dl, with his hematocrit rising from 27.0% to 30.8%, and with no transfusion reaction having been noted. The patient's steroid dosage was decreased on hospital day number 5, in response to improved gait and sensation, and he was discharged on day 10 with his only neurological deficit being decreased sensation in his feet bilaterally. Follow up imaging of the thoracic spine was performed at 2 months post discharge and showed significant improvement of the epidural masses within the mid thoracic spine with no evidence of cord compression and moderate spinal stenosis noted at the T6 level (Fig. 7).

DISCUSSION

EMH is the production of blood cell precursors outside the bone marrow that occurs in various disorders, such as thalassemia, sickle cell anemia, hereditary spherocytosis, polycythemia vera, myelofibrosis and other hematological diseases. In chronic anemia, it is a physiological response to increased erythropoietin. In some other conditions, such as myeloid metaplasia, polycythemia vera or chronic myeloid leukemia, EMH is due to a clonal disorder of hematopoiesis that enables progenitor cells to escape from the marrow and lodge in other organs (7). EMH can occur in any tissue of mesenchymal origin and has been described in a wide variety of organs, including in the chest, abdomen, and neural axis, but it typically involves the liver and spleen. The resulting masses can be seen as hepatomegaly, splenomegaly, paraspinal masses and extramedullary hematopoietic tissue. EMH may diffusely infiltrate the organ (such as in the liver and spleen) or form pseudotumors (such as in the paravertebral region of the chest). Rarely, peritoneal and small bowel involvement with EMH is seen, taking the form of pseudotumor masses, mural deposits such as serosal implants, or within abdominal lymph nodes seen at histology. Clinically presentations due to EMH lesions include neurological symptoms, upper airway distress, obstructive uropathy, or intestinal intussusception (4, 8, 10).

The onset of neurologic symptoms in a patient with an underlying blood dyscrasia should raise concern for cord or thecal sac compression by an extramedullary hematopoietic process (8). The first documentation of cases of spinal cord compression from extramedullary hematopoiesis was described by Gatto in 1954, based on clinical examination and myelography (11). At present, however, the imaging features of extramedullary hematopoiesis on CT or MR imaging are well defined and play the central role in diagnosis (4, 12).

The imaging findings of EMH are variable and have been described almost entirely for focal deposits of EMH. The variability of EMH on imaging has been hypothesized to be secondary to variations in the relative amounts of the normal marrow constituents such as fat, hematopoietic cells, and fibrosis deposited within the EMH mass (10). The appearance of ovoid masses with well-defined margins and soft tissue density is suggestive of extramedullary hematopoietic tissue. These masses are usually adjacent to bony structures such as ribs or vertebrae, and present specific trabeculations arising from the cortex. Destruction of the bone by an expansive medullary process is thought to generate these trabeculations

(4). On ultrasound, focal EMH can appear as echogenic, hypoechoic, or heterogeneous masses. On computed tomography, focal EMH is often a heterogeneous hypodense mass with absent, minimal, or heterogeneous enhancement. Burnt out EMH has been described as predominantly of fat density with little or no contrast enhancement or as showing iron deposition. Because the imaging appearances of focal and diffuse peritoneal EMH are nonspecific, histological diagnosis is required (10). Splenic EMH has also been noted to be able to be imaged to varying degrees via ^{52}FE citrate PET, ^{99m}Tc-SC, ^{99m}c-methylene diphosphonate (MDP), ^{201}Tl-chloride, ^{67}Ga-citrate, and FDG-PET scan imaging (13). EMH masses on MRI, (Fig. 2 – Fig. 6), can appear heterogeneous when they incompletely replace epidural fat, but can appear homogenous if they replace this fat completely. On T1W images EMH is almost always hyperintense to both the spinal cord and the infiltrated vertebral marrow. EMH is hyperintense on fast and conventional spin-echo T2W images except when there is excessive iron in the erythroid tissue, as in specific subtypes of myelodysplastic syndrome. In this specific instance, EMH will appear hypointense on T2W images. Although hematopoietic tissue is highly vascular, gadolinium enhancement of EMH is unpredictable, and has been reported to show moderate enhancement, (as was seen in our case), strong enhancement, or no enhancement. The reason behind this phenomenon is unclear (14). If clinically unusual history or inconclusive imaging is obtained, the diagnosis can be confirmed by fine-needle aspiration cytology, on which samples of EMH will demonstrate hematopoietic cells from all 3 hematologic cell lines (4).

