SPINAL CORD COMPRESSION DUE TO EXTRAMEDULLARY HEMATOPOIESIS IN THALASSEMIA: EFFECTIVE RESULTS OF RADIOTHERAPY: A REPORT OF TWO PATIENTS AND REVIEW OF THE LITERATURE

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ABSTRACT

Spinal cord compression due to extramedullary hematopoiesis is a rare complication in patients with thalassemia. Radiation therapy is one of the effective modalities of treatment. This is a report of two patients with thalassemia who had different degrees of paraplegia due to spinal cord compression from extramedullary hematopoietic tissues. The neurological symptoms relived after radiotherapy. The results confirm the role of radiation therapy as an effective treatment for this complication.

Keywords: Spinal cord compression, Extramedullary hematopoiesis, Thalassemia, Radiation therapy

INTRODUCTION

Extramedullary hematopoiesis (EMH) is a compensatory mechanism encountered in chronic anemia such as thalassemia, hemolytic anemia, myelofibrosis and other hemoglobinopathies.[1-12] The most common sites of EMH are liver, spleen and lymph nodes.[4]

Spinal cord compression from EMH is a rare condition. The ideal treatment is controversy. Treatment options include surgery, radiotherapy, blood transfusion, hydroxyurea therapy or any combination of this modalities.[14-20]

The reported cases presented with paraplegia and the diagnosis was based on clinical history and computed tomography findings. Awareness, carefully evaluation, early diagnosis and prompt treatment can prevent the irreversible damages to the spinal cord and help the patients to be relieved from the symptoms and get their good quality of lives back.

CASE HISTORY 1

A 36 years old Thai male with known history of thalassemia major presented with progressive lower limb weakness, numbness and progressive gait difficulties over a period of 4 weeks. He complained of impairing of sensation on the trunk, just above the nipple line down to both lower limbs and both feet. Two weeks before this visit he was unable to walk accompanied with uncontrollable micturation and defecation. His past medical history revealed right distal ureteric stone and gout. Splenectomy was done last 11 years. He has one sister with thalassemia.

Physical examination revealed pallor and mild jaundice. His blood pressure was 110/70 mmHg, pulse rate was 86/minutes with regular rhythm and normal body temperature. Systolic ejection murmur was detected along the left parasternal border. The liver was enlarged 7 cm. below the right costal margin. It has smooth surface with hard consistency on palpation.

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His neurologic examination revealed normal mental status, fully alert, oriented with normal speech and language. Cranial nerves were normal. He was paraparetic, and muscle strength was 2/5 for the proximal and 2/5 for the distal muscles on both sides. Neither muscular atrophy nor fasciculation was detected. Deep tendon reflexes were hyperactive and the plantar responses were extensor on both sides. There was sensory loss to pin-prick starting from the T4 dermatome downwards.

On laboratory examination, his hemoglobin levels were 6.1 gm%, Hct 24.0 %, RBC 3.13 ml/ cu.mm, MCV 76.6 fl, MCH 19.3 pg, MCHC 25.2 g/dl, leukocyte 32,000 cells/cu.mm. (PMN 42%, lymphocyte 48%, Band form 3%, Myelocyte 3%, Metamyelocyte 4%), platelet 589,000 cells/cu.mm. Blood smear showed few anisocytosis and poikilocytosis. Hypochromia (3+) was present.

The renal function tests were normal.

Chest radiography showed mild cardiomegaly with paravertebral soft tissue shadow along both sides of mid thoracic spines, compatible with extramedullary hematopoiesis. The bony trabeculations of the thoracic cage are coarse (Fig. 1).

Non-contrast enhancement CT scan of the thoracic spines was done and the result revealed hyperdense, nodular-shaped mass running along the posterior aspect of spinal canal, compressing the thecal sac and displacing the thoracic cord anteriorly, from the upper T3 level to mid T10 levels (Fig. 2, 3, 4).

