Ectopic extramedullary hematopoiesis: evaluation and treatment of a rare and benign paraspinal/epidural tumor

Case report

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Ectopic extramedullary hematopoiesis (EMH), defined as the formation of blood cells outside the bone marrow, usually occurs in a scenario of chronic anemia when, even after conversion of the bony yellow marrow to red marrow, the body is still unable to meet the demand for red blood cells. Ectopic extramedullary hematopoiesis most commonly occurs in the liver and spleen but may, in fact, occur almost anywhere in the body. Although previous reports have documented EMH presenting as paraspinal masses, such lesions have almost always been associated with a predisposing hematological disorder such as hemolytic anemia, myelofibrosis or myelodysplastic syndromes, thalassemia, polycythemia vera, leukemia, or lymphoma.

The authors of this report describe the first reported instance of EMH in a patient presenting with a symptomatic epidural and paraspinal cervical lesion arising from the posterior spinal elements and no known predisposing hematological disease. Initial radiographs revealed a bony lesion arising posteriorly from the C2–3 laminae and spinous processes. Subsequent imaging suggested the diagnosis, which was confirmed by CT-guided biopsy, peripheral blood smears, and bone marrow aspirate. Despite epidural compression and slight displacement of the cervical cord and thecal sac, the patient’s symptoms were limited to pain and diminished cervical range of motion. Therefore, surgery was deferred in favor of nonsurgical therapy. Several alternative modalities for the treatment of EMH have been suggested in the literature, including cytotoxic agents and radiotherapy. The authors opted for an approach utilizing directed low-dose radiotherapy of a total of 25 Gy divided in 2.5-Gy fractions. At the 3-month follow-up, the patient continued to be asymptomatic, and MRI demonstrated a significant reduction in the dimensions of the lesion.

Extramedullary hematopoiesis with spinal cord compression in the absence of a preexisting hematological disorder has not been described in the context of clinical neurosurgical practice. Recognizing that EMH may present as an epidural or paraspinal lesion is important since chemotherapy and radiotherapy are effective therapeutic options in the majority of patients who suffer few if any symptoms. Extensive evaluation for underlying hematological disorders is necessary before undertaking directed therapy. Inadvertent resection of these highly vascularized masses may risk catastrophic intraoperative hemorrhage with no proven benefit as compared with medical treatment, which usually provides excellent long-term outcomes.

Key Words • ectopic extramedullary hematopoiesis • epidural tumor • spinal cord compression • hemolytic anemia • beta thalassemia

Extramedullary hematopoiesis is defined as the formation of blood cells outside the bone marrow. Although physiological EMH commonly occurs in the spleen and liver during fetal development, hematopoiesis usually shifts to the bone marrow prior to birth. During adulthood, EMH usually occurs in the presence of anemia or other predisposing hematological disorders when, even after reconversion of the bony yellow marrow to red marrow, red blood cell production remains inadequate. Multiple case reports describe EMH occurring in various anatomical sites such as the mediastinum, presacral region, adrenal gland, thymus, kidney, pleura, pulmonary interstitium, breast, skin, peritoneum, dura mater and epidural space, peripheral nerves, middle ear, pancreas, urethra, pharynx, heart and pericardium, liver, thyroid gland, prostate gland, epididymis, and endometrium.

Extramedullary hematopoiesis predominates in males (5:1 male/female ratio) and is commonly seen in hematological diseases such as chronic anemia (most commonly hemolytic anemia), myelofibrosis or myelodysplastic syndromes, polycythemia vera, leukemia, lymphoma, or beta thalassemia or after irradiation of bone marrow. Extramedullary hematopoiesis almost never occurs in healthy patients. In fact, only 2 previous publications have documented EMH presenting as mass lesions in the absence of any predisposing hematological disease: one case in a patient with a mediastinal mass and the other in a patient with a lesion arising within the suprarenal gland and retroperitoneum.

This first presentation of ectopic epidural EMH in
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the absence of coexisting hematological anomalies re-
ported here emphasizes the importance of its recognition
as a nonsurgical entity, as radiologists may erroneously
diagnose this lesion as a primary bony tumor such as os-
teoblastoma, fibrous dysplasia, aneurysmal bone cyst, or
giant cell tumor—all lesions that may eventually require
surgical intervention.

Furthermore, the resection of paraspinal EMH risks
unexpected severe intraoperative blood loss due to its high
vascularity. Recognizing the unique radiological features
that characterize ectopic epidural EMH should lead to ap-
propriate referral and treatment with a combination of mul-
tiple transfusions, chemotherapy, and/or radiotherapy.

