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Spinal cord compression secondary to extramedullary hematopoiesis: a rareness in a young adult with thalassemia major

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Summary. We report a case of a thalassemia major male patient with back pain associated to severe weakness in lower extremities resulting in the ability to ambulate only with assistance. An urgent magnetic resonance imaging (MRI) of thoracic and lumbosacral spine was requested. A posterior intraspinal extradural mass lesion compressing the spinal cord at the level of thoracic T5-8 was present, suggesting an extramedullary hematopoietic centre, compressing the spinal cord. The patient was treated with blood transfusion, dexamethasone, morphine and paracetamol, followed by radiotherapy in 10 fractions to the spine (daily fraction of 2Gy from T3 to T9, total dose 20 Gy). His pain and neurologic examination quickly improved. A new MRI of the spine, one week after radiotherapy, showed an improvement of the extramedullary hematopoietic mass compression. In conclusion, EMH should be considered in every patient with ineffective erythropoiesis and spinal cord symptoms. MRI is the most effective method of demonstrating EMH. The rapid recognition and treatment can dramatically alleviate symptoms. There is still considerable controversy regarding indications, benefits, and risks of each of modality of treatment due to the infrequency of this disorder. (www.actabiomedica.it)

Key words: extramedullary hematopoiesis, spinal cord compression, thalassemia major, radiotherapy

Introduction

Extramedullary hematopoiesis (EMH), defined as the formation and development of blood cells outside the bone marrow, can occur to compensate for insufficient production of blood elements in hematologic disorders, such as leukemia, myelofibrosis and hereditary hemoglobinopathies (1).

The incidence of EMH in patients with thalassemia intermedia may reach up to 20% compared to polytransfused thalassemia major (TM) patients, where the incidence remains <1% (2-4). There is a clear male predominance (M:F ratio ≥4:1) (5).

EMH most commonly occurs in organs those have physiological hematopoiesis during embryonic life, especially the liver, spleen and lymph nodes (6, 7). EMH tissue causing cord compression is an unusual occurrence in childhood and adolescence, and only three cases have been reported during the first two decades of life in TM patients (aged 7 years - male; 17

years-female and 18 years-male) (8-10). We present a case of a TM patient with early spinal cord

compression treated successfully with radiotherapy alone.

Case report

A 19 year old Iranian male with β-thalassemia major (TM), on regular transfusions with packed red blood cells (every 3 weeks, since the age of 2 years; pretransfusional hemoglobin level of 9.5-10 g/dl) and iron chelation therapy with Deferasirox (30 mg/kg/ body weight, orally, once daily) was referred to the hospital for a 4-months history of progressive low-back pain. In the 5 days, prior the medical evaluation, the pain was particularly severe and located on the lumbar left side, radiating to the abdomen, and poorly responding to ibuprofen and tramadol therapy. The pain was associated with severe weakness in lower extremities resulting in the ability to ambulate only with assistance.

On admission, there was no history of fever or previous injury to the back.The patient was pale (hemoglobin level 8.5 g/dl, platelets count, white blood cells and biochemestry were normal, antibodies for HBV and HCV were negative)

His standing height was164 cm and body weight 52 kg. He had spontaneous full pubertal development.

Evaluation of nervous system revealed normal higher functions and cranial nerves. His motor power in the extremities was 3/5 with bilateral hyperreflexia and up going planter reflexes with 'mild focal tenderness localized on the mid-spine. Upper extremities examination was normal and there was no fecal and urinary incontinence.

Liver and spleen were palpable 4 and 6 cm, respectively, below the costal margin. Rest of clinical examination did not reveal any abnormality.

Serum ferritin (SF) was measured by electrochemiluminescence immunoassays. The manufacturer's normal reference range values were 30-350 μg/L. The highest SF level registered was 1500 μg/L and 619 μg/L at the last observation. His liver iron concentration (LIC) measured using Ferriscan®, few months before the hospital admission, was 6 mg/g dry tissue.LIC (mg Fe/gr dw) was classified into: normal (LIC <3); mild (LIC >3 and <7), moderate (LIC >7 and <14) and severe overload (LIC >14).

Dexamethasone was given to the patient for spinal cord syndrome and an urgent magnetic resonance imaging (MRI) of his thoracic and lumbosacral spine was requested. A posterior intraspinal extradural mass lesion compressing the spinal cord at the level of thoracic T5-T8 (Figure 1, A and B) was present, suggesting an extramedullary hematopoietic centre, compressing the spinal cord. A presumptive diagnosis of EMH was made. His chest radiograph was normal.

The patient was treated with blood transfusion, dexamethasone, morphine and paracetamol, followed by radiotherapy in 10 fractions to the spine (daily fraction of 2Gy from T3 to T9, total dose 20 Gy).

His pain and neurologic examination quickly improved. A new MRI of the spine, one week after radiotherapy, showed an improvement of the extramedullary hematopoietic mass compression (Figure 1, C and D). The patient was discharged 5 days after the radiotherapy.

At the follow-up, 6 months later, his neurological examination revealed no abnormalities, although there was a residual EMH mass inside the canal.