A suggested mechanism for EMH is expansion of marrow via tiny fractures associated with thalassemia. Because this usually develops in the second and third decades of life, extramedullary hematopoiesis is an unusual complication of beta thalassemia major in children (4). In the case of our patient, his history of transfusion reactions resulted in him not receiving blood transfusions for at least 13 years, and led him to instead be treated with the HbF stimulating agent hydroxyurea, and growth hormone. Although a relatively small number of previous studies suggest a modest response to HU therapy in β -thalassemia, more recent investigations have revealed that some transfusion-dependent patients can become transfusion-independent following HU therapy. HU has also been found to be effective in improving symptomatic cord compression because of paraspinal EMH (6). A growing body of literature suggests variability in response to HU therapy among β-thalassemia patients may be due to the genetic heterogeneity of the disease, with certain genetic mutations being more responsive to HU therapy than others (6, 15). Some studies have also shown recombinant human erythropoietin and hematopoietic growth factors may act in a synergetic manner if used in combination with agents such as HU (15).

Several treatment options involving permutations of blood transfusion therapy, HbF stimulating drugs such as HU, radiation therapy, and laminectomy have been proposed for cord compression secondary to EMH (4, 7, 12). Some sources claim up to 50% of treated patients can be managed by radiation therapy alone, stating that this regimen is the treatment of choice because hematopoietic tissue is very sensitive to radiation damage (16). Cario's paper showed radiotherapy to be effective in the majority of treated patients and superior to previously used surgical procedures, where a modest dose of 10–30 Gy often achieved a rapid response (8, 17), (Our patient received 15Gy targeted to the T5-T7 levels as Five 300 cGy fractions). Others consider radiation therapy treatment of a spinal cord that is already damaged by advanced extramedullary hematopoietic tissue as an additional exposure to potential cord injury, and suggest surgical intervention is a superior alternative (8). Niggeman et al described an adolescent patient for whom radiation therapy originally appeared effective, but who then experienced recurrence of symptoms after a short period, making an operative approach necessary (16). Overall, it appears that the relative benefit of one treatment over another has not been clearly established, perhaps partly due to the infrequency of this disorder.

Salehi et al. performed a review of literature that found 5 documented cases of Extramedullary Hematopoiesis in adolescents. In these cases patients all presented with paraparesis, 2 of which achieved full recovery after surgical intervention, 1 case achieved partial recovery after surgery and 2 cases achieved partial recovery after XRT and or transfusion (8). Khen-Dunlop et al. presented a case of EMH in the pelvis of a 15 yr old girl with thalassemia intermedia who was treated surgically after treatment with HU and blood transfusions failed (4). Tai et al described an adolescent with cord compressions secondary to EMH whose disease course occurred after splenectomy, while receiving intermittent transfusions over her disease course (9). In our case the patient achieved near full neurological recovery after medical treatment with steroids, hypertransfusion and radiation therapy.

In this current era of managing children with blood dyscrasias with bone marrow transplantation, chronic transfusion, and HbF stimulating drugs such as HU, EMH in adolescent patients is rare. However, when faced with an adolescent with known blood dyscrasia and new onset of neurological symptoms, CNS compression by EMH secondary to variations in treatment should be considered as a potential etiology. The well defined imaging features of extramedullary hematopoiesis on CT or MR imaging can play a central role in its diagnosis and management, especially because surgical and / or radiotherapeutic intervention are often considered in cases of failed medical treatment.

TEACHING POINT

Among adolescent patients with known, reportedly managed blood dyscrasias and new onset of neurological symptoms, the currently standard practices of bone marrow transplantation, chronic transfusions and HbF stimulating medications make EMH a rare occurrence. This case illustrates the value of recognizing variations in management due to secondary factors, such as a remote history of transfusion reaction or variability in response to therapy, as a catalyst for making relatively uncommon etiologies such as extramedullary hematopoiesis more likely.

