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# Extramedullary Hematopoiesis with Atypical Localization in Patients with Hemolytic Anemia

## Hemolitik Anemili Hastalarda Atipik Lokalizasyonlu Ekstramedüller Hematopoez

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**ÖZ**

**Amaç**: Bu çalışmada bölgemizde takip edilmekte olup çoğunluğu hemoglobinopati tanısı almış hemolitik anemili hastalarda ekstramedüller hematopoez (EMH) atipik lokalizasyonlarını saptamak amaçlanmıştır.
**Araçlar ve Yöntem**: 01.07.2020-28.02.2022 tarihleri arasında hastanemiz Çocuk Hematoloji Kliniğinde takip edilen hemolitik anemili hastaların dosyaları ve görüntüleme tetkikleri retrospektif olarak tarandı. Hastalardan şikayetleri nedeniyle ya da başka nedenlerle görüntüleme yapılıp lezyonlar saptananlar değerlendirildi. Hastaların bir kısmı 18 yaş üzerindeydi ve olgular daha çok bu yaşlarda saptandı.
**Bulgular**: Çalışmada toplam 247 hasta tarandı.Görüntüleme tetkiklerinde öncelikle akciğer filmleri ve sonrasında gerekli görülen daha ileri yöntemlerle (toraks bilgisayarlı tomografisi, manyetik resonans görüntüleme gibi) tarama yapıldığında 5 hastada atipik lokalizasyonda EMH saptandı. Hastalarda tek veya çift taraflı torakal paraspinal EMH saptandı. Bir hastada ek olarak sağ böbrek EMH odağı mevcuttu.
**Sonuç**: Hemolitik anemili hastalarda saptanan kitle lezyonunun atipik lokalizasyonda EMH olma olasılığının klinisyen ve radyolog tarafından değerlendirilmesi hastayı gereksiz tanısal ve girişimsel işlemlerden koruyacaktır. Hastaların düzenli takip ve tedavileri esnasında bu lezyonların varlığı açısından da öngörülü olunmalıdır.

**Anahtar Kelimeler:** anemi; görüntüleme; hemoglobinopati; hematopoez

**ABSTRACT**

**Purpose**:This study aimed to determine the atypical localizations of extramedullary hematopoiesis (EMH) in patients with hemolytic anemia, most of whom were diagnosed with hemoglobinopathy and are followed in our region.
**Materials and Methods**: The files and imaging examinations of hemolytic anemia patients in the Pediatric Hematology Clinic of our hospital between 01.07.2020-28.02.2022 were retrospectively scannedPatients who were imaged for complaints or for other reasons were evaluated for lesions. Some of the patients were over the age of 18 and the cases were mostly detected at this age.
**Results**: A total of 247 patients were scanned in the study, and EMH was detected in atypical localization in 5 patients as a result of imaging studies, firstly with lung films and then with more advanced methods (such as chest computed tomography, magnetic resonance imaging) when necessary. Unilateral or bilateral thoracic paraspinal EMH was detected in the patients. One patient had an additional right kidney EMH focus.
**Conclusion**: Clinical and radiological evaluation of the probability of a mass lesion detected in patients with hemolytic anemia to be EMH at atypical localization will protect the patient from unnecessary diagnostic and interventional procedures. During the regular follow-up and treatment of the patients, the presence of these lesions should also be predicted.

**Keywords:** anemia; hemoglobinopathy; hematopoiesis; imaging

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## INTRODUCTION

The presence of hematopoietic tissue except bone marrow in order to increase hemoglobin value while causing growth, shape change and even structural changes in tissue is called Extramedullary hematopoiesis (EMH).[1] It is seen mostly where low hemoglobin levels due to insufficient erythrocyte production or transfusion policy cannot prevent tissue hypoxia in diseases like hemolytic anemias or rarely in the bone marrow myeloproliferative diseases.[2]

It can be observed under even physiological situations that the main location of fetal hematopoiesis are in liver and the spleen as EMH at embryonic and fetal life.[3] However, pathologic EMH is observed when normal hematopoiesis in the bone marrow cannot function properly, and it may be interrupted by myelofibrosis, thalassemias, or other conditions affecting the hematopoietic system. Therefore-pathological EMH regions may be associated with the reactivation of the embryonic hematopoietic structure in many organs where they are observed.

The correct interpretation of mass lesions that are unexpectedly detected in radiological examinations performed for other purposes in patients with hematological anemia who receive either transfusion or other other treatments, is of a great importance both for the patient and the clinician. Since non-benign diagnostic interpretations may lead to unnecessary diagnostic and even surgical interventions keeping extramedullary hematopoiesis (EMH) in mind even though they are in atypical localizations.

