A Case of Multifocal Extramedullary and Non-Hepatosplenic Extramedullary Hematopoiesis in a 43-Year-Old Man with a History of Congenital Eisenmenger Syndrome

Krzysztof Gawroński, Kamila Kruczkowska-Tarantowicz, Piotr Rzepecki, Daniel Lisicki

Corresponding Author: Krzysztof Gawroński, e-mail: kgawronski01@gmail.com

Financial support: None declared

Conflict of interest: None declared

Patient: Male, 43-year-old
Final Diagnosis: Extramedullary hematopoiesis
Symptoms: Pain of legs
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: Extramedullary hematopoiesis in organs outside the bone marrow most commonly occurs in the liver and spleen. This report is of a case of multifocal extramedullary and non-hepatosplenic extramedullary hematopoiesis a 43-year-old man with a history of congenital Eisenmenger syndrome.

Case Report: We present the case of a 43-year-old patient with complex heart disease and full-blown Eisenmenger syndrome associated with ventricular septal defect, bicuspid right ventricle, and pulmonary hypertension. In July 2020, the patient began to report neurological symptoms in the form of lower-limb numbness and weakness of lower-limb strength, with additional increasing lower-limb edema. A CT scan of the abdomen and pelvis revealed a 63×102×103 mm soft-tissue mass in the pelvis, located behind the urinary bladder. Due to the suspicion of proliferative disease, mainly of the lymphatic system, a diagnostic trephine biopsy was performed first, but no tumor cell infiltration was found.

Then, the patient was qualified for diagnostic surgery. During the operation, tumor sections were harvested. Histopathological examination of the tissue sections showed extramedullary hematopoiesis in the tumor lining. Hydroxycarbamide was used as first-line treatment. However, it was not effective in controlling clinical symptoms. Therefore, the patient was qualified for radiotherapy as a second-line palliative treatment.

Conclusions: This report presents a patient with cyanotic heart disease and extramedullary and non-hepatosplenic hematopoiesis presenting as masses that mimicked malignancy. In this case, palliative radiotherapy effectively reduced the symptoms due to the size of the mass lesion.

Keywords: Heart Defects, Congenital • Hematopoiesis, Extramedullary • Retroperitoneal Neoplasms

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/935141
Background

Extramedullary hematopoiesis in organs outside the bone marrow most commonly occurs in the liver and spleen. In adults, hematopoiesis occurs properly only in the bone marrow, and only in pathological states is this different. In pathological states, when red blood cell values are low or hemoglobin oxygen saturation decreases, ultimately resulting in tissue hypoxia, erythropoietin produced by the liver and kidney cortex is increased [1]. Erythropoietin stimulates the hematopoietic system, and if the state of tissue hypoxia is severe, chronic, and the conversion of yellow marrow to red marrow in the long bones alone does not provide adequate erythropoiesis, hematopoiesis eventually increases outside the marrow cavities. Such a condition is called extramedullary hematopoiesis (EMH) [2]. Extramedullary hematopoiesis is most commonly seen in congenital anemias, in which there is a defect in hemoglobin structure, resulting in impaired oxygen uptake by hemoglobin and subsequent impaired oxygen transport. Such diseases are additionally accompanied by hemolysis (breakdown of red blood cells) and consequent worsening of tissue hypoxia. Examples of congenital anemias in which extramedullary hematopoiesis can be found are sickle cell anemia and spherocytosis [3]. Extramedullary erythropoiesis can also be seen in patients with a myeloproliferative disorder such as primary myelofibrosis. The EMH phenomenon in this disease occurs when marrow fibrosis leads to displacement of the normal hematopoietic system. Hematopoietic cells must then “find” another environment in which to grow [2]. A similar situation also occurs as a result of irradiation of a large part of the skeletal system, which ultimately results in damage to the normal hematopoietic system [2]. EMH can also be found in patients with cyanotic heart defects, which is related to the previously discussed mechanism [4].

This report is of a case of multifocal extramedullary and non-hepatosplenic extramedullary hematopoiesis in a 43-year-old man with a history of congenital Eisenmenger syndrome.