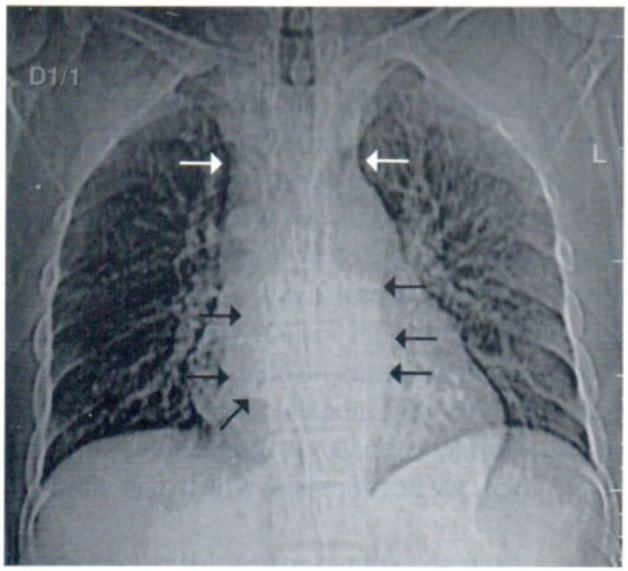

Fig.1 Chest roentgenograph demonstrates coarse bony trabeculations and paravertebral soft tissue shadow along both sides of mid thoracic spines.

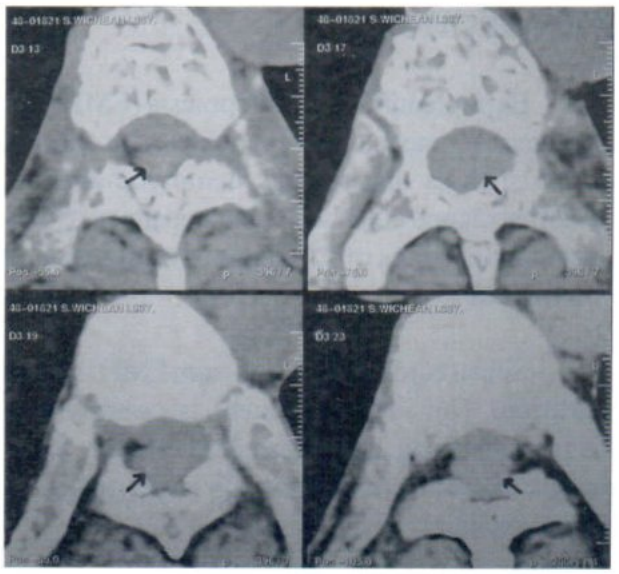

Fig 2 Axial non-contrast enhancement CT scan shows the mass causing compression and anterior displacement of the spinal cord.

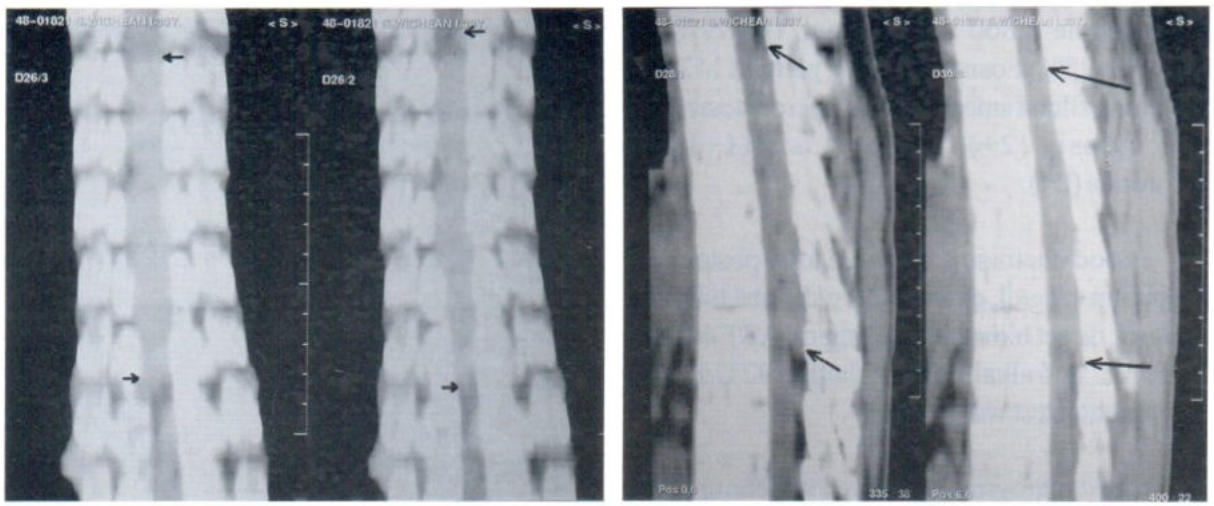

Fig 3&4 Curve coronal and sagittal reconstruction of non-contrast enhancement CT scan showed hyperdense, nodular-shaped masses, running in the posterior aspect of spinal canal, compressing the thecal sac and displacing the thoracic cord anteriorly.