Case Report

History and Examination. This 23-year-old woman
initially presented with complaints of posterior neck pain
and limited cervical range of motion 6 months after a
minor trauma. She was struck on the head by a falling
box while at work. She sustained no evident concussion
or syncope, but neck pain and neck stiffness developed
over the next day. Her symptoms lingered, eventually
prompting an evaluation including cervical radiographs
at an outside institution. Those films revealed a posterior
cervical mass at C2–3, and the patient was referred for
further evaluation and treatment.

In retrospect, she recalled minimal limitation in neck
motion since childhood, and she stated that a friend had
noticed a prominence in the posterior left cervical region
approximately 3 years prior to her minor head injury at
work. The neck pain persisted after the injury despite nar-
cotic analgesics, which provided only intermittent relief.
She denied any progressive loss of neck movement during
the interval since her injury. She remained ambulatory
and continued to work. She complained of intermittent
numbness in her hands and feet but experienced no limb
or hand weakness, no imbalance, and no bowel or bladder
difficulties.

Her medical history revealed asthma, gastroesophagi-
al reflux disease, and acute biliary pancreatitis, for which
she underwent cholecystectomy in 2009. She had recently
become pregnant. Examination revealed a very firm, slight-
ly tender palpable mass offset to the left of midline just be-
neath the occiput. Cervical range of motion was limited in
flexion, extension, and lateral bending to both the right and
the left. Her neurological examination was benign, present-
ing no significant sensory or motor deficits, normal tendon
reflexes, no clonus, and absent extensor plantar responses.
Balance, stance, and gait were normal.

Review of her prior radiographs revealed an osseous
3- to 4-cm mass arising from the spinous processes and
laminae of C-2 and C-3 just to the left of midline (Fig. 1).
The expansile mass had thin cortical margins and mini-
mally protruded upon the spinal canal. Her cervical lordo-
sis was slightly diminished, and dynamic films revealed a
slight anterolisthesis of C-3 over C-4 in flexion. Cervical
spine CT scanning confirmed an exophytic expansile C2–3
bony mass with thin cortical margins and a partial congen-
tual fusion of C2–3 laminae and facets bilaterally (Fig. 2).
The internal architecture of the mass was predominantly
lytic with some septations and areas of dense calcification.
The mass deformed the left laminae of C-2 and C-3 and
slightly narrowed the spinal canal. Subsequent cervical
spine MR images confirmed spinal canal encroachment
with effacement of the CSF envelope, mild flattening of the
left posterior portion of the spinal cord, and mild distortion
of the adjacent left dorsal roots. The smoothly margined
mass was slightly hyperintense on T1-weighted images,
isosintense to bone on T2-weighted images, and minimally
enhanced after the administration of Gd (Fig. 3). Accord-
ing to the radiologist’s report, the mass was considered to
be consistent with osteoblastoma, fibrous dysplasia, aneu-
rysmal bone cyst, or giant cell tumor. Chest radiography
results obtained that same day were benign.

Biopsy and Results. Computed tomography–guided
needle biopsy was requested to aid treatment planning,
although her pregnancy, in the clinical context of her
indolent course and benign neurological status, would
probably lead to a delay in treatment should surgery be
necessary. Medical oncology and pain management con-
sultations were also arranged.

The biopsy yielded tissue consistent with benign he-
matopoietic bone marrow tissue with reactive lymphoid
aggregates, normal cellularity and maturation, and nor-
mal immunohistochemical characteristics for all 3 cell
lineages (erythroid, lymphoid, and myeloid). In the ab-
sence of a demonstrated connection with normal medul-
lar spaces, the tissue mass was best considered to be an
“extramedullary” focus of hematopoiesis. Further stud-
ies of peripheral blood smears and bone marrow aspirate
were suggested.

Magnetic resonance imaging of the thoracic and lum-
bar spine revealed no additional lesions. Peripheral blood
smears were normal. Subsequent analysis of bone mar-
row aspirate from both iliac crests revealed normocel-
lar marrow with adequate trilineage hematopoiesis. A
solitary lymphoid aggregate was present in the left speci-
men, again suggesting a reactive etiology. There was no
evidence of a myeloproliferative neoplasm or increased

Fig. 1. Lateral (left) and anteroposterior (right) plain radiographs
demonstrating an osseous lesion of 3–4 cm arising from the spinous
processes and left laminae of C-2 and C-3. Arrows indicate the limits
of the lesion.
marrow fibrosis. Cytogenetic analysis revealed normal chromosomes.

