Progressive Spinal Cord Compression Due to Epidural Extramedullary Hematopoiesis in Thalassemia Intermedia

A Case Report and Literature Review

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Key words: extramedullary hematopoiesis, epidural, spinal cord compression

SUMMARY – *Extramedullary hematopoiesis (EMH) can occur in patients with thalassemia intermedia as a physiologic response to insufficient erythropoiesis to meet circulatory demands. Rarely, EMH involve the epidural space causing spinal cord compression. We describe a case of EMH in a 21-year-old man with β -thalassemia intermedia presenting with progressive low back pain, worsening paraparesis and sphincter disturbance. Magnetic resonance imaging (MRI) demonstrated spinal cord compression by EMH epidural mass lesions extending from T3 to T10 levels. An emergency multilevel decompressive laminectomy was performed with excision of the masses and complete rehabilitation of the patient.*

Introduction

During infancy red marrow occupies the entire ossified skeleton except for the epiphyses and apophyses. Gradually red marrow 'retreats' centrally, such that by adulthood it is essentially confined to the axial skeleton. In some chronic diseases demanding overproduction of blood components red marrow reconversion and bone marrow expansion takes place, but insufficient red cell production by the bone marrow (ineffective erythropoiesis) forces expansion of the hematopoietic tissue outside the bone marrow. This phenomenon is termed extramedullary hematopoiesis (EMH)¹.

EMH occurs most often in sites related to hematopoiesis during fetal development such as the spleen and liver and occasionally in the lymph nodes. EMH may occur in other organs, such as the pleura, lungs, gastrointestinal tract, breast, skin, the dura mater of brain and spinal cord, kidney, and adrenal glands^{2,3}.

EMH is commonly associated with cases of primary and secondary myelofibrosis. It is ex-

tremely rare in association with other hematological diseases, such as inherited anemias (especially thalassemia) and chronic myeloproliferative disorders including myeloid metaplasia, polycythemia vera, leukemia and Hodgkin's disease⁴.

Unlike thalassemia major patients, who receive regular blood transfusions from an early age, which suppress excessive bone marrow activity, patients with thalassemia intermedia (TI) do not receive regular blood transfusions. Chronic anemia and ineffective erythropoiesis are responsible for the clinical symptoms of TI. EMH is a rather common complication in TI and inadequately transfused thalassemia major patients but spinal cord compression is rare⁵.

Case Report

A 21-year-old-man with a known medical history of TI had not received blood transfusions in last few years and was not on any regular medications. He presented with progressively

Figure 1 Plain chest X-ray revealed remarkable expansion of the anterior and posterior ends of the ribs (arrows).

A

B

Figure 2 CT chest scan at bone (A) and soft tissue (B) window settings, confirmed remarkable marrow expansion and cortical breakthrough of the ribs with extrapleural soft tissue masses (arrows).

increasing chronic back pain, gradual weakness and numbness in both legs and a recent history of urinary urgency and incontinence.

On clinical examination, he looked thin and pale. Mental status and cranial nerve examinations were intact. Motor examinations revealed significant spasticity in both legs with sustained ankle clonus. He had a pyramidal weakness in both legs. The power was graded as 4/5 in hip flexors and knee flexors, 4–/5 in dorsiflexors and 4+/5 in planter flexors. Upper extremities power was intact. His reflexes were 3+ in the upper extremities with no Hoffman's but 4/4 in the lower extremities and he has bilateral upgoing planters. Sensory examination revealed decreased pinprick and touch sensation up to the knees. No sensory level was de-

tected. Proprioception and vibration were impaired up to the ankles.

Abnormal laboratory findings revealed decreased HB level (10.0 g/dl) and RBC count (4.2 million/mm³).

Plain X-ray chest (Figure 1) revealed remarkable expansion of the anterior and posterior ends of the ribs, CT chest scan (Figure 2) confirmed remarkable marrow expansion and cortical breakthrough of the ribs with extrapleural soft tissue masses. MRI of thoracic and lumbar spine was performed on a 1.5 Tesla system using a body coil including different pulse sequences (T1-weighted W, T2 W with fat saturation (fat sat) and T1 post i.v. gadolinium (Gd) contrast with fat sat). MRI revealed multilevel posterior epidural mass lesions compressing

the spinal cord and extending from T3 to T10. The lesions displayed intermediate signal intensity on T1- and T2-weighted images with mild enhancement in post contrast images. The lesions occupied more than 50% of the spinal canal compressing and thinning the spinal cord most at T4 and T5 levels denoting secondary compression myelopathy (Figure 3).

A diffuse decrease in T1 and T2 bone marrow signal of the vertebral bodies and posterior rib ends due to red marrow conversion and bilateral paracostal extraosseous and extrapleural masses similar to the above described epidural masses were also noted (Figure 3).