ABBREVIATIONS

ED = Emergency department
EMH = Extramedullary hematopoiesis
GH = Growth hormone
HbF = Fetal hemoglobin
HU = Hydroxyurea
MDP = Methylene diphosphonate
SC = Sulfur colloid

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FIGURES

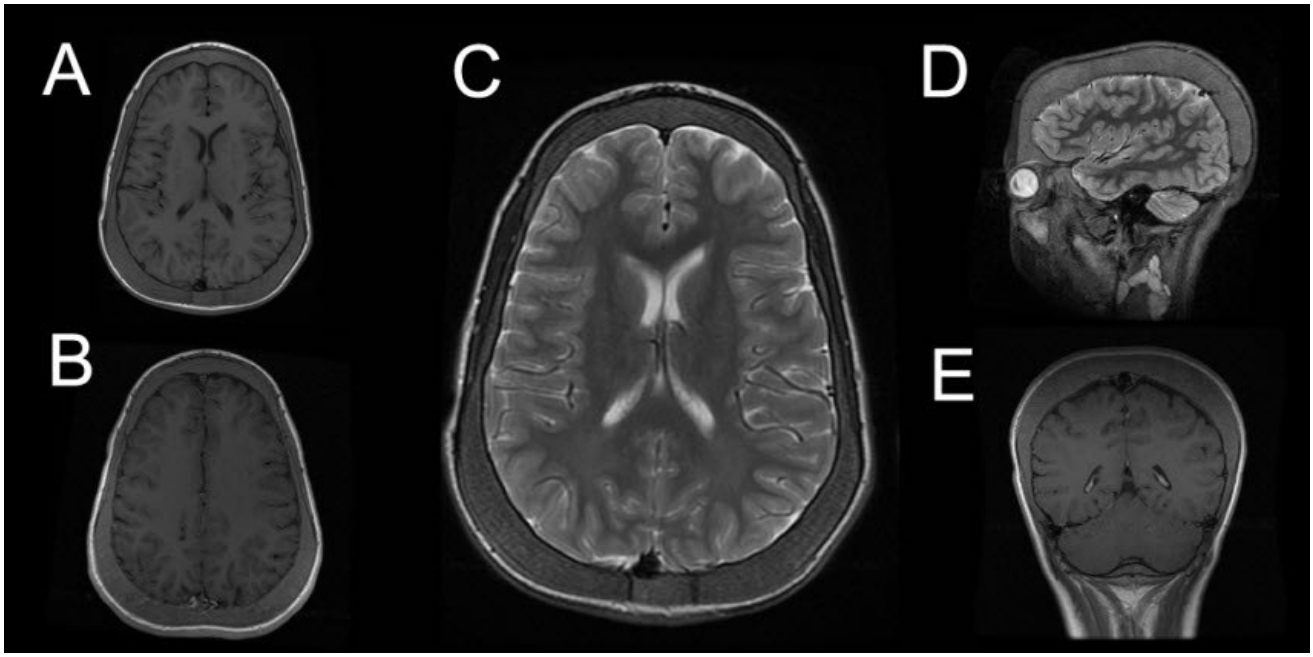

Figure 1: 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Observed calvarial thickening on initial MRI brain study. A: Axial T1 pre contrast, B: Axial T1 post contrast, C: Axial T2 pre contrast, D: Sagittal STIR pre contrast, E: Coronal T1 post contrast. All images obtained on a 1.5T MRI machine.