Discussion

Thalassemia is caused by unbalanced hemoglobin synthesis due to defective production rates of polypeptide chain synthesis. Blood transfusion in β-TM aims to suppress ineffective erythropoiesis, limit morbidity from chronic anemia, and minimize bone changes from marrow expansion and EMH (11), the mechanisms that regulate this latter response are not fully known.

A potential role for the Bone Morphogenetic protein 4 (BMP4), a key player in the expansion of erytroid progenitors in the fetus, in this process is yet to be confirmed (12, 13).

Recently it has been shown that the ineffective erythropoiesis in β-TM is also the result of a reduction in the erytroid cell cycle and cell differentiation as well as of apoptosis. It has been suggested that an excess of iron and/or heme (in addition to α-globin) could alter the relationship between proliferation and

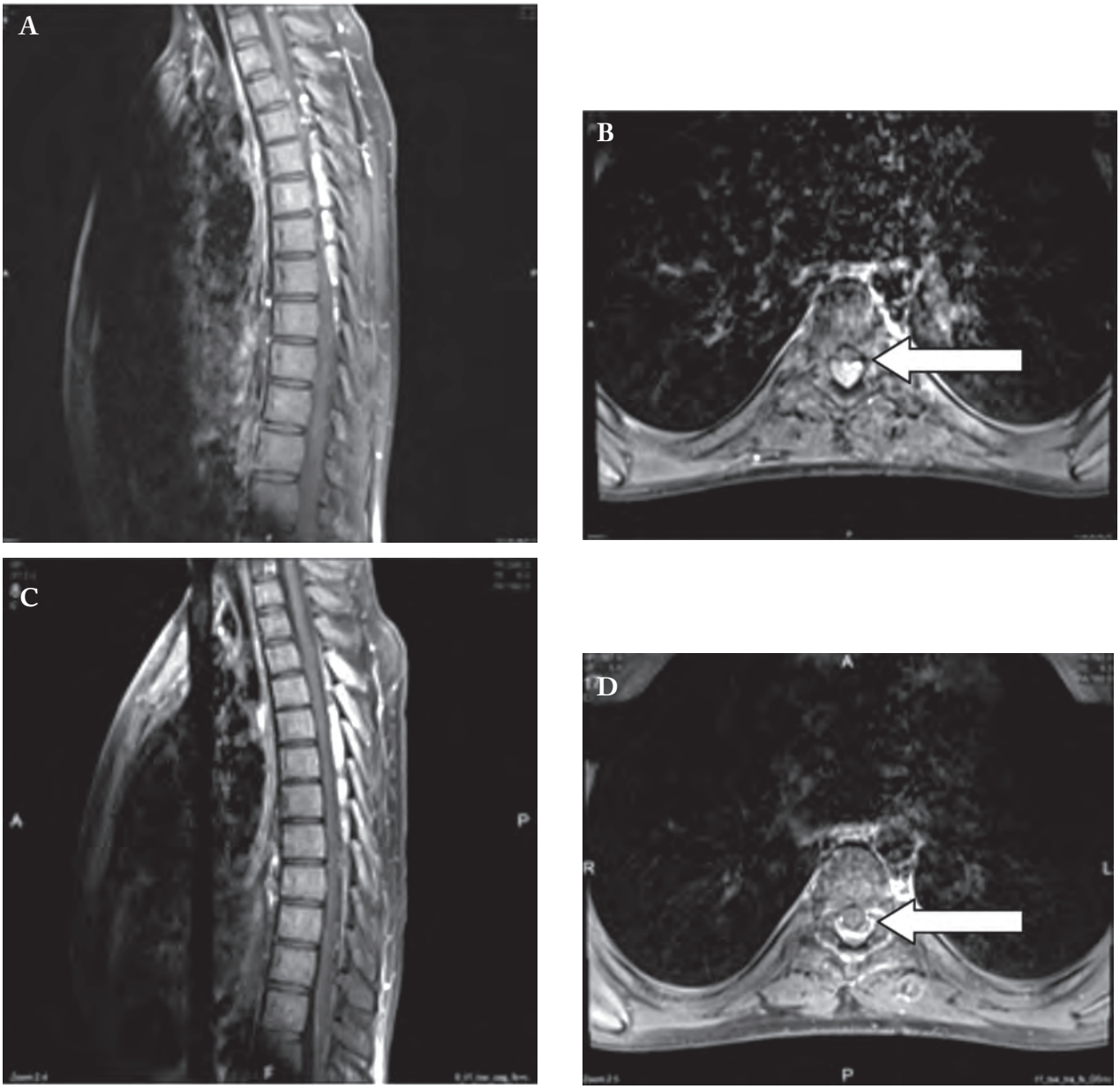

Figure 1 (A-D). A and B, sagittal and axial post contrast fat saturated images of the thoracic spine show intraspinal posterior epidural enhancing mass extending from T5-T8 levels with marked compression of the cord at T6-7-disc level in B.
C and D, sagittal and axial post contrast fat saturated images of the thoracic spine after treatment show improvement of the condition with mild posterior cord compression at T6-7-disc level in D (arrows)

differentiation of erythroid cell when the synthesis of globin chains is compromised. However, further studies are needed to determine if somehow the synthesis of a and β-chains can be modulated, to evaluate the role of heme and reactive oxygen species in the erythroid differentiation/proliferation, and to determine the mechanisms by which hepcidin agonistis influence normal and especially EMH, in particular for its effective prevention (14).