Based on imaging appearances and clinical scenario, the diagnosis of spinal cord compression due to posterior epidural EMH was made.

Because of progressive neurological deterioration our patient underwent multilevel laminectomy and surgical removal of the spinal EMH masses from the posterior epidural space was achieved successfully. No adjuvant radiotherapy was given to avoid possible complications. The patient's postoperative outcome was favorable. He was then put on scheduled blood transfusions and remained imaging and disease-free for one year post surgery.

Discussion

Extramedullary hematopoiesis (EMH) tends to occur in sites that were normally engaged in active hematopoiesis in fetal life. The dura mater of brain and spinal cord were one of those sites, and it is likely that EMH of the epidural space develops from these primitive rests, i.e. by re-stimulation of retained hematopoietic capacity in fetal life^{3,6}.

As in our case, there is a notable predilection for spinal epidural EMH to occur in the mid to lower thoracic region and several hypotheses have been proposed to explain this localization⁷. Firstly, the development of spinal EMH tissue has been attributed to extension from expanded bone marrow cavities of the vertebrae or thinned trabeculated proximal end of the ribs and costovertebral junctions^{8,9}. Our case showed the EMH masses occurred in the posterior epidural space and did not reveal on imaging erosions causing extension in contiguity with the expanding marrow cavities of the spine or rib ends, and the above proposition is therefore unlikely¹⁰.

Secondly, since associated masses of hematopoietic tissue also occur in the thorax, in

the paraspinal, pleural and retro-pleural areas, it is therefore likely that these activated blood-forming masses possibly originate from commonplace embryonic rests, including epidural, paraspinal and retropleural corpuscles or lymph nodes^{1,9,11,12}. A commonplace vascular territory proposition has also been introduced accordingly, relating the thoracic predilection to development of EMH from branches of the intercostal veins¹³, or metameric arterial embolic phenomena¹⁴.

EMH usually forms a soft deep red mass which resembles a hematoma on its cut surface. Histologically, these tissues are composed of all hematopoietic elements, i.e. myeloid, erythroid and megakaryocytic. Active hematopoietic extramedullary lesions have a rich vasculature while inactive older lesions have more fatty tissue and iron deposits^{15,16}.

β -thalassemia is an inheritable disorder of autosomal recessive type. It involves defective synthesis of beta globulin and compensatory synthesis of gamma chain globulin, leading to synthesis of hemoglobin F. Diverse phenotypes exist within the homozygous and heterozygous states. At the severe end of the spectrum are thalassemia major patients who present to medical attention in the first year of life with profound anemia, and require regular transfusions. Other patients with inheritance of two mutant beta alleles have a milder illness, with at least in early childhood, an asymptomatic state. Patients in this group have thalassemia intermedia (TI). They present to medical attention in later childhood and remain largely transfusion-independent. However, transfusion-independence in TI does not come without its own side effects, as ineffective erythropoiesis precipitates EMH^{1,17}. As this compensatory proliferative mechanism might need time to produce neurological deficits, this clinical presentation is not limited to the children and adolescents and symptoms are most frequently being reported during the third and fourth decades of life, although few reports described presentation as early as the first decade of life^{1,6}.

Given the appropriate clinical setting, findings on conventional radiography and CT scanning are usually sufficient to diagnose spinal cord compression due to EMH, but due to its multiplanar capability, MRI contributes further by accurately delineating the extent of the lesion and thereby helps to localize the optimal field if radiation therapy or surgery is contemplated.

As in our case, active lesions show inter-

mediate signal intensity in both T1- and T2-weighted MRI (Figure 3) higher than the adjacent hemopoietic marrow within vertebral bodies, whereas old inactive lesions may show either high or low signal intensity in both T1- and T2-weighted MR images due to fatty infiltration or iron deposition respectively. Active EMH are vascular lesions and show post i.v. gadolinium enhancement except for early lesions that show often minimal enhancement, whereas old inactive lesions show decreased contrast enhancement. MRI may show massive iron deposition in patients treated with blood transfusions. On the other hand, fatty degeneration is most probably related to oxidative stress in non-transfused patients leading to lipid peroxidation of cell membranes and production of oxygen-free radicals. Fatty replacement and fibrosis also occur after radiation therapy^{15,16,18-20}.

The appearance of well-demarcated multisegmental thoracic spine masses, with the above-described signal characteristics are fairly specific in the proper clinical context, and hazardous histological proof should be avoided as in our case because of the highly vascular nature of the EMH masses¹⁵. A diagnostic problem exists when a solitary, unilateral active EMH lesion occurs; and mesenchymal tissue tumors, hematologic malignancy (lymphoma, granulocytic sarcoma), tumors from neural tissue elements, metastasis or infection (abscess) should then be considered as a differential diagnosis^{6,16}.