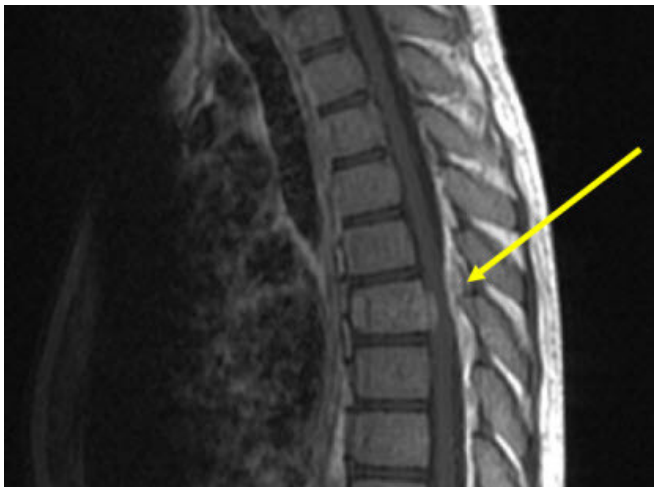

Figure 2: 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Sagittal T1-weighted post contrast image obtained on a 1.5T MRI machine. Arrow shows epidural enhancing mass resulting in cord compression at approximately the level of the T6 vertebral body.

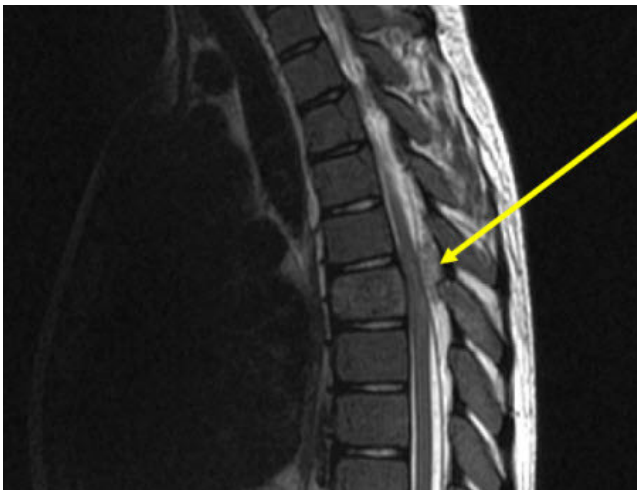

Figure 3: 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Sagittal T2-weighted pre contrast image obtained on a 1.5T MRI machine demonstrates posterior epidural mass resulting in cord compression and cord edema at approximately the level of the T6 vertebral body.

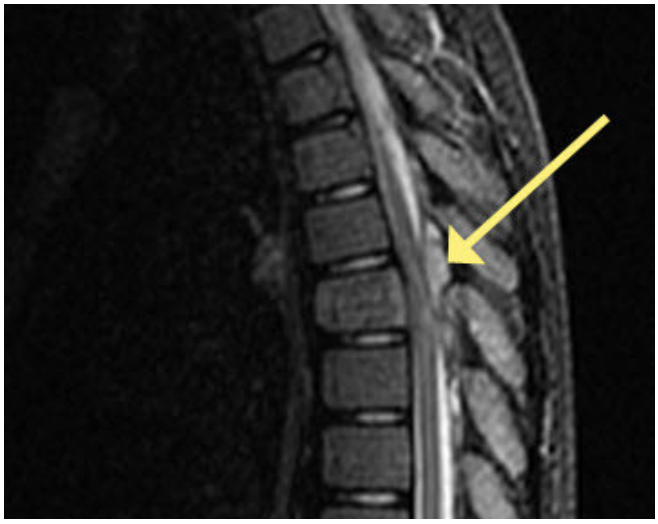

Figure 4: 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Sagittal STIR pre contrast image obtained on a 1.5T MRI machine demonstrating posterior epidural mass (arrow) resulting in cord compression and cord edema at approximately the level of the T6 vertebral body.

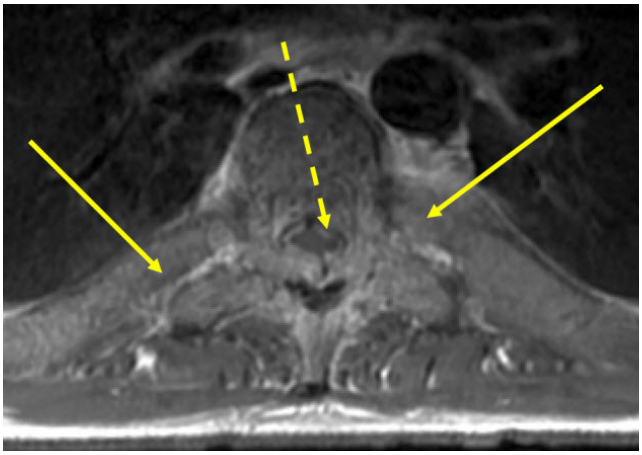

Figure 6: 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Axial T1-weighted post contrast image obtained on a 1.5T MRI machine at level of T6 vertebral body demonstrates paraspinal masses (arrows) consistent with extramedullary hematopoiesis and enhancing epidural masses (dashed arrow) resulting in thoracic spinal cord compression.