A surgical biopsy was considered, but not performed due to the awareness of the risk of hemorrhage and the strong clinical evidence of EMH. Intravenous steroid was administered and radiotherapy was the selected treatment. The patient was treated with fractionated radiation to a field which included T3-T10 vertebrae to a total dose of 20 Gy in 10 fractions in 2 weeks through a posterior field.

By the end of the 1st week of treatment, there was marked improvement in motor neurological symptoms and at the completion of radiotherapy he enjoyed spontaneous ambulatory with mild residual weakness and numbness. Twenty months later, the patient showed normal gait, no motor weakness, no sensory impairment. His micturation and defecation returned to normal. He can do his daily life activities and house works.

CASE HISTORY 2

This patient was a 26 years old Thai male, who was diagnosed with thalassemia since during childhood. He presented with low back pain, progressive lower limb weakness, numbness and gait difficulties for 8 months. He complained of impairment of sensation on the trunk, at the level of nipple down to both lower limbs and both feet, without the symptoms of bladder and bowel dysfunction.

Physical examination revealed pallor and mild jaundice. His blood pressure was 120/70 mmHg, pulse rate was 84/minutes and rhythmic and his body temperature was 37.7 °C. The liver was enlarged 8 cm. below the right costal margin. Splenomegaly was also detected. The spleen was palpable 9 cm. below the left costal margin.

His neurologic examination revealed normal mental status, fully alert, oriented with normal speech and language. Cranial nerves were normal. Motor examination was normal in upper extremities, lower extremities revealed mildly increased tone, no atrophy or fasciculation. The muscle strength was 4/5 on the proximal and 4/5 on the distal muscles on both sides. Deep tendon reflexes revealed hyperreflexia of both knees and ankles and the plantar responses were extensor on both sides.

On laboratory examination, his hemoglobin levels were 7.4 gm%, Hct 23.8 %, RBC 3.45 ml/cu.mm, MCV 68.9 fl, MCH 21.4 pg, MCHC 31.0

g/dl, leukocyte 8,800 cells/cu.mm. (PMN 72%, lymphocyte 25%, Eosinophil 3%), platelet 142,000 cells/cu.mm. Blood smear showed microcytosis (2+), poikilocytosis (2+), anisocytosis (1+) and hypochromia (2+).

Blood chemistry revealed total protein 7.7 g/dl, albumin 4.7 g/dl, globulin 2.7 g/dl, total bilirubin 3.79 mg/dl, direct bilirubin 0.67 mg/dl, AST 44 U/L, ALT 13 U/L, and alkaline phosphatase 92 U/L. The kidney function test was normal.

Chest radiography showed widening of the costal end of anterior ribs bilaterally, as the result of underlying hemolytic anemia and multilobulated paravertebral soft tissue along both sides of mid thoracic spines, the left is larger than right, representing extramedullary hemopoiesis (Fig. 5).

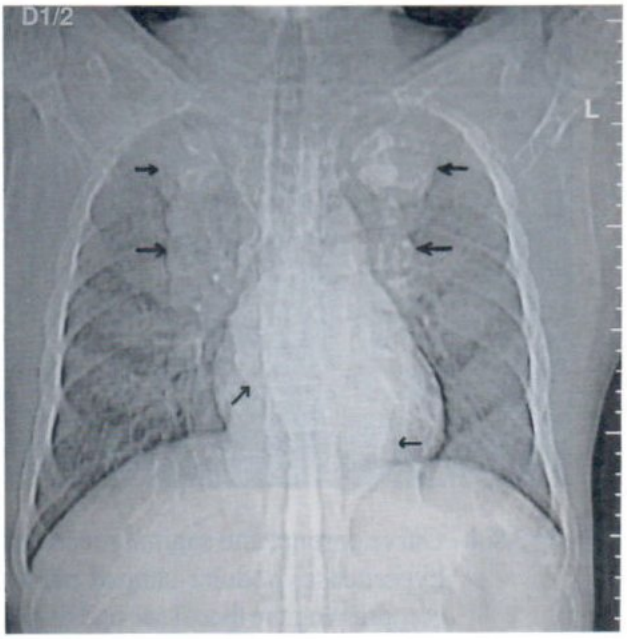

Fig. 5 Chest roentgenograph demonstrates expanded anterior ribs ends consistent with medullary hyperplasia. Multilobulated paravertebral masses are seen along both sides of mid thoracic spines.

