## Paraplegia due to extramedullary hematopoiesis in thalassemia treated successfully with radiation therapy

**Spinal cord compression due to extramedullary hematopoiesis (EMH) is a rare complication of thalassemia and generally presents as paraparesis with sensory impairment. Complete paraplegia is extremely rare in EMH due to thalassemia although it is known to occur in polycythemia vera and sickle cell anemia. Treatment options mostly include surgery and/or radiotherapy. Whereas cases presenting with paraparesis have been treated with either surgery or radiotherapy with equal frequency and efficacy, almost all reported cases with paraplegia have been treated with surgery with or without radiation therapy. We hereby report a case of thalassemia intermedia with paraplegia treated successfully with radiotherapy.**

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*Introduction*

Thalassemia intermedia includes a wide spectrum of disorders with defective synthesis of the globin moiety of hemoglobin. Extramedullary hematopoiesis (EMH) is a compensatory phenomenon and commonly involves the liver, spleen and lymph nodes. Spinal cord compression due to EMH is an extremely rare complication. Only isolated reports have described patients with complete paraplegia, none of whom have been treated with radiotherapy alone.[1] We present a case of a patient of thalassemia intermedia with paraplegia treated successfully with radiotherapy alone.

*Case report*

A 27-year-old male presented with a 12 month history of parasthesias and weakness of both lower limbs, progressive difficulty in ambulation and sphincter disturbances. He was diagnosed as case of thalassemia at the age of 2 years when he presented with a hemoglobin level of 6.8 g/dL following a febrile episode. Through the first decade of life, he maintained a hemoglobin level of 9-10 g/dL without blood transfusions which was attempted only once at the age of seven years and abandoned due to acute transfusion related reactions, details of which were not available. In the second decade of life his hemoglobin level was maintained at 6-7 g/dL. He also had a history of recurrent fractures, either spontaneous or following trivial trauma, involving long bones of the extremities from the age of three years. Sites of fracture were the right tibia thrice (at the ages of 3, 25 and 26 years), right ulna twice (at age of 10 and 18 years), left radius at the age of 7 years and right tibia and fibula simultaneously at the age of 27 years.

Physical examination revealed a young male with a height of 158 cm and weighing 38 kgs with poor muscular development. He had characteristic *facies* with frontal bossing, prominent malar prominences due to maxillary hypertrophy and depression of nasal bridge. He was pale and icteric. Liver and spleen were enlarged, 5 and 6 cm below costal margin respectively. Higher mental functions and cranial nerve examinations were normal. Motor system examination revealed increased tone in lower limb muscles with complete loss of power (grade 0/5) in all muscle groups of the right and proximal muscles of the left lower extremity. Power in the distal muscle groups of the left lower limb was 1/5. Deep tendon reflexes were exaggerated in both lower limbs with bilateral extensor planter response. There was complete sensory loss below T6 level. Superficial reflexes were absent below T6. There was tenderness over the T4 vertebra.

Laboratory investigations were; hemoglobin 6.6 g/dL, WBC count 12.8x10$^9$/l platelet count 273x10$^9$/l, mean corpuscular volume 70.9 fl. Peripheral smear showed anisopoikilocytosis, tear drop cells, polychromasia, nucleated RBCs and target cells. Hemoglobin electrophoresis showed 97.4% HbF and 2.6% HbA2. HbA was absent. Biochemical investigations were: serum bilirubin-7.8 mg/dL (uncongugated bilirubin – 6.8 mg/dL), blood urea 15 mg/dL, serum creatinine 0.6 mg/dL, serum calcium 9.6 mg/dL, serum phosphorous 3.6 mg/dL, random blood sugar 105 mg/dL, alanine aminotransferase 14 IU/dL, aspartate aminotransferase 11 IU/dL, serum ferritin 237 ng/mL. Tests for viral hepatitis markers (HBsAg, HCV antibody) were negative. Plain radiographs of the limbs showed diffuse osteopenia with coarse trabecular pattern and cortical thinning. Dexa scan showed a Z score of less than 4 standard deviation compared to the mean. Magnetic resonance imaging (MRI) of the spine (Figure 1, Figure 2) showed extradural and paravertebral masses extending from T5 to T10 causing cord compression. The appearances of the masses along with the known underlying hematological condition was strongly suggestive of EMH.

