Spinal cord compression due to intraspinal extramedullary hematopoiesis in thalassemia intermedia

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ABSTRACT

Extramedullary hematopoiesis is a common phenomenon in thalassemia. During the disease there are very rare occasions when compensatory hematopoietic tissue is located in the intraspinal epidural space, causing spinal cord compression. This complication requires urgent neurosurgical consideration and decision for further treatment. We present a case of thoracic spinal cord compression secondary to extramedullary hematopoiesis in thalassemia intermedia, treated with irradiation therapy. The therapeutic options are discussed, and the need for more explicit therapeutic directions is highlighted.

Neurosciences 2007; Vol. 12 (3): 261-264

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Received 20th June 2006. Accepted 14th October 2006.

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Extramedullary hematopoiesis (EMH) is a compensatory mechanism to insufficient hemoglobin synthesis. In thalassemia, it regularly occurs in the liver, spleen, and lymph nodes.[1,2] Less common locations of EMH are the thymus, hilum of the kidney, adrenal glands, breast, lungs, and paraspinal retroperitoneal tissue.[2,3] Bone marrow expansion in the intraspinal epidural space due to EMH, sufficiently severe to cause spinal cord compression (SCC), is already reported as a very rare complication in thalassemia.[2-4] The first report of this unusual complication of thalassemia was in 1954 by Gatto et al.[2,4-6] Since then, extramedullary intraspinal hematopoiesis has been reported in different hemoglobinopathies.[4,6] Controversy over the optimal treatment of SCC in thalassemia still exists. Our 27-year-old male patient with thalassemia intermedia and thoracic SCC due to EMH was treated by irradiation therapy with good clinical recovery and minimal resolution of intraspinal mass. We present a case of neurological deficit caused by intraspinal hematopoietic tissue (IHT) in thalassemia, and unusual persistence of intraspinal mass after radiation despite clinical improvement.

Case Report. A 27-year-old male patient presented to the neurosurgery clinic complaining of lower limb "heaviness" for the last 3 months. He was known to have intermediate B-thalassemia since childhood. He underwent splenectomy at 7 years of age and cholecystectomy 6 years ago. He received transfusion therapy 4 times before he was seen in the neurosurgery outpatient clinic. At that time he reported "heaviness" in his lower limbs, no back pain, no sensory disturbances, no sphincter problems, and no other associated symptoms. On clinical examination, he was pale and jaundiced. The liver was palpable at 4 cm below the costal margin. Neurologic examination disclosed overall brisk reflexes, lower limbs more than upper limbs, left leg more than the right, unsustained clonus bilaterally, and positive Babinski sign on the left side, equivocal on the right side. There was very mild motor weakness in the lower extremities and no evidence of sensory or sphincter disturbances. Investigations, complete blood count: white blood count 33.1 k/ul with segmented neutrophil 40%; red blood count 3.69 Mil/u, hemoglobin 9.5 gm, hematocrit 30.5, platelets 496 k/ul, hemoglobin electrophoresis: hemoglobin F= 90.75%, hemoglobin A= 9.3%. Further investigation with MRI of the thoracic and lumbosacral spine revealed the presence of an intraspinal extradural mass lesion compressing the spinal cord from the posterior and lateral sides at the level of thoracic 4-10. The signal intensity of the mass was isointense on T1 and high intense on T2, with no significant post-contrast enhancement (gadolinium intravenous) (**Figure 1**). Similar masses were evident in the intraspinal epidural region at the level of L5-S1, as well as in the presacral region. The overall bone signal was abnormal with associated bone marrow expansion seen in the vertebral bodies, ribs, and in the sacral

Figure 1 - Sagittal postcontrast MRI of the thoracic spine revealing the spinal cord compression at T4-T10. Arrows indicate the spinal mass.

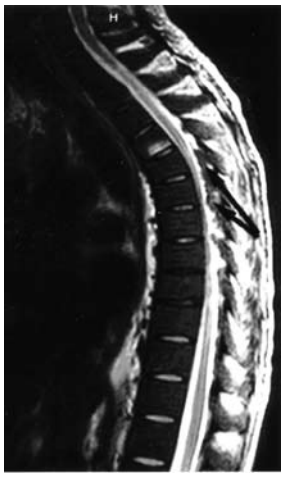

Figure 2 - Sagittal MRI of thoracic spine 5 months after irradiation. Note minimal reduction of intraspinal EMH tissue. Arrows indicate the spinal mass. EMH - extramedullary hematopoiesis.