Here we intended to summarize our EMH cases with with their clinical and radiological imagings while discussing clinical variations and management.

## MATERIALS and METHODS

The files of the 247 patients in the Pediatric Hematology Clinic of our hospital with the diagnosis of hemolytic anemia between July 2020 and February 2022 were reviewed retrospectively. All of the patients were scanned for their previous Chest X rays and abdominal ultrasonography if performed. Patients without previous X-ray were excluded. Patients with congenital anemia can be followed in the pediatric hematology department at this age. In radiological examinations, EMH foci in rare localizations such as paraspinal, kidney, adrenal and mesentery were investigated, except for common localizations such as spleen, liver, thymus and lymph nodes.

The study was approved by Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: 27.01.2022, Session No: 98, Decision No: 1763).

### Statistical Analysis

The data was analyzed using SPSS 20.0 software package for windows. Categorical variables were summarized as numbers and percentages while continuous variables were summarized as mean and standard deviation (median and minimum-maximum if necessary).

## RESULTS

Of the patients included in the study, 6 were being followed with a diagnosis of pyruvate kinase deficiency, 120 with sickle cell anemia, and 121 with β thalassemia. Some of the patients were over the age of 18 and the five EMH cases were mostly detected at this age group. EMH in atypical localization was detected in 5 patients. Unilateral or bilateral thoracic paraspinal EMH was detected in all patients. One patient had an additional right kidney EMH focus. Their disease diagnosis distribution were mostly hemoglobinopathies as in Table 1. The details of patients were given below with their treatments and transfusion schedules. EMH patients were older and have higher platelet levels. Diagnostic distributions, some hemogram values and demographic data of the patients are shown in Table 1.

**Case 1:** A 23-year-old female patient with hemolytic anemia, is being followed up in a chronic transfusion regimen, and receives 1-2 Units of erythrocyte suspension every 2 months. A few years ago, the patient underwent abdominal USG during gallstone/hypersplenism investigations and was diagnosed with a right renal mass, and a CT scan was recommended for mass characterization. Splenomegaly and cholelithiasis were observed in axial abdominal CT scans with oral and IV contrast (Figure 1). In the sections

passing through the lower thoracic level, there were bilateral paravertebral masses of 23x13 mm at the level of the T9 vertebra on the right and 23x10 mm at the level of the T8-T9 vertebrae on the left in the posterior thoracic section. A mass lesion with a size of 12x9 cm, well-circumscribed, solid and heterogeneous internal structure, developed from the right kidney, which was observed to compress the liver (Figure 1) was observed. Surgery was recommended with the diagnosis of malignant lesion of renal origin in the initial evaluations; however, a diagnosis of EMH was considered after a comprehensive evaluation of the images and the patient's clinical picture. In the follow-up images, the diagnosis was confirmed as the mass began to shrink with regular erythrocyte transfusions and elevation of basal hemoglobin.

**Table 1.** Diagnostic distributions, some hemogram values and demographic data of the patients.

| | **All patients n=247 (100%)** | **EMH (-)** | **EMH(+)** |
|---|---|---|---|
| Male sex, n (%) | 110 (44%) | 108 (44%) | 2 (40%) |
| Diagnosis, n(%) | | | |
| PKD | 6 (2%) | 4 (2%) | 2 (40%) |
| SCA | 120 (49%) | 120 (50%) | - |
| β Thal | 121 (49%) | 118 (48%) | 3 (60%) |
| | | **Mean±SD Median (min-max)** | **Mean±SD Median (min-max)** |
| Age (months) | 175.6±83.9<br>184.0 (7.0-348.0) | 171.4±83.1<br>181.0 (7.0 – 348.0) | 271.6±22.6<br>282.0 (242.0-296.0) |
| Hg (gr/dL) | 9.9±2.2<br>9.3 (4.9-15.5) | 9.9±2.2<br>9.3 (4.9-15.5) | 8.6±0.9<br>8.4 (7.9-10.2) |
| Platelet (/μL) | 454100±241190<br>(201000-1123000) | 445000±242690<br>(210000-1123000) | 647800±57070<br>(566000- 709000) |

PKD; Pyruvate Kinase Deficiency, SCA; Sickle Cell Anemia, β Thal; Beta Thalassemia