The patient underwent packed red blood cell transfusion to keep his hemoglobin level above10 g/dL. He was also started on calcium and folic acid supplements. Due to severe osteoporosis, he received intravenous infusion of zoledronic acid 4 mg. A neurosurgical opinion was sought, but the patient was opined to be a poor candidate for surgical decompression in view of large extent of lesion, risk of spinal instability due to severe osteoporosis, possibility of hemorrhage and hemodynamic instability due to anemia. He was planned for radiation therapy to the involved region of the spine. He received a

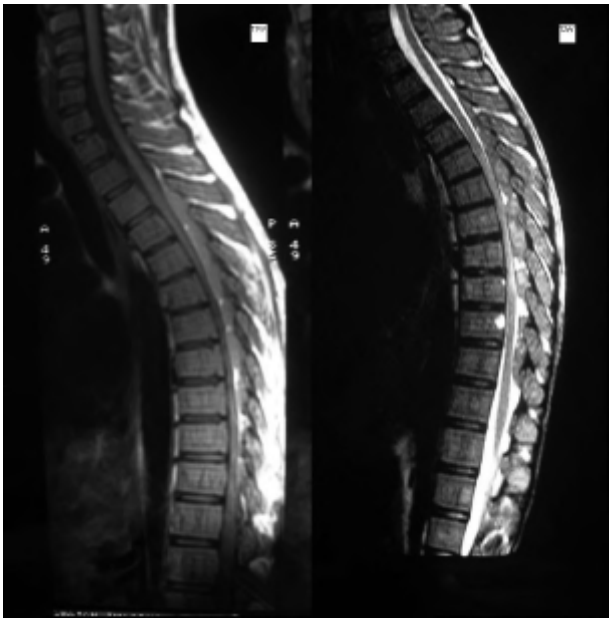

Figure 1. sagittal T1W and T2W images show a large epidural mass (isointense to marrow on both T1W and T2W) occupying the posterior part of the spinal canal, extending from D5 to D10 level. The mass is displacing the spinal cord anteriorly and compressing it. Also noted is the diffuse hypointensity of marrow of all vertebrae suggestive of reconversion of marrow.

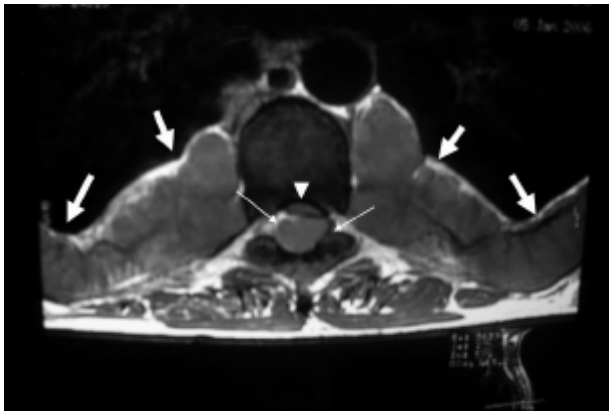

Figure 2. Axial T2W image shows that the cord is flattened and displaced anteriorly (arrowhead)by the epidural mass (thin white arrow). In addition the large bilateral paravertebral mass and expanded posterior ends of ribs are seen (thick white arrow).

total dose of 2000 cGy in 10 fractions (200 cGy per fraction) over 2 weeks delivered by a cobalt-60 teletherapy unit using a single direct posterior field at a skin-source-distance of 80 cm with dose prescribed at a depth of 5 cm. Bilateral lower extremity power improved to grade 3/5 after the first fraction of radiotherapy and to 4+/5 by the end of treatment. He also regained sphincter control and sensations by the end of treatment.

