

## Palliative Radiotherapy for Spinal Extramedullary Hematopoiesis in Thalassemia Major

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### Authors' contributions

This work was carried out in collaboration between all authors. Author FK designed the study and wrote the protocol. Author CUA wrote the first draft of the manuscript and managed the literature search. All authors read and approved the final manuscript.

### Article Information

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### ABSTRACT

**Introduction:** Non-hepatosplenic Extramedullary Hematopoiesis (NHEMH) is seen as a compensation mechanism in the patients with hematologic dysfunction. Thalassemia is an autosomal recessive hematologic disorder. The tissue involvement is seen very rarely in thalassemia major.

**Case:** A 45-years old patient diagnosed with thalassemia major was presented in this case report. The patient had splenectomy after 12 years from diagnosis and he was followed with continuous blood transfusions. Due to the newly emerged chest pain and dyspnea, he was evaluated with computed tomography. The operation was done for paraspinal masses caused by NHEMH. But

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same complaints were seen after 5 years from the operation. Paraspinal and sacral recurrences were detected in screening examinations. External palliative radiotherapy (ERT) was given to the patient with 3000 cGy total doses. Both clinical and radiological response was obtained with ERT.

**Conclusion:** Radiotherapy might be considered as an efficient palliative treatment option for the thalassemia major patients with NHEMH masses recurring after operation.

*Keywords: Thalassemia; extramedullary hematopoiesis; radiotherapy.*

## 1. INTRODUCTION

Thalassemia is an autosomal recessive hematologic disease and its characteristic finding is a genetic defect in globin chain of hemoglobin. It is commonly seen in Southern Iran society. The most common manifestation of the disease is anemia. It is divided into two subgroups according to the location of deficient chain as  $\alpha$ -thalassemia and  $\beta$ -thalassemia. Only one allele mutation in  $\beta$  globin chain is called  $\beta$ -thalassemia minor and two allele mutations in the same chain is called  $\beta$ -thalassemia major. Additionally, thalassemia intermedia cover the groups which are located between above mentioned groups [1].

Non-Hepatosplenic Extramedullary Hematopoiesis (NHEMH) is commonly seen in patients with thalassemia major, thalassemia intermedia and sickle cell anemia as a result of hematologic dysfunction [1]. The patients with thalassemia intermedia include heterogeneous groups in terms of clinic and genetic features [1]. High hemoglobin levels in some patients are due to extensive NHEMH [2]. Heterotrophic bone marrow can commonly occur due to the erythropoietic stress. The development and growth of unexpected masses outside of bone marrow is called NHEMH tissue (NHEMHT). EMH appears as a compensation mechanism to hematologic dysfunction in thalassemia major, thalassemia intermedia and sickle cell anemia [3]. EMH is commonly seen in liver, spleen and lymph nodes which are providing hematopoiesis in the embryologic period. EMH occurring outside of hematopoietic system is associated with myelofibrosis caused by myeloid metaplasia [4]. Intra-thoracic NHEMH is rare and usually has an asymptomatic course. Intra-thoracic NHEMH does not need treatment except the symptoms such as massive hemothorax, symptomatic pleural effusion and spinal cord compression [5]. Fine needle biopsy and radionuclide screening are appropriate for the diagnosis of NHEMH. Computed Tomography (CT) and/or Magnetic Resonance Imaging (MRI) are required for the patients with NHEMH symptoms [6,7].