Case Report

Our patient was a 43-year-old man with complex heart disease, involving ventricular septal defect, bicuspid right ventricle, pulmonary hypertension, and Eisenmenger syndrome. In July 2020, the patient began experiencing neurological symptoms in the form of lower-limb numbness and increasing lower-limb edema. A CT scan of the abdomen and pelvis revealed a 63×102×103 mm soft-tissue contrast-enhancing mass in the pelvis located posterior to the bladder. Enlarged external iliac lymph nodes were also demonstrated – the largest on the right side (47×14 mm) and on the left side (33×31 mm). Irregularly-shaped abnormal masses, which could also correspond to enlarged lymph nodes, were found between the spleen and pancreas and periaortically. The spleen was significantly enlarged, with a volume of 1300 cm³. Numerous osteolytic and sclerotic foci consistent with meta-lesions were found in the bones examined (Figures 1, 2). The pathological tissue, liquids, and lymph nodes demonstrated on the PET CT scan could be related to the neoplastic process. Due to suspected proliferative disease primarily of the lymphatic system, a diagnostic trephine biopsy was performed. The trephine biopsy showed a marked predominance of the red blood cell system in the prominent rich-cell marrow, with megaloblastic renewal E: M=5:1. No infiltration of lymphoma cells or other solid tumors was demonstrated.

Due to the suspicion of advanced malignancy with an unknown starting point, the patient was qualified for surgery. During the operation, 3 tumor fragments of the precordial region and the iliac nodes were harvested. The histopathological examination of the tissue fragments in the fibrous lining of the tumor revealed extramedullary hematopoiesis including erythroid islands with rejuvenation characteristics (megaloblasts), mainly immature forms of granulocytes (MPO+) and megakaryocytes (CD61+) without clear atypia. No blasts with CD34 expression were found, and CD117 was weakly positive in 10% of cells. There were a few small B lymphocytes (CD20+) and T lymphocytes (CD3+). The microscopic picture was consistent with the diagnosis of extramedullary hematopoietic tumor. In the histopathologic examination of the tumor, extramedullary hematopoiesis among the fibrous connective tissue was detected. Hematopoiesis was represented mainly by immature erythroid and, slightly less noticeably, myeloid lineages. Scattered megakaryocytes were noticed. Overt dysplasia was not observed within any of the 3 hematopoietic lineages. Only sparse CD34-positive blasts were found. Instead, 10% of the cell count
comprised scattered CD117-positive cells. Small foci of EMH were also found in enlarged regional lymph nodes (Figure 3).

The blood count showed HCT 70%, Hb 22.1g/dl, and SpO2 gasometry 81%. Hydroxycarbamide was used as a first-line treatment [5], but it is not effective in controlling clinical symptoms. The patient was qualified for palliative treatment with radiotherapy as secondary treatment [6]. We then administered targeted low-dose radiation therapy of 25 Gy to the area of the largest pelvic lesion in the sacral region in December 2021. The radiotherapy was divided into 10 fractions of 2.5 Gy. To date, there has been significant improvement in the patient’s quality of life. A significant reduction of pain related to nerve root compression has been achieved. We have not yet performed a follow-up CT scan due to the fact that the radiotherapy treatment ended in December 2021.

Discussion

Our case is of significant clinical value because it presents a situation in which a giant pelvic tumor infiltrating the lumbosacral region...
region turned out to be a tumor originating from hematopoietic tissue and not a malignant neoplastic process. Extramedullary hematopoiesis, or the appearance of hematopoietic tissue, can occur virtually anywhere, in any organ or tissue. The clinical manifestations depend on the location where the EMH appeared. It may also (at least initially) produce no symptoms.

Different authors have tried and are trying to explain the phenomenon of EMH in different ways. The phenomenon was already of interest to researchers in the 1940s, and thus the “tumor theory” was established [7]. These researchers observed that people who develop marrow fibrosis significantly over-grow their spleen. They called the phenomenon they observed “aleukemic myelosis”.

The “myelostimulation theory” [8] put forward by Dameshek assumed that there is a hypothetical factor that stimulates the hematopoietic system. Subsequently, Wolf and Neiman [9] suggested that EMH in myelofibrosis results from hematopoietic cells being filtered out by the spleen. Therefore, hematopoietic cells settle in the spleen and begin their development there. The theory of filtration of hematopoietic cells by the spleen or liver is probably correct. However, we have much documented evidence of extramedullary hematopoiesis in a wide variety of organs and tissues [10]. EMH outside of hematopoietic diseases is rare but should also be considered. In most patients who do not have established hematologic conditions, we find EMH as an incidental finding. This makes it all the more important to sensitize physicians to the possibility that EMH may exist when the disease causes chronic hypoxemia or chronic anemia [4]. The main clinical significance of EMH is that if present as a tissue mass, especially infiltrating organs, it can mimic the infiltration of lymphoma or solid tumors. In the case we present, massive multilocular EMH developed in a patient with cyanotic congenital heart disease, and the diagnosis of the disease was made only after histopathologic examination of the pathologic tissue. Previous imaging studies strongly suggested a developing, generalized neoplastic process with an unknown starting point. Above all, the pathological tissue masses could have been indicative of lymphoma. Ultimately, however, histopathological examination of the lesions indicated extramedullary hematopoiesis. The problem is treatment, as there are no clearly delineated standards for the management of extramedullary hematopoiesis. The only appropriate management is treatment aimed at reducing the symptoms caused by infiltrative, nodular lesions. This is especially true because the cause that leads to hematopoietic proliferation outside the bone marrow often cannot be eliminated, so no causal treatment is possible [11,12]. This precisely the case we have described. Unfortunately, in the case of EMH, there are not many options. The only treatment choices are debulking surgery, cytoreductive treatment, and low-dose chemotherapy. All treatment options are palliative only.

