Author's response to reviews

Title: intracranial extramedullary hematopoiesis in Beta Thalassemia; case report

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Author's response to reviews: see over
Cover letter

With Due Respect, first of all we should appreciate for considering our manuscript.

Reply to the first comment made by the Deputy Editor:

Two previously published case reports have been referenced and the similarities and differences were discussed and indicated by the red color in the Discussion section. The figures were split up into figures 1, 2, 3 and 4 and to show the lesion in the scan arrows were provided.

Reply to the second comment made by the Deputy Editor:

The discussion section was added to the manuscript and all changes indicated by Reviewers and the Deputy Editor were marked in red color on the revised manuscript.

Reply to Reviewer 1:

- To explain why the patient would have loss of vision in both eyes, we should say that the visual loss in our case may be due to secondary effects of increased ICP and/or mass lesion upon adjacent structures of visual pathways. Moreover, intracranial extramedullary hematopoiesis arising from the base of the cranium near the sphenoid and ethmoid bones, may extend into the intracranial cavity, and compress the visual pathways with resultant progressive visual failure.

- The patient’s identifiable information is removed from the MRI images.

Reply to Reviewer 2:

- To answer the questions No. 1 to 3 we should explain that, as far as our patient was a known case of thalassemia we did hematologic consultation and according to his note the EMH was one of the differential diagnoses. But in our case the findings were not sufficient to confirm the diagnoses of EMH and therefore the subsequent treatment with radiation therapy (by considering this fact that the extra medullary hematopoietic masses are highly sensitive to radiotherapy). Moreover, other entities should be considered in the differential diagnosis including lymphoma, neurosarcoidosis and etc. Additionally,
because of the signs and symptoms of increased intracranial pressure secondary to direct mass effect in our case, we decided to perform an emergent neurosurgical intervention.

- According to hematologist consultation, Laboratory investigations were: hemoglobin 8 g/dL, WBC count: 13.2x10^9/l, platelet count: 265x10^9/l, mean corpuscular volume: 68.9 fl. Peripheral smear showed anisopoikilocytosis, tear drop cells, polychromasia, nucleated RBCs and target cells. Hemoglobin electrophoresis showed 96.7% HbF and 3.3% HbA2. HbA was absent. In his family history his parents were both carrier (minor thalassemia). The patient did not consume any kind of medicine and his past medical history is written in our manuscript.

- Postoperatively, patient was followed for 4 months. He showed rapid recovery of signs and symptoms of increased intracranial pressure but incomplete recovery of visual lost i.e. Visual acuity was improved to detect hand motion. During this period patient was referred to hematologist again and radiotherapist for continuation of his treatment.

- Just as mentioned in the last paragraph of case presentation, patient received standard treatment of EMH by hematologist.

**Reply to Reviewer 3:**

- The patient’s identifiable information is removed from the MRI images.

- With special thanks for your suggestion, we added both articles to our references and we addressed them.

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Intracranial Extramedullary Hematopoiesis In Beta Thalassemia; Case Report

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Abstract

Introduction: Extramedullary hematopoiesis occurs in approximately 15% of cases of thalassemia. Intracranial deposits of extramedullary hematopoiesis are an extremely rare compensatory process in intermediate and severe thalassemia.

Case Presentation: We present an unusual case of an intracranial extramedullary hematopoiesis with choroid plexus origin, in a 34-year-old, Caucasian intermediate beta thalassemic man with the complaints of chronic headache and rapid progressive visual loss.

Conclusion: Intracranial extramedullary hematopoiesis, although extremely rare, should be considered as a potential, ancillary diagnosis in any thalassemic patient and therefore appropriate studies should be performed to investigate the probable intracranial ectopic marrow before any surgical intervention.
Introduction

Extramedullary hematopoiesis (EMH) occurs commonly in severe thalassemic patients who received inadequate treatment. In this condition, beside the usual regions of hematopoiesis, blood cells can be formed in unusual sites like liver, spleen, lymph nodes to meet the demands for hematopoiesis [1,2]. There are few reports that EMH has involved some rare places such as perirenal and paravertebral region, para nasal sinuses, clivus, meninges, spinal and epidural spaces, prostate, adrenals, pleura, breast, thymus, kidney, sweat gland, broad ligament and retroperitoneal space [2-11]. This unusual phenomenon especially when involves central nervous system (CNS) can act as a space-occupying lesions and lead to neurological deficits [12-15]. In this study we describe a rare case of intracranial extramedullary hematopoiesis with choroid plexus origin, in a patient with intermediate beta thalassemia which involved left occipital horn and resulted in rapid progressive visual loss.

Case Report

A 34-year-old Caucasian man, a known case of Beta thalassemia intermediate with the complaints of chronic headache during last 4 months, with recent onset nausea, vomiting, disequilibrium and rapid progressive visual loss.

He was pallor with cachectic appearance and had a prominent skull deformity and hepatomegaly. Neurological examination showed bilateral severe optic disc atrophy and the visual acuity revealed no light perception (NLP) in both eyes. Extraocular movements and other
cranial nerves examination were normal. His speech and sensorium were intact but there was gait disturbance due to disequilibrium. GCS score was 15 and there were no paresis in his extremities. Deep tendon reflexes and cerebellar functions showed no abnormality and Babinski’s sign was absent. The patient had irregular blood transfusions, splenectomy and cholecystectomy in his past medical history. In his family history his parents were both carrier (minor thalassemia) and the patient did not consume any kind of medicine.