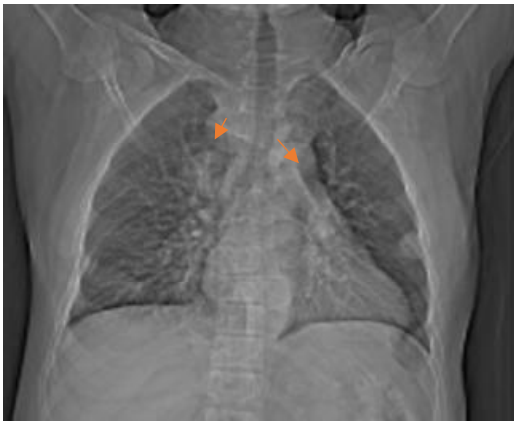
Spinal NHEMH tissue is seen rarely and the hypothesis for spinal NHEMHT occurrence is spreading with trabecular bone of vertebral corpus or proximal costa. Hematopoietic tissue caused by anemia obtains extra branches including intercostal veins [6]. In early evaluation, immature erythroid and myeloid cells in dilated sinusoids are seen which are located in paraspinal NHEMHT. Also, iron depots are found in adipose tissue and in massive fibrotic tissue. These small intraspinal NHEMHT causes cord compressions.

While NHEMHT is seen in 20% of thalassemia intermedia, the rate of NHEMHT is <1% for the patients with thalassemia major requiring frequent blood transfusion. Paraspinal hematopoiesis has 11-15 % incidence rate between all NHEMH cases [6]. Paraspinal masses have usually asymptomatic clinic progress. The major symptom is spinal compression which can be shown in CT easily. Neurologic symptoms appear in 3<sup>rd</sup>-4<sup>th</sup> decade of disease due to the chronic progress of the pathogenesis [8-10]. Very few cases are diagnosed in early age. It is five times more frequent in males than females [11,12]. Our presented case is important in terms of being thalassemia major and obtaining great benefit from irradiation.

## 2. CASE

A 45-years-old male patient was diagnosed with thalassemia major due to his physical examination and hemoglobin electrophoresis in 1983. His laboratory findings were as WBC: 11.800/mm<sup>3</sup> Hemoglobin: 9,6 mg/dL HCT: 29.2% HbA1: 0%, HbA2: 2.4%, HbF: 97.6%. The patient had blood transfusion during 12 years for 2-3 times in a week. In 1995, splenectomy operation was done for painful splenomegaly. In 2008, he had operation from paravertebral NHEMHT. Because of his high iron status, he was followed with folic acid and deferasirox treatment till 2011. His serologic markers for hepatitis and HIV (human immuno-deficiency virus) were negative. Whole body tomography

screening was done in 2011 because of ongoing complaints of chest pain and dyspnea. Multifocal soft tissue lesions located in paravertebral area were detected in the CT and lesions were compatible with NHEMH focuses starting from upper level of mediastinum and continuing in pelvic and the presacral area. Bilateral paravertebral nodules were more marked on the left than the right side. The maximum size of them was 3x2 cm. Pelvic masses were bigger than the paravertebral ones and their maximum size was 6x4.7 cm. Masses located in posterior mediastinum and the presacral area, which were defined as NHEMHT, were shown in Figs. 1-3. His laboratory findings for homovanillic acid and vanilmandelic acid were negative. The patient was evaluated and external palliative radiotherapy (RT) was planned to be given to those postoperative recurrent masses for obtaining symptomatic improvement. Palliative RT, consisting of 18 MV photons, was given with 15 fractions, 2 Gy daily doses and totally 30 Gy. Paravertebral field was planned bilaterally on the other hand; box field was accepted suitable for pelvic irradiation field. Complete clinical response was obtained after palliative RT and partial radiological response was seen in control CT after 18-months follow-up period (Figs. 4 and 5).