and transverse process. A CT scan of the thoracolumbar spine showed bone medullary expansion associated with coarse trabeculation and thinning of the cortex involving the spine, ribs, sternum, and pelvic bone. Hematology consultation did not recommend any transfusion therapy for the present. He refused proposed CT guided fine needle biopsy of the extradural mass. His neurologic status did not imperatively require any immediate surgical decompression, and he was sent for emergency radiation therapy (RT) of the IHT. He received a total dose of 1400 cGy in 4 fractions to the thoracic spine (T3-T11), and also to the lumbosacral area (L3-S3). The thoracic spine was treated with direct posterior field, and the dose was presented to a depth of 5 cm. The lower lumbar and sacrum were treated with a parallel opposed pair. After radiation, and a very short period of mild low back pain and numbness in the lower extremities, he showed full recovery. Five months after irradiation, MRI of the dorsal spine did not reveal significant decrease in the amount of IHT (**Figure 2**), however, he is symptom free and followed up closely in the Neurosurgical clinic.

Discussion. Thalassemias are forms of hematologic diseases, which are highly regionally accentuated as particular health problems. Populations in the near East, Southeast Asia, and in the countries surrounding the Mediterranean Sea are particularly exposed to this inherited genetic disorder, characterized chiefly with disarrangement, and inadequate hemoglobin synthesis.[1,4,6,7] It is well known that all hemoglobinopathies are the result of insufficient hemoglobin synthesis, and in order to compensate hemoglobin insufficiency, appropriate blood cell producing mechanisms occur usually in the spleen, liver, lymph nodes, mediastinum, thymus, lungs, adrenals, and other organs and tissues capable of producing blood cells.[6] Since Gatto et al's first presentation of SCC due to epidural EMH in thalassemia in 1956,[2,4-6] there were occasional publications devoted to this entity not only in thalassemia but also in other hemoglobinopathies as polycythemia, sickle cell anemia, myelofibrosis, and so forth.[4-6] Despite substantial advancement and easiness of contemporary diagnosis of EMH, development of intraspinal epidural erythropoietic tissue (EET), causing SCC, is still rarely reported. While the spleen, liver, and lymph nodes are well known as potentially capable for production of blood cells in certain circumstances, the presence of erythropoietic cells in the extradural intraspinal space is a rare event. The growth of extradural erythropoietic tissue cells is still controversial. Among 3 possible explanations: a) query transformation of embryonic multipotent extradural fat cells to the erythropoietic cells, b) a propagation of visceral bone marrow cells released by subclinical venous bleeding in the subdural space, and c) direct expansion of bone marrow from surrounding bones (vertebrae, ribs) facilitated by vertebral bone marrow hyperactivity and hypertrophy and consequent microperforations of vertebral cortical bone, the last option is now generally accepted.[3,4]

The clinical picture of SCC due to intraspinal epidural EMH has all the characteristics of a common presentation of slow progressing cord compression without any specific attribute to this particular entity.[1,2,8] Diagnosis is not a major problem. The presence of positive history, laboratory, and somatic signs of hemoglobinopathic disease, with neurological

signs of spinal cord affection necessitates further CT and MRI investigation of the spine. Although CT has some advantages regarding presentation of vertebral bony proliferation (usually thickness of lamina), MRI is a superior method for presentation of contours of spinal cord and contents of the spinal canal. An MRI can exactly outline newly formed erythropoietic tissue, the extent of compression of the spinal cord as well as possible changes in the spinal cord itself. The extradural intraspinal erythropoietic tissue is presented on MRI on T1 and T2 with the same or slightly higher intensity than that surrounding extensive bone marrow expansion in adjacent vertebrae and in the ribs.[9-11] The final confirmation of diagnosis of intraspinal EMH can be carried out pathohistologically, analyzing material taken by CT guided fine needle biopsy, or a sample taken during decompression (if carried out). Clinical confirmation is definite neurological clinical improvement on conservative therapy. Chehal et al[2] believes that biopsy "should be reserved for older patients and for cases in which the clinical picture is not completely clear." The diagnosis in our patient was founded on clear history and clinical presentation of presence of thalassemia intermedia, neurologic evidence of slow progressing SCC, and characteristic findings on both CT and MR imaging of the thoracolumbar spine. We did not obtain pathohistological confirmation because the patient's clinical status did not require urgent decompressive operation when the specimen could be taken, and the patient refused fine needle biopsy. Radiological confirmation of extradural EMH in our case was doubtless: CT of the dorsal spine showed a dorsally positioned extradural mass in connection to marked vertebral lamina marrow hypertrophy with perforating cortical bone and bone marrow density of the mass in the intraspinal extradural space. The MR images of the dorsal spine (**Figure 1**) showed lobulated soft tissue in the extradural space, pressing the spinal cord at the level of T3–T11. On T1, this extramedullary mass has the same signal intensity as the bone marrow in the adjacent ribs and vertebral bone.