*Discussion*

Extramedullary hematopoiesis (EMH) can occur in many disorders including thalassemias, polycythemia rubra vera, myelofibrosis, hemolytic anemia and other hemoglobinopathies. Spinal cord compression due to EMH in thalassemia was first reported by Gatto in 1954.[2] It usually has a predilection for the lower thoracic spine where the limited mobility and narrow spinal canal predisposes itself to spinal cord compression.[3,6] Most cases present with paraparesis, sensory impairment and occasionally sphincter disturbances. Complete paraplegia has been reported very rarely in thalassemia and occurs more frequently in polycythemia rubra vera and sickle cell anemia.[1] The diagnostic procedure of choice is magnetic resonance imaging (MRI) which characteristerically shows an isointense mass with a high spinal intensity rim on T1-weighted images and a hyperintense mass on T2-weighted images.[4] The diagnosis is based on strong clinical suspicion in the presence of diffuse bone marrow hyperplasia along with symmetric paraspinal and epidural masses. Most authors do not favor a tissue biopsy in this situation.[5]

Treatment options for cord compression are surgery, radiation therapy, blood transfusions, hydroxyurea or various combinations thereof. Due to the extreme rarity of this condition, direct comparisons between various treatment modalities are not possible. Most reported cases of paraplegia due to EMH from any cause have been treated with surgical decompression with or without radiation therapy.[1] The bias towards surgery in these cases is due to its immediate decompressing effect. Some authors also believe that radiation therapy may cause initial worsening of symptoms due to tissue edema. However, this can be easily prevented or controlled with concomitant steroid therapy.[6] Hemopoietic tissue is extremely sensitive to radiation and low doses cause rapid shrinkage. In cases of EMH causing cord compression in thalassemia, improvement is clinically evident after an average of three fractions of radiotherapy and near complete recovery is generally observed by the end of treatment.[7] Doses used have ranged from 750-3500 cGy.[4] With these low doses, the only significant toxicity that may occur is a further decrease in blood cell counts which need to be frequently monitored.[8] Excellent results have been obtained in cord compression due to EMH in thalassemia with radiotherapy alone. Recurrence rates of about 19% have been reported but these cases are amenable to treatment with further radiation.[4,9]

Salehi *et al.*[1] have reviewed cases of spinal cord compression due to EMH. Of the 56 cases, 42 (34 males and 8 females) were patients of thalassemia none of whom had paraplegia with complete motor and sensory loss. There were 5 cases with complete paraplegia, 4 associated with polycythemia vera and 1 with sickle cell anemia. 4 of these cases were treated with surgical decompression with or without radiotherapy and transfusions but none of them showed any recovery. A 52- year-old male with polycythemia vera was treated with external radiation alone and showed good partial recovery.[10] In cases where radiation therapy as a sole modality fails to control the symptoms, surgical decompression with postinterventional radiation therapy can achieve good results.[11]

EMH in thalassemia has been treated with transfusion therapy with the rationale that correction of anemia would downregulate erythropoietin and lead to reversal of EMH. However, improvement is usually incomplete and short lived.[12] Currently, it can be recommended only in cases of mild spinal cord compression[13,14] or in special cases like pregnant patients where it may obviate the need for surgery or RT.[15] It is useful as an adjunct to surgery and RT. A few authors have reported good results with the use of hydroxyurea along with hypertransfusion.[16,17] The drug, in addition to its cytostatic effects, has a favorable effect on foetal hemoglobin production. Gamberini *et al.*[17] treated a 24 year old patient of thalassemia intermedia with paraplegia due to EMH, with hydroxyurea 1000 mg/day for 5 months followed by 500 mg/day upto 25 months. Neurological improvement occurred in 6 weeks but symptoms recurred in 5 months and were managed with radiotherapy. Since our patient showed 97.4% foetal hemoglobin on electrophoresis, hydroxyurea was not considered.

Our patient showed rapid and near complete recovery with radiation therapy alone despite having long standing paraparesis and paraplegia. Therefore, we conclude that radiation therapy may be the optimal therapeutic approach in such cases.

*Conclusions*

In cases of paraplegia due to EMH, there seems to be a bias towards surgical decompression with the aim of causing rapid decompression. Surgery may be associated with various complications including bleeding, hemodynamic instability, spinal instability etc. Radiation therapy is a simple, safe and effective approach for the treatment of spastic paraplegia consequent to spinal cord compression due to EMH. Fears of neurological deterioration due to radiation induced edema remain unfounded. Recovery of neurological function is rapid.

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