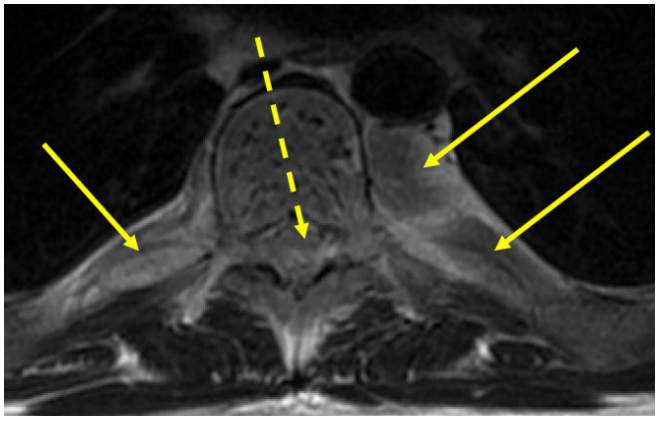

Figure 5 (left): 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Axial T2-weighted pre contrast image obtained on a 1.5T MRI machine at level of T6 vertebral body shows paraspinal masses (arrows) consistent with extramedullary hematopoiesis. Dashed arrow demonstrates region of central canal compromise by mass.

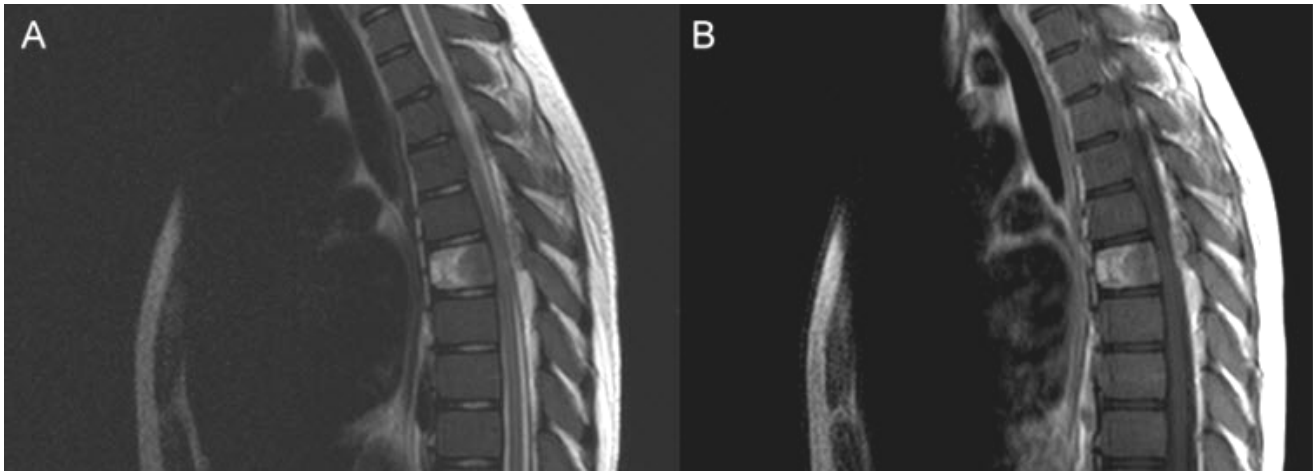

Figure 7: 16 year old man with cord compression due to with Thalassemia major related extramedullary hematopoiesis. Two month follow up imaging demonstrating interval improvement of paraspinal masses at T6 level with mild residual spinal stenosis but no definite cord compression. A: Sagittal T2 pre contrast, B: Sagital T1 post contrast. All images obtained on a 1.5T MRI machine.

KEYWORDS

Adolescent extramedullary hematopiesis, cord compression, thalassemia

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