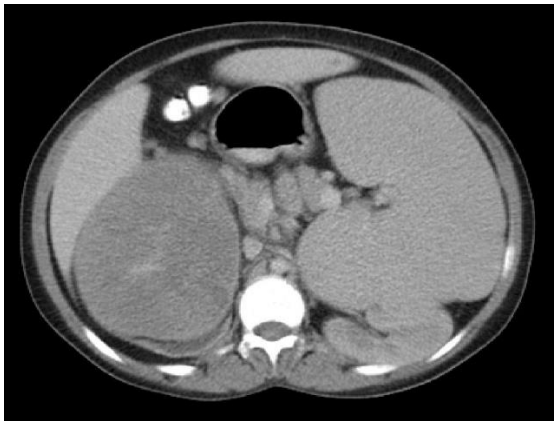

**Figure 1.** Contrast-enhanced axial CT scan shows a smooth-circumscribed slightly enhanced hypodense mass originating from the right kidney.

**Case 2:** A 25-year-old female patient with hemolytic anemia (with a preliminary diagnosis of membranopathy) was out of follow-up because she started working in another province after her graduation. After being followed for a long time without blood transfusion, she was referred to the clinic where she was followed up before, due to mediastinal enlargement in the chest X-ray. In her new genetic evaluation, she was diagnosed with Pyruvate Kinase deficiency. In the thoracic vertebra MR examination, an oval, well-circumscribed, EMH focus was found in the right paravertebral localization in the axial T2W section (Figure 2).

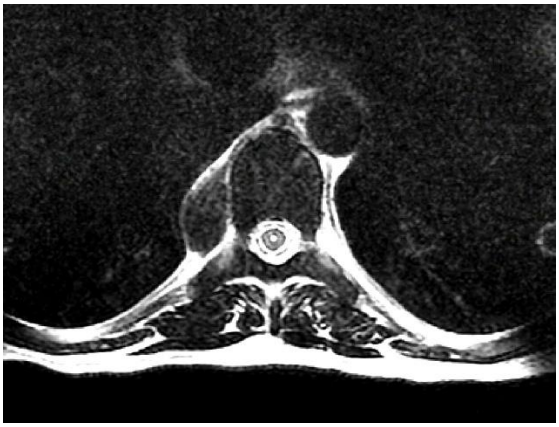

**Figure 2.** Axial T2W thoracic vertebra MRI scan shows well-circumscribed EMH in the right paraspinal area.

**Case 3**: A 24-year-old female patient with a diagnosis of thalassemia intermedia who was not transfused because she was out of follow-up for a long time presented with respiratory symptoms. EMH was detected with thorax CT taken after chest X-ray. On CT imaging, a mass extending between T2-T4 vertebral corpus levels in the left paraspinal area and measuring 46x36 mm at T4 vertebral corpus level was observed . At the level of the T5 vertebra corpus, a separate 46x17 mm mass with lobulated contours was measured in the left paraspinal area. Mass lesions were observed extending bilaterally in the paraspinal area along the T6-T11 vertebrae, and their axial dimensions were

69x28 mm on the right and 48x12 mm on the left at the level of the T10 vertebral body (Figure 3).

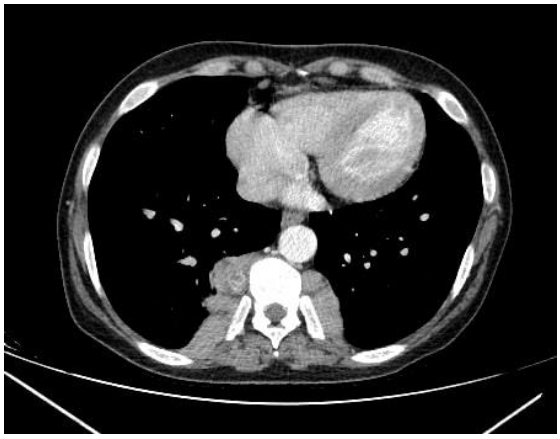

**Figure 3.** Axial contrast-enhanced thoracic CT scan shows bilateral paravertebral lobulated contoured EMH.

**Case 4:** A 20-year-old Thalassemia Major patient was on a regular transfusion regimen and had thoracic paraspinal EMH on CT examination.

**Case 5:** A 21-year-old thalassemia intermedia patient was alive with transfusion-free subnormal hemoglobin levels, and bilateral paravertebral EMH foci were present in the MRI images of the thoracic vertebrae.