At admission a sample of blood sent for laboratory investigations, the results were; hemoglobin 8 g/dL, WBC count: 13.2x10^9/l, platelet count: 265x10^9/l, mean corpuscular volume: 68.9 fl. Peripheral smear showed anisopoikilocytosis, tear drop cells, polychromasia, nucleated RBCs and target cells. Hemoglobin electrophoresis showed 96.7% HbF and 3.3% HbA2. HbA was absent.

In skull x-ray, expansion of the diploic space with a so called hair-on-end appearance according to extra medulary hematopoisis was seen. Computed tomography (CT) study of the brain disclosed a large hyper dense lobulated lesion in the vicinity of the left occipital horn with significant surrounding edema which enhanced after IV contrast injection Magnetic resonance imaging (MRI) study of the brain revealed a hyper intense lesion in T1 which was signal void in T2 and with significant peripheral edema (Figure 1, 2, 3). There was a left to right shift of midline and thickening of calvarium in sagittal plane.

After correcting the hemoglobin level before operation, with the impression of meningioma of lateral ventricle or high grade glioma, the patient underwent a craniotomy by left posterior parietal transcortical approach.

Intraoperatively, the lesion was found lobulated, very well differentiated from the peripheral white matter without adhesion to it and well capsulated with prominent vessels over the capsule.
of tumor. The lesion excised entirely until its final attachment to choroid plexus which came into the view and the occipital horn exposed.

Pathologic examination of the surgical specimen was compatible with hematopoietic tissue. Macroscopically the specimen measured 2/5×1/5×1cm and it was soft and Grayish white colored. Microscopically, the specimen was composed of brain tissue, hematopoietic cells and megakarocytes (Figure 4 Left). Immunohistochemically, the megakarocytes and endothelial cells were positive for factor VIII related antigens (Figure 4 Right). Postoperatively, patient was followed till 4 months. He showed rapid recovery of signs and symptoms of increased intracranial pressure but incomplete recovery of visual lost i.e. visual acuity was improved to detect hand motion. During this period patient was referred to hematologist and radiotherapist for continuation of standard treatment.

Discussion

Spinal cord compression due to EMH is a well-known condition, however its intracranial involvement is extremely rare and there are few reported cases about this disorder [13, 15]. EMH is described as an ectopic production of bone marrow elements which is believed to be a compensatory mechanism subsequent to body’s hematologic demands and bone marrow stress [16]. In some conditions this ectopic mass is as a result of bone marrow extension from the adjacent bony structures. A variety number of modalities have been advocated to relieve the bone marrow compression [8, 15]. Multiple blood transfusion and low-dose radiation are some
of these proposed treatments which can lead to shrinkage of the ectopic marrow, decline in its compression signs and symptoms.

In our case, the patient had symptoms of increased ICP and Visual loss. The later symptom may be due to secondary effects of mass lesion upon adjacent structures of visual pathways and/or increased ICP. Moreover, intracranial EMH arising from the base of the cranium near the sphenoid and ethmoid bones, may extend into the intracranial cavity, and compress the visual pathways with resultant progressive visual failure [15].

In one previous case report, Aarabi and his colleagues presented a similar case of intracranial EMH in a thalassemic patient with symptom of decreased VA. They also surgically excised the intrasellar mass, but their patient was a previously known case of EMH arising from the base of the cranium near the sphenoid and ethmoid bones, extending into the intracranial cavity and their Management included partial resection of the mass [15].

Musolino and his colleagues also reported another similar case of Intracranial EMH with sympoms of decreased VA and endocranial hypertension, but their patient was a case of Acquired Immune Deficiency Syndrome (AIDS) with chronic bone marrow dysfunction. It was mentioned that the decreased VA was due to cytomegalovirus chorioretinitis, contrary to that seen in our case which was due to compressive effect of intracranial EMH [13].
An interesting finding in the current case report was that, we presented a rare case of intracranial EMH originating from choroid plexus and the patient underwent successive total surgical resection by which the signs and symptoms of increased ICP were subsided. Although the total resection of this lesion is a hemorrhagic procedure, it seems that in operable cases, the total resection may be safe and help to early remission of the clinical signs and symptoms.

**Conclusion**

This case report showed that although rare, intracranial extramedullary hematopoiesis should always be considered in a differential diagnosis of any mass lesion and increased intracranial pressure symptoms in patients with thalassemia. Therefore appropriate investigations should be performed to diagnosis the probable intracranial ectopic marrow lesion before any intervention.
Abbreviations

Consent
Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
SAF performed the chart review and manuscript preparation. HT, ASH, SA and SAF carried out the operation. PM and MM were the pathologists who examined the specimen. All authors read and approved the final manuscript.
References


Figure 1) An axial T1-WI MRI image demonstrates a well-demarcated isointense lesion in the left trigone with significant surrounding edema and mass effect.

Figure 2) An axial T2-WI MRI image shows signal void brain lesion in left trigon area. Surrounding vasogenic edema is well demonstrated.

Figure 3) An axial T1-WI MRI image with IV contrast demonstrates a large homogenously enhanced lesion in left trigone area.

Figure 4) Microscopic view of the excised brain lesion demonstrating the infiltration by foci of hematopoietic cells and megakaryocytes (H & E, original magnification × 40) (Left) and megakaryocytes and endothelial cells is positive with factor VIII related antigen (H & E, original magnification × 40) (Right).