Finally, because of its rarity, no evidence-based guidelines for the treatment of spinal or paraspinal pseudotumors caused by EMH exist. Management options include corticosteroids, blood transfusion, hydroxyurea, radiotherapy, surgical decompression, or a combination of these modalities. Therapy usually depends on the severity of symptoms, size of the mass, the patient's clinical condition, and previous treatment^{6,21}.

Amelioration of the anemia with transfusion therapy decreases the need for EMH leading to shrinkage of the mass, decompression of the spinal cord, and neurologic improvement. The initial response results primarily from a decrease in blood flow to these tissues even before reduction in the size of the mass can be detected^{22,23}. Some authors have reported cases of EMH treated exclusively by this treatment as a first choice or in cases where surgical decompression or radiotherapy were contraindicated, e.g. pregnancy or severe anemia²⁴⁻²⁶.

However, while blood transfusion may pre-

vent further progression of EMH, it is unable to reverse preexisting cord compression. Therefore its role as a first-line therapeutic approach is usually insufficient and temporary. Moreover, blood transfusion is not a harmless procedure with infectious risks, iron overload being a clearly recognized side-effect, and red cell alloimmunization excludes its use^{23,26-28}.

The combination of blood transfusion and radiotherapy has also been reported as a therapeutic option, either for cases of recurrence or as an initial treatment regimen^{29,30}. In addition, many advocate the use of blood transfusion as an adjunct to surgery (pre- and/or post-operative course) to insure optimal oxygenation of the spinal cord during the surgery^{31,32}.

Low dose radiation therapy can be considered a primary mode of treatment because EMH masses are extremely sensitive to radiation. However a favorable prognosis in these lesions depends on early diagnosis, with some authors reporting as many as 50% of patients could be successfully managed by this therapy alone with neurological improvement observed as soon as three to seven days after initiation of treatment³³. The risks of radiotherapy in the treatment of cord compression in such patients include neurological deterioration during the initial phase of treatment due to tissue edema associated with radiation, but this can be prevented by concomitant high-dose steroid therapy. Radiotherapy can also cause marked myelo-suppression with a drop in white cell count and infectious risk and radiotoxicity, the latter two complications being determining factors in stopping further radiotherapy treatment^{29,34,35}.

However, the main drawback of radiotherapy is the high risk of recurrence, occurring in up to 19-37% of cases. Fortunately, these recurrences are often amenable to further radiotherapy doses^{29,33}. Accordingly, in patients who need a rapid therapeutic response due to severe neurological symptoms, radiotherapy might be considered the primary treatment of choice especially if surgery is contraindicated. In addition, it is commonly employed as a post-operative adjunct following laminectomy to reduce the likelihood of recurrence^{32,37,38}.

Hydroxyurea is a ribonucleotide reductase enzyme inhibitor that acts by reducing the globin chain imbalance through stimulating synthesis of fetal hemoglobin, and a cytoreductive effect decreasing ineffective erythropoiesis and secondarily reducing the volume of EMH required. Successful treatment of patients with spinal EMH with the use of hy-

droxyurea has been reported as an alternative therapy in patients who are unable to receive blood transfusions, or as adjuvant therapy in combination with low-dose radiation and blood transfusion^{38,39}.

Laminectomy remains the mainstay in treating patients with acute presentation who fail to respond to adequate transfusion or radiotherapy, and confers the benefits of both immediate relief of cord compression and histological diagnosis^{31,33}. The disadvantages of laminectomy include the risk of bleeding associated with the high vascularity of the EMH masses, the risks of operating on anemic individuals who are predisposed to shock, spine instability and kyphosis associated with multilevel laminectomy and incomplete excision in cases of diffuse involvement. Furthermore, immediate total resection of EMH masses can lead to clinical deterioration because these masses play a crucial role in maintaining an adequate hemoglobin level^{32,33}. For these reasons, surgery should be reserved for cases of acute, progressive, and severe neurologic deterioration. Decompressive surgery is immediately effective in most cases and radiotherapy can be introduced as an adjunct to surgery to prevent recurrence, or if excision of EMH masses is incomplete. As an alternative op-

tion, radiation can be saved as a salvage procedure for recurrence^{7,32}.

Our patient was successfully treated with surgical removal of the spinal EMH masses. No post-operative radiotherapy was applied and he was further controlled with regular blood transfusions.

Conclusion

Spinal cord compression from epidural extramedullary hematopoiesis (EMH) should be suspected in patients with chronic anemia and hematological disease who present with neurological disorders. Early diagnosis of EMH will affect the course of management and may reduce the incidence of irreversible neurologic damage that would otherwise occur with prolonged undiagnosed cord compression. The medical history remains important to rule out other entities in the differential diagnosis of epidural masses including metastatic malignant disease, lymphoma, multiple myeloma, vascular anomalies, or epidural abscess. Currently, MRI has replaced other imaging modalities and is considered the technique of choice for the diagnosis and evaluation of spinal cord compression resulting from EMH.

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