## DISCUSSION

When we examine the literature, there are over 3000 articles and we see that the number of publications has increased every year since the 1980s and has reached more than a hundred per year in recent years. This may be related to the increase in complications as a result of the increasing survival rates of these congenital hemolytic anemia patients as ß thalassemia and sickle cell anemia in recent years. The total number of publications in these two disease groups is around one third of all publications. In general, case reports have been reported and, rarely, studies and reviews have been included.[4-6]. In screening for this group of diseases, as in our thalassemia patients, non-transfusional thalassaemia patients had higher EMH rates than those who had transfusions, whereas in sickle cell anemia patients the EMH rate was higher, which we couldn't detect in our study.The fact that Pyruvate Kinase deficiency patients, which are detected in very few numbers in the literature, are seen in 40% of the patients we screened, this may be due to the difficulties in diagnosis of this disease group, as well as the difficulties in detecting EMH.

As the literature revealed, EMH can also be caused by also ineffective erythropoietic conditions (such as pernicious anemia, hypochromic anemia, erythroblastosis fetalis, folate or vitamin B12 deficiency), loss of stem cell differentiation (such as in myelosclerosis, myelofibrosis, and polycythemia rubra vera); or non-myeloid neoplastic diseases with bone marrow myelophysical effects (such as leukemia, lymphoma, carcinomatosis). Hematologically normal individuals also may present with EMH.[7] Also, it has been widely reported in the literature to occur in places that are not expected to include hematopoiesis.[8-11] EMH tends to develop in serous membranes such as the pleura, pericardium, mesentery, and omentum, as well as in tissues such as the adrenal glands, gastrointestinal tract, epididymis, uterus, peripheral nerves, thoracic cavity, breast, heart, adipose tissue, cartilage, brain, and spinal cord.[7] Although it is most commonly seen in the posterior mediastinum, it has also been reported in the retroperitoneum and kidneys.[7] EMH is very rare in the kidney parenchyma, as in one of our patients.

In X-ray examination, they are observed as well-circumscribed masses in the paraspinal areas.[12-13] On CT scans, they are observed as paravertebral lesions of muscle density, which do not cause destruction in the adjacent bone, with smooth borders and lobulation at the edges. Contrast enhancement is homogeneous. However, in chronic lesions, iron accumulation and fat deposition may lead to a heterogeneous appearance in the lesion.[12] Paravertebral masses show intermediate signal intensity on both T1- and T2-weighted MR images. Enhancement with IV Gadolinium agents is minimal or absent. Chronic inactive lesions are observed heterogeneously. If fat deposition has developed, areas with high signal intensity are observed on both T1 and T2-weighted MR images. Treating the patients with blood transfusion reduces the sizes of the lesions, and low signal intensity can be observed in both T1 and T2-weighted MR images of the mass due to massive iron deposition on MRI.[13]

In renal involvement, EMH may be located in the renal parenchyma or renal pelvis, or it may be located perirenal.[14] Generally, EMH has a diffuse appearance and it is rare to

present as a focal mass-like lesion. EMH as a solitary renal mass has been reported in only a few cases in the literature. In all these cases, renal cell carcinoma or other secondary malignancies were the initial diagnosis.[15] It has been reported that the lesions were hypodense on non-contrast CT and showed mild enhancement with contrast in the patient who had EMH foci that filled and enlarged the pelvicalyceal system of both kidneys.[16]

As the treatment concerned, blood transfusions are typically used to treat such situations, which can lessen the hematopoietic drive for EMH. Other alternatives include surgery, radiation, hydroxyurea, or a case-by-case mix of these.

The small number of patients and the retrospective design are limitations of the study. Considering the relative rarity of the disease process and the time required to collect sufficient number of patients, it is unfortunately not possible to conduct a prospective study.

In conclusion, EMH can occur in a variety of locations, familiar or unfamiliar to the clinician, with expected and unexpected sites. Especially in hematologic diseases, the evaluation of these lesions should include benign hematopoiesis efforts of the hematopoietic system. Thus, unnecessary evaluation and interventions can be avoided.

**Conflict of Interest**

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

**Ethics Committee Permission**

The study was approved by Adana City Training and Research Hospital Clinical Research Ethics Committee (Date: 27.01.2022, Session No: 98, Decision No: 1763).

**Authors' Contributions**

Concept/Design: ŞL, MÇ. Data Collection and/or Processing: ŞL, MÇ, AB. Data analysis and interpretation: ŞL, AB. Literature Search: ŞL, MÇ, AB. Drafting manuscript: ŞL, MÇ, AB. Critical revision of manuscript: ŞL, MÇ, AB.

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