Before the marrow biopsies, the patient suffered a spontaneous miscarriage. When seen again on follow-up 2 months after the initial consultation, she remained clinically and neurologically stable. Her neck pain and limited cervical range of motion persisted but were no worse. Repeated cervical imaging confirmed no significant growth of the osseous C2–3 mass. Her situation was discussed with a consultant medical oncologist and with our institutional tumor board. Possible treatment options were continued observation, a trial of hydroxyurea chemotherapy, or radiotherapy.

**Treatment.** After an interdisciplinary discussion, adjuvant treatment with radiotherapy was chosen (total of 25 Gy delivered in 2.5-Gy fractions), which was initiated about 1 month after the bone marrow biopsy.

**Posttreatment Course.** At the 3-month clinical follow-up, the patient remained neurologically asymptomatic, and control MRI demonstrated a significant reduction in the dimensions of the lesion. The patient is currently undergoing 3-month intervals of follow-up for 2 years until total disappearance of the lesion is confirmed on future control images.

**Discussion**

The first report of tumoral EMH in the paraspinal region dates from 1954 by Gatto et al., who described a 23-year-old patient with thalassemia major presenting with paraparesis due to a thoracic epidural lesion.

A recent retrospective review of the radiological records of 44 patients with EMH revealed 12 patients (27%) who had presented with focal mass-like lesions. Ten (83%) of the 12 patients had 1 or more masses located along the axial skeleton. Nine of them (90%) had multiple mass lesions, and 8 (80%) had paraspinal lesions. The thoracic spine and, to a lesser extent, the lumbar spine were the most commonly involved sites. Seven patients (70%) demonstrated radiological evidence of internal fat within the lesions, and 7 patients (70%) had splenomegaly.

A predisposing condition for extramedullary hematopoiesis was present in 10 (91%) of the 11 patients for whom a clinical history had been recorded, including various anemias (5 patients [45%]), myelofibrosis or myelodysplastic syndrome (4 patients [36%]), and bone marrow proliferative disorder (1 patient [9%]). Only 1 patient, whose lesion involved the suprarenal gland and retroperitoneum, had no known predisposing condition.

In the present case, although no underlying hematological disease was identified to explain the occurrence of EMH, we hypothesized that pregnancy might have been a significant predisposing condition for the development of such disease. As recent studies have suggested, several systemic alterations in immunity occur in the midtrimester of pregnancy, particularly with respect to a polarization toward a Th2 activation, which may lead to a higher incidence of malignancy as a consequence of the natural underlying maternal immune-privileged environment.

In fact, it has already been demonstrated that the progesterone-induced blocking factor, which may be induced by normal lymphocytes during pregnancy as well as by malignant tumors, has a natural role in modulating the Th2-dominant immune response during pregnancy but may also facilitate tumor growth by suppressing local antitumor immune responses.

**Pathophysiology of EMH**

Ineffective red cell production (erythropoiesis) may force proliferation of the hematopoietic tissue outside the bone marrow. When the liver and spleen cannot provide adequate additional hematopoiesis, EMH (as a compensatory phenomenon, most commonly presenting in the form of distinct tumoral masses) may occur at other anatomically distant sites. Thus, EMH commonly arises in association with a predisposing hematological disorder.

The exact origin of the paraspinal hematopoietic tissue is still unknown. Da Costa et al. (and more recently Ginzel et al.) hypothesized that paraspinal EMH could arise directly by extrusion through the trabecular bone of the vertebral body or the rib heads. Development of hematopoietic tissue from small paraspinal branches of
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the intercostal veins has also been suggested.\(^\text{39}\) Others attribute the masses to some arterial embolic phenomenon of hematological stem-like cells.\(^\text{2,9}\)

Early in its evolution, the paraspinal extramedullary site of hematopoiesis presents both immature and mature cells (primarily from the erythroid and myeloid series) as well as dilated sinusoids containing red cell precursors. When these lesions eventually become inactive, cellular elements are replaced by fatty tissue—a common radiological finding of the inner core of EMH presenting as mass-like lesions—iron deposits, or fibrosis. This fatty degeneration is thought to be the result of oxidative stress leading to lipid peroxidation of cell membranes and production of oxygen free radicals.\(^\text{20}\) Hence, fat deposition is more commonly seen in nontransfused, nonchelated patients with thalassemia major (in whom conditions of oxidative stress occur) than in transfused and iron-chelated patients with thalassemia major (whose inactive lesions typically develop iron deposits).\(^\text{22}\) Although both iron deposition and fatty replacement suggest that the EMH focus is inactive, they do not coexist because they result from different conditions of oxidative stress.