Myelography was done and showed partial blockage of the contrast flow from T9 up to C6 levels (Fig. 6-9)

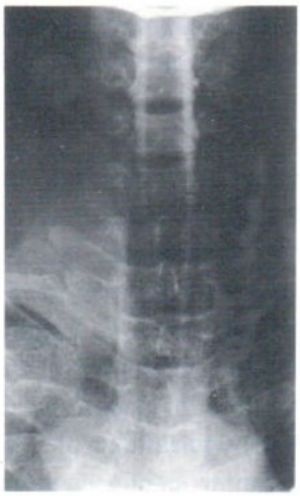

Fig. 6

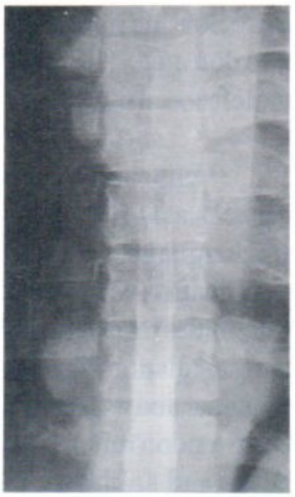

Fig. 7

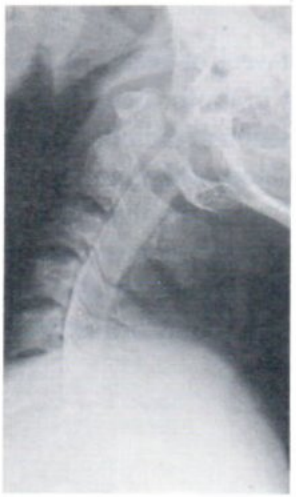

Fig. 8

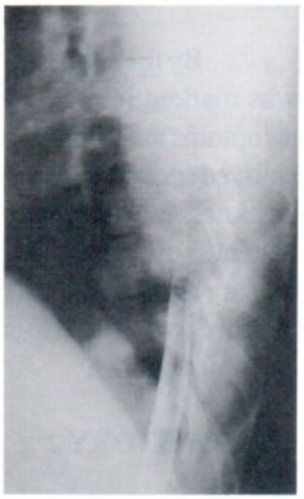

Fig. 9

CT scan post myelogram showed bilateral lobulated paravertebral masses from T1 to T12 levels accompanied with intraspinal extradural mass along the posterior aspects of the spinal canal, extending from lower T2 to upper T10 levels, causing compression and anterior displacement of thecal sac and spinal cord (Fig.10-12).

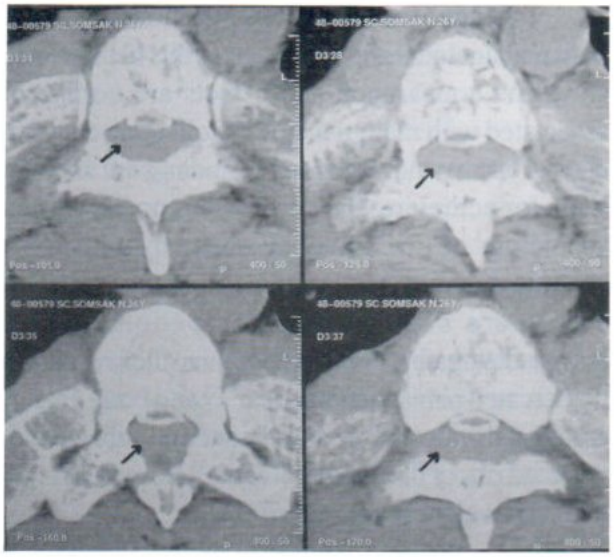

Fig. 10 CT myelography in axial view shows extradural mass producing compression and anterior displacement of the spinal cord.