Our patient was regularly transfused and chelated. However, it is uncertain how much blood should be transfused to each patient for optimal long-term

health and to minimize complications. Due to a clear male predominance (M:F ratio ≥4:1) in the development of EMH (5), Hapgood et al. determined whether there were differences in erythropoietic activity between male and female adult β-TM patients receiving a regular transfusion regimen in accordance with current international recommendations (15).

Erythroprotein (EPO) levels were significantly higher in males: 72 mIU/mL (41-149) *versus* females: 52 mIU/mL (35-89); (p=0.006). EPO levels were significantly higher in splenectomized males compared to females: 77 mIU/mL (41-145) *versus* 48 mIU/mL (30-67); p=0.01. However, this difference was not observed in non-splenectomized patients. Serum ferritin levels were significantly higher in splenectomized females compared to males. There were no gender differences in Hb, reticulocyte or nucleated red blood cell counts based on splenectomy status (15).

Furthermore, an incidence of para-spinal EMH was documented with MRI in 13% of TM patients (14 of 110). There were 11 cases in males and 3 cases in females (M:F ratio= 3.66), resulting in an incidence in males and females of 22% (11 of 50) and 5% (3 of 60) (p=0.01), respectively. Thirteen of the 14 patients with paraspinal EMH were splenectomized. No cases of epidural EMH with cord compression were documented (15).

The Authors concluded that males are more prone to EMH with current transfusion practices. Their findings strongly support the notion that erythropoiesis is not being equally suppressed in males compared to females and hence males are being under-transfused with current practices and EPO levels may have a role in clinical practice for monitoring the suppression of erythropoiesis with transfusion (15).

EMH should be considered in every patient with ineffective erythropoiesis and spinal cord symptoms. The size and location of lesions and the extent of spinal cord involvement determine the severity, acuteness, and multiplicity of signs and symptoms. Patients may present with complaints of back pain or spinal cord compression symptoms.

The diagnostic procedure of choice is MRI which characteristerically shows the contours of spinal cord and contents of the spinal canal. 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. Gadolinium enhancement has been found to be unpredictable despite the tissue being highly vascular with patterns varying from no enhancement to strong enhancement (16-20).

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. Table 1 reports the pros and cons of different treatments in TI and TM patients.

Hemopoietic tissue is extremely sensitive to radiation and low doses cause rapid shrinkage. In our case, the patient's clinical recovery was complete, but MRI investigation did not reveal a complete decrease in the intraspinal mass. Similar findings were reported also in other studies (5, 21, 22). Therefore, although we agree with the indication that radiation therapy should be the treatment of choice in most of the cases of EMH tissue, especially if there is no need for immediate surgical spinal cord decompression, we also believe that further data and evaluation of different treatment modalities are needed (21-24).

A decrease of EMH volume (~16.4%) immediately after radiotherapy (25) and a recurrence rate of 19-37.5% has been reported in the literature, but retreatment provides excellent chance for second remission (23, 26).

In summary, EMH compression is an unusual occurrence in childhood and adolescence, and only few cases have been reported in literature. Males are more prone to EMH with current transfusion practices. Therefore, optimal pre-transfusion Hb required to adequately suppress erythropoiesis and prevent the development of EMH may be higher for males than females (15). EMH should be considered in every patient with ineffective erythropoiesis and spinal cord symptoms. MRI is the most effective method of demonstrating EMH and is indicated on an urgent basis when symptoms of spinal cord compression are present. The ideal management scheme remains contro-

Table 1. Current treatment options for spinal cord compression secondary to extramedullary hematopoiesis (EMH) in thalassemia intermedia (TI) and major

Option	Benefits	Disadvantages
Transfusions	Down regulation of erythropoietin production. Currently, it can be recommended in TI patients with mild spinal cord compression or in special cases like pregnant patients where it may obviate the need for surgery.	The improvement is usually incomplete and short lived.
Hydroxyurea (HU)	It is a well-known chemo therapeutic agent acts by enhancing the HbF production and eryhthropoises. In doses of 10- 20mg/Kg/ day in an intermittent on continuous schedule has been shown to have sustained haematological efficacy with minimal toxicity.	Leucopenia and thrombocytopenia which are usually reversible after a few days of discontinuation.
Surgical decompression	Immediate decompression of the mass. Histological diagnosis can be established.	General anaesthesia, cardiovascular instability due to anemia, excessive bleeding during the marrow tissue removal and difficulty in total excision due to the diffuse nature of the process. Spinal instability post laminectomy. Risk of reoperation due to rapid recurrence.
Radiotherapy	Effectiveness in the resolution of symptoms in a short period and reduction of local recurrence. The radiation dosage used mostly in different treatment protocols included a range between 10 and 30 Gy.	Radiation exposure.

versial. Until large prospective trials evaluate the efficacy and safety of the available treatment options an individualized approach should be entertained.

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