Operative decompression, multiple transfusions, and radiation therapy, as well as a combination of these 3 modalities are recommended options for management of SCC caused by EMH in thalassemia patients. There is still considerable controversy regarding indications, benefits, and risks of each of these modalities. The rarity of this disease gives us restricted opportunity to be sure of the best treatment option in every case. In the limited literature, there are reports advocating each of these therapeutic options alone or in combination with the others. Practically all authors agree that the surgical option has to be preserved for patients with acute paraplegia, or progressive neurological deficit.[6,8,9,12,13] Surgical treatment should be preserved also for persistent or progression of neurological deficit despite irradiation. This therapeutic option is usually followed by postoperative low dose irradiation.[6,13] The benefits are immediate neural tissue decompression and possibility for pathohistological confirmation of diagnosis. The risks of operation include those of general anesthesia, cardiovascular instability due to anemia, excessive bleeding during the marrow tissue removal in a patient who has low hemoglobin due to his basic disease, practical inability to remove all the extradural mass due to the nature of the disease, possibility of common postoperative complications, including regrowth of hematopoietic tissue, possible spinal instability, postlaminectomy membrane formation, and so forth.[6,12,13] Several reports present results of transfusion therapy,[2,9,12,13] and recommend it mainly as adjunctive therapy and a diagnostic tool. Most authors consider transfusion as a solo treatment in cases of EMH with SCC questionable and insufficient in the prevailing number of cases. The drawbacks of transfusion therapy are incompleteness of improvement and quick recurrence of symptoms. Reported complications are convulsions, cerebral hemorrhage, hypertension, and other commonly possible complications of blood transfusion.

Hematopoietic tissue is very sensitive to irradiation injury, and consequently radiotherapy is the treatment modality advocated in most contemporary reports[2,4,7,8,12,14-16] as the treatment of choice for efficient treatment of SCC caused by EMH in all cases in which urgent surgical decompression is not necessary. Reported advantages of radiation therapy are significant: quick inhibition of tissue hematopoietic activity, shrinkage of EMH tissue mass, subsequent prompt and clinically evident improvement, lower local recurrence rate, extended availability, and low cost.[6,14-16] Disadvantages and risks of irradiation therapy include those usually attributed to radiation exposure, especially increased risk for further irradiation injury in already injured spinal cord tissue. This option does not provide the possibility of pathologic confirmation of diagnosis. There are considerable variations and a great disparity between different treatment protocols of irradiation on epidural EMH tissue. Locally applied doses vary between 1000-3000 cGy,[11] number of fractions (3-15 fractions) are different; period of irradiation varies from 3 days to 3-4 weeks. However, reported results of irradiation therapy almost unanimously reveal rapid resolution of neurological symptoms in 3-7 days.[2,7,15,16]

Most publications also describe prompt reduction of epidural EMH tissue.[6,7,14,15] Our patient showed a brief period of very mild increase of paresthesia and back pain, and full recovery in the next 7-10

days after radiotherapy. An MR after irradiation did not reveal marked reduction of EMH tissue in our patient. Decrease of EMH after radiation therapy is reported from a complete resolution to significant percentage of reduction of EMH volume. There are also reports presenting inadequate decrease of intraspinal hematopoietic tissue, incomplete improvement, need for operative decompression, repeated irradiation, and so forth.[12] Our patient is on the border line – despite clinical recovery there is still evidence of presence of almost an unchanged amount of EMH inside the canal.

From a neurosurgical point of view, satisfactory irradiation protocol theoretically offers quick and permanent release of SCC, maximal reduction or absence of any x-ray generated spinal cord damage, and avoidance of other negative effects of irradiation therapy. In our case, the patient's clinical recovery was complete, but MR investigation did not reveal a significant decrease in the intraspinal mass. Due to that finding, and similar reported cases,[6,9,13] one can open to question applied protocols of irradiation in our patient, and other patients. As mentioned earlier, because of the limited number of cases and insufficient data, it is difficult to scientifically determine different protocols and how much reduction of hematopoietic tissue mass depends on irradiation protocol in comparison with other elements (form of hemoglobinopathies, age of patient, and hemapoietic tissue).

In conclusion, due to our, and other reports, presenting insufficient post irradiation reduction of epidural EMH tissue, we believe that close follow up of such patients is extremely important. We agree with the implicit consensus that radiation therapy should be the treatment of choice in most of the cases of SCC with intraspinal extramedullary hematopoietic tissue, especially if there is no need for immediate surgical spinal cord decompression. However, we believe that our report is another case supporting the need for further careful collection of data and evaluation of different treatment modalities. Also, we are convinced that there is a need for accomplishment of a more concomitant and explicit irradiation treatment protocol for the treatment of epidural EMH.

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