

Review Article

Extramedullary Haemopoiesis in Hemoglobinopathies

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Abstract

Extramedullary hematopoiesis is a common compensatory phenomenon to chronic hemolytic anemias. When the primary sites of hemopoiesis in the adult fail, as in hemoglobinopathies (especially thalassemia and sickle cell disease), various extramedullary sites take on the role of blood formation. Extramedullary hemopoiesis favors certain sites such as the liver, the spleen, and the paraspinal regions of the thorax and rare the process can involve virtually any organ or tissue and can often manifest as a mass mimicking a neoplasm. The diagnosis of EMH can be established with reasonable certainty on the basis of the characteristic radiologic findings in a patient with a predisposing hematologic condition.

INTRODUCTION

Extramedullary hematopoiesis [1] (EMH) defined by the presence of hematopoietic tissue outside the bone marrow, is a physiological phenomenon in the liver during the normal fetal development, but it is not normal after birth and must be considered a pathological finding. Chronic anemia states such as thalassemia (especially thalassemia intermedia) and sickle cell disease can cause hematopoietic tissue to expand in certain locations. Ineffective erythropoiesis [2] in patients with hemoglobinopathies drives extramedullary hematopoietic tumor formation in several parts of the body. EMH is commonly associated with cases of primary and secondary myelofibrosis but it is extremely rare in association with other hematological diseases, such as chronic myeloproliferative disorders including myeloid metaplasia, polycythemia vera, leukemia and Hodgkin's disease. This review revisits the pathophysiology, clinical manifestations, diagnosis and management of extramedullary hematopoiesis in hemoglobinopathies.

Pathophysiology of extramedullary hematopoiesis

Extramedullary hematopoiesis is a physiological compensatory phenomenon occurring because of insufficient bone marrow function that becomes unable to meet circulatory demands. Almost all body sites may be involved including the spleen, liver, lymph nodes, thymus, heart, breasts, prostate, broad ligaments, kidneys, adrenal glands, pleura, retroperitoneal tissue, skin, peripheral and cranial nerves, and the spinal canal because they normally engage in active hematopoiesis in the fetus during gestation. This pathway normally stops after birth, but the extramedullary hematopoietic vascular connective tissues retain the ability to produce red cells under conditions of longstanding ineffective erythropoiesis [3,4]. It has been proposed [4] that some embryological hematopoietic cell remnants would be stimulated along the course of chronic anemia and hypoxia. In

sickle cell disease investigators attribute the masses to embolic phenomena. Histologically [5] extramedullary hematopoiesis has immature and mature cells of the erythroid and myeloid series and dilated sinusoids containing precursors of red cells which are inactive in steady state and reveal some fatty tissue and fibrosis or massive iron deposits.

Clinical findings

Massive marrow proliferation with extramedullary tumor masses is observed in inadequately transfused b-thalassemia homozygotes but more commonly in untransfused patients with thalassemia intermedia and sickle cell disease [6-8]. In most cases EMH is asymptomatic. Among the various body regions reported, paraspinal involvement deserves special attention due to the debilitating clinical consequences and challenges in diagnosis and management. Experience to date comes from scattered case reports and small cases series.

Intrathoracic extramedullary hematopoiesis [9,10] is generally localized at the posterior mediastinum, and the middle and lower paravertebral areas. The mechanism of spinal cord [6,11,12] compression at this site is the mass lesion location and limited spinal cord mobility at the same localization. There is a predilection for thoracic spine EMH to cause cord compression; the narrow diameter of spinal canal in this region may be relevant. The clinical presentation includes a progressive motor impairment of the lower limbs, associated with spinal pain or neuralgia and paresthesia. Bladder and bowel dysfunction might be observed more lately [13,14]. The diagnosis must be suspected early in predisposed patients, in order to prevent irreversible neurological damage.

Pulmonary EMH has been rarely reported [15]. While the majority of the pulmonary EMH masses are asymptomatic, patients can sometimes present with hemoptysis, acute or progressive dyspnea or chest pain. Life threatening complications

such as massive pleural effusion, hemothorax, chylothorax, or spinal cord compression (posterior mediastinal EMH) have been reported [16-19]. As the manifestation is variable, it is difficult to distinguish EMH from other mediastinal tumors such as neurogenic tumors, lymphomas, paravertebral abscesses, extrapleural cysts, primary and metastatic malignant neoplasms and mediastinal lymph node hyperplasia [20].

Very few cases of EMH involving the heart have been reported in the literature. Almost all patients presented with massive pericardial effusion, leading to cardiac tamponade [21,22].

Abdominal involvement usually recapitulates fetal development, with the most commonly involved organs being the liver and spleen. The classic clinical finding is hepatosplenomegaly [23,24]. Masses of hemopoietic elements can involve the mesentery and can be mistaken for lymphadenopathy or neoplastic disease [25].

Intracranial EMH is extremely rare [26-29]. Most patients do not have signs and symptoms related directly to the disorder. Most foci of EMH are noted as incidental findings on imaging studies or postmortem examination. EMH in the intracranial or intraspinal epidural space can lead to serious neurogenic complications increased intracranial pressure, hemiplegia, altered levels of consciousness, or visual disturbances, including subdural hemorrhage, delirium, papilledema, coma, motor and redundant sensory impairment, and limb paralysis due to direct mass effect upon adjacent structures [28,29].

Reported CNS sites of involvement include the choroid plexus and dura mater (over the cerebral convexities, along the falx cerebri, and within the epidural space of the spinal canal), optic nerve sheath, and the diploic space of the skull. Intraparenchymal mass is a rare presentation of EMH [30].