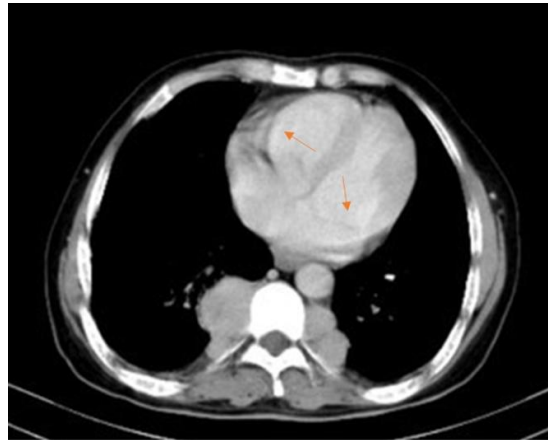


**Fig. 1. Bilaterally located paravertebral masses in the chest radiograph of the patient**

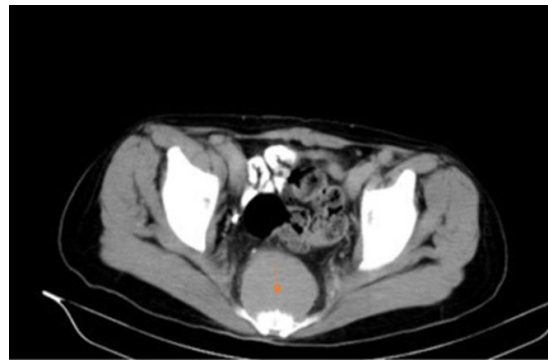
### 3. DISCUSSION

NHEMH is very rarely seen in thalassemia major. The main treatment of thalassemia major is blood transfusion. Surgery and RT options are suggested for NHEMHT treatment. Clinically symptomatic masses require treatment immediately. Chronic anemia and continuous blood transfusions can cause and facilitate the occurrence of NHEMHT [13].

NHEMHTs, which are located in the paraspinal area, can trigger neurologic complications as a result of spinal cord compression. Target hemoglobin level is usually >10 g/dl in thalassemia major treatment. Significant difference at hemoglobin levels draws attention after the operation of NHEMHTs. Additionally, oxygenation of the postoperative tissues differentiates and this is useful for the improvement of neurological symptoms caused from paraspinal masses [14,15].



**Fig. 2. Soft tissue lesions located at the paravertebral area in computed tomography**



**Fig. 3. Soft tissue lesion located at the sacral area in computed tomography**

Surgery is the main treatment for symptomatic NHEMHTs. It is stated that obtaining normal hemoglobin level in case of progressive clinical status is contingent with clinic decompression. Nevertheless, the risk of recurrence is high for diffuse mature masses. Briefly, it is cited that surgery provides improvement for the patient with acute, progressive disease and with symptomatic neurologic deficits [16]. The

treatment results of blood transfusion and RT combination is promising.



**Fig. 4-5. Partial regression of the masses were seen in thoracic and pelvic computed tomography screening**

It was shown that neurologic deficits could recover with low dose RT in approximately 50 % of patients after 3-7 months from therapy. Hematopoietic tissues are quite sensitive to RT. Hematopoietic tissue volume is reduced by 16.4 % after RT. The doses between 900 and 3500 cGy were seen effective [17]. On the other hand, there is a high (19-37 %) recurrence risk after RT. It is suggested that RT and operation should be considered to use concomitantly. It was seen that the recurrence risk with RT applied after laminectomy was lower than the RT alone option [18-21]. Therefore, immediate palliative RT should be preferred for the patient with neurologic symptoms which have favorable response to RT. Furthermore, it is reported that combined treatment of low dose RT with blood transfusion and hydroxyurea represents excellent results [22,23]. There is a review for complete recovery from paraparesis by emergency RT in literature [24].

Neurologic symptoms may get worse at the beginning of RT as a result of tissue edema. Additionally, it should be kept on mind that RT is a common factor for occurring pancytopenia due to its immunosuppressive effect. Blood count should be followed continuously during RT [19].

Another treatment option is the drug called hydroxyurea. Hydroxyurea is a kind of ribonucleotide enzyme inhibitor which is used to treat the patients with paraspinal NHEMHTs [25,26].

#### **4. CONCLUSION**

Management of the patients with NHEMHT changes from patient to patient. The treatment algorithms will be matured with the help of understanding the molecular, clinical and pathologic characteristics of thalassemia major. Single or combined treatment modalities are experienced for the patient with NHEMHT located in the paraspinal and pelvic area. Our case is important in terms of presenting a good radiological and clinical response with the use of RT.

#### **CONSENT**

It is not applicable.

#### **ETHICS STATEMENT**

The patient's informed consent was taken for publication.

#### **COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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