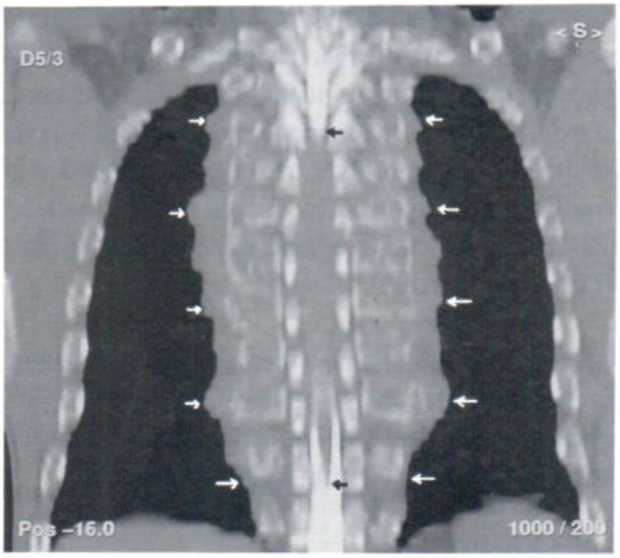

Fig. 11 Curve coronal reconstruction of CT intraspinal myelography shows both lobulated paravertebral masses and intraspinal extradural lesion.

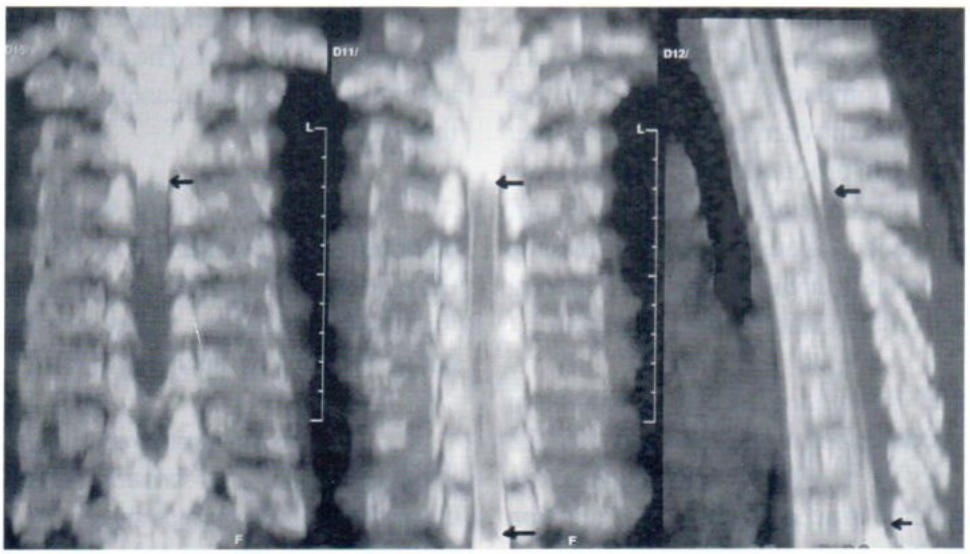

Fig. 12 Curve coronal and sagittal reconstruction of CT myelography show the levels of the compression and extension of the lesion.

A surgical biopsy was considered, but not performed due to the risk of significant hemorrhage and the strong clinical evidence of EMH. Intravenous steroid was administered and radiotherapy was the selected treatment. The patient was treated with fractionated radiation to a field which included T2-T10 vertebrae to a total dose of 20 Gy in 10 fractions in 2 weeks.

After the treatment there was an improvement in sensory perception and motor neurological symptoms. Clinically he has demonstrated no further neurological deficit during 2 years of follow up.

DISCUSSION

Thalassemia is a genetic disease with defective systhesis of alpha or beta globin chain (s) of hemoglobin, resulting in chronic anemia which causes expansion of the red marrow space and secondary bony changes.[21]

Extramedullary hematopoiesis (EMH) is a compensatory phenomenon encountered in this condition that may occur when there is chronic over stimulation of red cell production on bone marrow spaces. The most common sites of EMH are the liver, spleen and lymph nodes. Unusual locations include kidneys, adrenal glands, breast, spinal cord, pleura, pericardium, dura mater, adipose tissue and skin.[22]

Spinal EMH causing cord compression in thalassemia, first described by Gatto et al. in 1954 23 is extremely rare.[1-3, 13, 23-38] A number of mechanisms have been postulated to account for the predilection for involvement of the thoracic region in spinal EMH. These include extension of EMH tissue through the thinned trabeculae at the proximal rib ends,[39] direct expansion from adjacent vertebral bone marrow, and development of EMH tissue from branches of the intercostals veins. The narrow central canal,[30, 32] and limited mobility of the thoracic spine predisposes itself to spinal cord compression.