EMH in the adrenal is uncommon, with less than 10 cases reported [4,31,32]. It is thought to be a compensatory, physiological mechanism that occurs during altered medullary haematopoiesis which is commonly seen in the haemoglobinopathies, leukemias, lymphomas and myelofibrosis. Recently, it has been postulated that the hematogenous spread of multipotential stem cells occurs with eventual infiltration of various tissues and organs. Patients with adrenal EMH are generally known to have beta-thalassemia major or other major haemoglobinopathies [33], such as sickle cell disease. Differential should be considered from myelolipomas which originate from reticuloendothelial cells of the blood capillaries.

Renal extramedullary [34-36] hematopoiesis occurred in the setting of hematological malignancies including primary myelofibrosis, essential thrombocythemia, and an unclassified chronic myeloid neoplasm is available in literature. EMH lesions are frequently asymptomatic, nevertheless hemorrhagic manifestations can be observed. Patient history can help for making a diagnosis, which can be established by CT scan and/or MRI. Surveillance is recommended for asymptomatic cases while local therapies such as low dose radiation or surgery can be used to treat bleeding lesions

The most common indication for renal biopsy was renal dysfunction.

Imaging findings

Although the history and physical examination may help narrow the differential diagnosis, radiographic imaging remains essential to confirm the existence of hematopoietic tissue.

In the past, the diagnosis of intrathoracic, pulmonary or paraspinal EMH in patients. With hemoglobinopathies was suspected from the typical osseous abnormalities.

Found on chest radiographs or was confirmed after surgical removal of the mass. Plain radiographs often reveal well-demarcated paraspinal masses and bony changes associated with chronic hemolytic anemia such as trabeculation, widened ribs, or thickened calvaria [37,38].

CT can give accurate information about encroachment into the spinal canal of soft tissue masses [39-41]. The paraspinal active hemopoietic masses are well marginated and show mild homogeneous enhancement on contrast-enhanced CT, whereas old, burnt-out lesions may show iron deposition or fatty degeneration. Rarely, hemopoietic elements can involve the precardiac and pleural spaces, but patients are usually asymptomatic. Pulmonary interstitium EMH mimicking an inflammatory or neoplastic diffuse interstitial process have been reported and have resulted in cardiopulmonary insufficiency [42,43]. Abdominal involvement usually recapitulates fetal development, with the most commonly involved organs being the liver and spleen. The classic imaging finding is that of hepatosplenomegaly. Involvement of these organs is usually diffuse, but mass like foci of hemopoiesis can be seen that may be confused with a neoplastic process [45,46].

MRI is the best method for demonstrating EMH [47-49]. MRI findings described well-defined, lobulated, smooth marginated masses. The MRI signal is variable and appeared to be dependent on the proportion of red marrow and fat in the mass. Cases demonstrated isointense or hypointense signal (relative to skeletal muscle) on T1-weighted and T2-weighted images, corresponding to red marrow. Following the intravenous administration of gadolinium contrast enhancement is variable, but usually heterogeneous [50,51].

Extramedullary hemopoiesis can also, rarely, involve the kidneys. Parapelvic hemopoietic masses can be seen because this location is active during in utero hemopoiesis. In this case extramedullary hemopoiesis manifests as uniform, enhancing perinephric masses that appear to engulf the kidneys without however distorting their shape. Rare manifestations, as mesenteric EMH may need biopsy for definitive diagnosis [52,53].

Several nuclear medicine tracers can be used for diagnosing extramedullary haematopoiesis. Colloids labelled with Technetium 99m (99mTc) show the reticuloendothelial system which reflects the richness of the medullary stroma. If there is an extramedullary haematopoietic focus, the scintigram will not show any fixation if there is little stroma [54,55].

Fluorodeoxyglucose (FDG) positron emission tomography combined with CT (PET-CT) shows metabolically active lesions. The absence of metabolically active lesions is characteristic of EMH [56,57].

Additional examinations may need: myelogram, bone marrow biopsy, medullary karyotype, plasma protein electrophoresis and biopsies

TREATMENT

Management options include blood transfusion, radiotherapy, surgical decompression, hydroxyurea, or a combination of these modalities. Therapy depends on the severity of symptoms, size of the mass, patient's clinical condition, and previous treatment.

Most reported paraplegia cases due to EMH have been treated with surgical decompression [58-60] with or without radiation therapy' in emergency cases, intravenous steroids may be used as the temporizing measure until definitive treatment is applied.

Radiation is an applicable therapy [61-65] and this avoids surgical procedure and associated risks. Suppression of bone marrow due to radiation may be observed in already anemic patients. Haemopoietic tissue is extremely sensitive to radiation and low doses cause rapid shrinkage. In EMH cases causing cord compression in thalassaemia intermedia, improvement is clinically evident after an average of three fractions of radiotherapy and near complete recovery is generally observed by the end of treatment. Doses used have ranged from 750-3500 cGy. With these low doses, the only significant toxicity that may occur is a further decrease in blood cell counts which need to be frequently monitored.

In some patients where surgery and radiation therapies may cause special risks (e.g. heart failure) transfusion has proven successful in relieving the anemic stress which leads to suppression of the hematopoietic tissue.

Hydroxyurea [66-68] successfully increases fetal haemoglobin in patients with sickle cell disease but there is limited experience with hydroxyurea in thalassaemia. Hydroxyurea has been administered in an effort to reduce extramedullary haemopoiesis. The initial dose is 500-1000mg/day.

Hypertransfusion [69-71] to keep the hemoglobin level at 12-14 g/dL seems to be an acceptable method of treatment that should be recommended as a first-line approach or as an adjuvant therapy to other methods.

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