In the treatment of our patient, we used hydroxycarbamide as first-line treatment according to the published data [5,13], but without clinical or CT improvement. The patient continued to have very severe pain in the lower extremities, which was a manifestation of compression on the nerve roots of the LS segment of the spine. Subsequently, targeted radiotherapy of the largest pelvic lesion was applied as a secondary treatment to reduce the neurological symptoms involving the lower extremities [6,14].

A similar situation occurred in the described case [14]. The authors reported a tumor-like tumor that was infiltrating the spinal cord region. The authors concluded that low-dose radiation therapy of 25 Gy divided into fractions of 2.5 Gy would be the best treatment option. The patient remained asymptomatic after 3 months of follow-up. The authors also pointed out the important fact that massive bleeding can occur when surgical decompression of the spinal canal is attempted.

Conclusions

We report the case of a patient with cyanotic carditis and extramedullary and extrahepatic hematopoiesis presenting with masses mimicking a malignant neoplasm. In this case report, palliative radiotherapy was effective in reducing symptoms due to the size of the mass lesion. However, treatment can be a major problem. The use of hydroxycarbamide for large lesions may not be effective. This leaves palliative radiotherapy for masses that compress important organs and cause compression symptoms.
Declaration of Figures’ Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Short C, Lim H, Tan IKH, O’Neill HC. Targeting the spleen as an alternative site for hematopoiesis. BioEssays. 2019;41(5):e1800234
2. Sohawon D, Lau KK, Lau T, Bowden DK. Extra-medullary haematopoiesis: A pictorial review of its typical and atypical locations. J Med Imaging Radiat Oncol. 2012;56(5):538-44
3. Katchi T, Kolandaivel K, Khatwar P, et al. Extramedullary hematopoiesis presented as cytopenia and massive para spinal masses leading to cord compression in a patient with hereditary persistence of fetal hemoglobin. Biomark Res. 2016;4(1):17
4. Taylor CL, Maynard F, Liebman J, et al. Extramedullary hematopoiesis causing paraparesis in congenital cyanotic heart disease. Neurology. 1998;51(2):636-37
5. Karimi M, Cohan N, Pishdad P. Hydroxyurea as a first-line treatment of extramedullary hematopoiesis in patients with beta thalassemia: Four case reports. Hematology, 2015;20(1):53-57
6. Fontanesi I, Margolis H, Fontanesi GR, Extramedullary hematopoiesis causing spinal cord compression with excellent durable response after radiation therapy: Case report and review of the literature. J Family Med Prim Care. 2020;9(7):3741-44
7. Heller EL, Leisohn MG, Palim WE. Aleukemic myelosis, chronic non-leukemic myelosis, agnogenic myeloid metaplasia, osteosclerosis, leukoerythroblastic anemia, and synonymous designations. Am J Pathol. 1947;23:327-65
8. Dameshek W. Some speculations on the myeloproliferative syndromes. Blood. 1951;6:372-75
9. Wolf BC, Neiman RS. Hypothesis: Splenic filtration and the pathogenesis of extramedullary hematopoiesis in agnogenic myeloid metaplasia. Hematol Pathol. 1987;1(1):77-80
10. Lee MC, Salzmann KL, Blumenthal DT et al. Intracranial extramedullary hematopoiesis: Brief review of response to radiation therapy. Am J Hematol. 2005;78(2):151-52
11. Ginzel AW, Kransdorf MI, Peterson JJ, et al. Mass-like extramedullary hematopoiesis: Imaging features. Skeletal Radiol. 2012;41(8):911-16
12. Haidar R, Mhaidli H, Taher AT. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia. Eur Spine J. 2010;19(6):871-78
13. Taher A, Skouri H, Jaber W, Kani N. Extramedullary hematopoiesis in a patient with beta-thalassemia intermedia manifesting as symptomatic pleural effusion. Hemoglobin. 2001;25(4):363-68
14. Mattei TA, Higgins M, Joseph F, Mendel E. Ectopic extramedullary hematopoiesis: Evaluation and treatment of a rare and benign paraspinal/epidural tumor. J Neurosurg Spine. 2013;18(3):236-42