Diagnostic difficulties may arise in terms of both management and treatment of this benign lesion since the appearance and effects are commonly associated with malignancies.[38] Collecting data from clinical history and radiographic findings are important tools for achieving the correct diagnosis. Clinical suspicions of EMH may be raised by a history of chronic haemolytic anemia, evidence of EMH elsewhere such as hepatoslpenomegaly or lymphadenopathy. Plain radiographs often reveal well demarcated paraspinal masses[25, 33] and bony changes associated with chronic anemia such as trabeculation, widened ribs or thickened calvaria.[25] Bony destruction or pathological fractures are absent.

Because the EMH lesions are very vascular so biopsy is not considered for the fear of serious hemorrhage.

With modern imaging technique ie. computed tomography (CT) scan, magnetic resonance imaging (MRI), the diagnosis and differential diagnosis is more easily than in the past. The site and extension of the lesion within the spinal canal can clearly be shown by these techniques.[40-43]

MRI is currently the gold standard for demonstrating spinal EMH[27, 34, 44] and for delineating the extent of spinal cord involvement.[33] CT scan is a valuable investigation for patients in whom MRI is contraindicated or unavailable.[40]

There is still controversy regarding the optimal management of spinal cord compression due to EMH. Treatment options include surgery, blood transfusion, radiotherapy or any combination of these modalities.[14-20] More recently,the use of drugs such as hydroxyurea, which act by enhancing haemoglobin levels has been reported.[45-46]

Surgical decompression can provide both an accurate tissue diagnosis and rapid decompression to prevent permanent spinal cord damage.[27, 47-51]

However, when the evidence of EMH is confirmed by radiological findings in a patient with history of chronic hematologic disorder such as thalassemia, histologic proof may be less important to the overall treatment.[33, 44] Disadvantages include the risk of surgery (hemodynamic compromise, spinal cord injury or instability19 and kyphosis associated with multilevel laminectomy), the difficulty in completely resection because of the diffuse nature of EMH and the possibility of recurrence.

Blood transfusion therapy is another method and has been used as first-line treatment with complete neurologic recovery.[52] This suppresses the erythropoiesis which results in a regression of the EMH mass, thereby relieving the symptoms of cord compression to some extent.[53-56] Issaragrisil and colleagues.[21] Reported successful initial suppression of EMH by transfusion in 12 patients with spinal cord compression and thalassemia; however, because recurrences were noted in all patients, it is generally accepted that transfusion therapy should be used in concert with another modality.[21,24] Slow achievement of response in patients with rapidly progressive symptoms and iron accumulation with hemosiderosis are major drawbacks to this form of therapy.

Radiation is considered as treatment of choice in EMH as hematopoietic tissue is extremely radiosensitive and low-dose radiotherapy is enough to relieve the spinal cord compression and provides a rapid lasting response.[3, 23, 31, 57-59] In the literature, different dose of radiation are mentioned varying from 10 to 35 Gy fractionated with 1-2 Gy per day over 1-3 weeks.[3, 38, 41-42, 58, 60-64] Tissue edema associated with radiation can sometimes result in neurological deterioration during the initial phase of treatment[24, 65] which is minimized by concomitant steroid therapy. In addition to primary treatment, radiotherapy is commonly employed with other treatment such as post-operative following laminectomy to reduce the likelihood of recurrence[27, 28, 30] or combined with blood transfusion in cases in which there is recurrence after a single treatment (blood transfusion or radiotherapy).[66]

Hydroxyurea (HU) has been associated with increase of the total percentage of fetal hemoglobin and the number of F-cells, as well as the total hemoglobin concentration and mean corpuscular volume in sickle cell patients.[67, 68] Although there is limited experience with HU in thalassemia, some studies have demonstrated successful regression of EMH with HU therapy.[46, 47, 67-68] However, prospective studies to define influence factors to response and rate of EMH recurrence after HU therapy are necessary.

CONCLUSION

Spinal cord compression from extramedullary hematopoiesis is uncommon but can cause severe and irreversible neurological sequelae. After low-dose radiotherapy alone in these 2 patients, rapid responses occurred without significant adverse reaction. The result suggests that low-dose radiotherapy should be considered as an effective and safe treatment for this situation.

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