**Disease Diagnosis**

Paraspinal foci occur in 11%–15% of patients with EMH.\(^\text{48}\) As many as 80% of these patients are asymptomatic, and their lesions are discovered incidentally.\(^\text{42}\) Extramedullary hematopoiesis tumoral masses arising ectopically in the paraspinal region or epidural space may be misinterpreted as a primary or secondary bony neoplasm.\(^\text{1,3,12,41,45,54}\) Extramedullary hematopoiesis has been described as occurring as a paravertebral lesion\(^\text{46}\) or, more commonly, as an epidural mass causing spinal cord compression.\(^\text{20,34,50}\) Both plain radiographs and CT scans
obtained in patients with paravertebral EMH lesions may demonstrate an exophytic expansile bony lesion as well as important additional abnormalities related to an underlying hematological condition, such as trabeculation, widened ribs, thickened calvaria, or other bony changes suggestive of chronic anemia.14,52

Computed tomography and MRI characteristics of EMH lesions are determined by the presence or absence of active hematopoietic foci. A recent imaging classification of EMH lesions divided patients into 4 basic groups.53 The first group contains patients with active extramedullary paraspinal hematopoietic foci. The CT density of such lesions is similar to that of adjacent soft tissue, whereas MR images demonstrate intermediate signal intensity on both T1- and T2-weighted sequences with minimal or no enhancement after intravenous Gd administration. This relative lack of enhancement is helpful in differentiating EMH from other epidural lesions such as abscess or metastasis.31 The second group includes patients with inactive lesions containing massive iron deposits. The iron deposits result in high CT density and low MRI intensity on both T1- and T2-weighted images without enhancement after intravenous Gd administration. Most of these patients suffer from beta thalassemia and have undergone repeated blood transfusions to treat their chronic anemia. The third group is composed of patients with complete fatty replacement of the extramedullary paraspinal hematopoietic foci. These masses present very low CT density and high MRI signal intensity on both T1- and T2-weighted images. Magnetic resonance imaging signal suppression on STIR sequences and minimal enhancement after Gd administration are also characteristic of fatty replacement. The fourth group includes patients with mixed types of extramedullary paraspinal hematopoietic lesions. These lesions present foci of fatty replacement intermixed with other foci suggesting active hematopoietic activity.

The imaging diagnosis of EMH currently relies on a combination of plain radiography, CT scanning, and MRI sequences. In the past, other diagnostic techniques (such as technetium-99m bone scan) have been suggested as adjunctive tools, which might be helpful in suggesting the diagnosis of EMH.4 If limited to a single modality, MRI is the examination of choice, providing the greatest amount of diagnostic information.32

Treatment Options

Several effective treatment options have been described for EMH involving the paraspinal and epidural space, including multiple blood transfusions,56 radiotherapy,35,56,28 chemotherapy with agents that diminish hematopoietic drive (such as hydroxyurea)56 and even laminectomy for spinal cord decompression and resection in selected symptomatic patients who did not respond to initial nonsurgical measures.31,32 The ideal management remains controversial, however. Without solid studies comparing the efficacy and safety of these treatment options, an individualized approach should be considered, taking into account the location of the lesion, the extent of spinal cord compression, the presence or absence of significant neurological deficits as well as the presence of any predisposing hematological disease that may also require a specific treatment. For example, because EMH encountered in thalassemic patients is a compensatory mechanism for the chronic anemia, correction of the anemia with blood transfusions may lead to significant shrinkage of the lesion, potentially reducing spinal cord compression and improving neurological deficits.45 In fact, repeated blood transfusions have been successfully used as the principal or exclusive treatment for patients with EMH consequent to an underlying hematological condition.1,50,52

Low-dose radiation has been reported to yield excellent results in up to 50% of patients, with neurological improvement observed as soon as 3–7 days after initiation of treatment.35,37,40 Some authors argue that severe spinal cord compression and the presence of neurological deficits should not be considered contraindications for considering radiotherapy as the first-line treatment.35 A relatively high risk of recurrence (reported to be around 19%–37% of the irradiated cases) is the main disadvantage of radiotherapy.41 Hydroxyurea has also been used as an effective treatment modality for EMH.10 This ribonucleotide reductase enzyme inhibitor reduces the globin chain imbalance through stimulation of fetal hemoglobin synthesis, thereby ameliorating ineffective erythropoiesis, which is the primary stimulus for EMH development progression.11

Laminectomy for spinal cord decompression should be reserved for those patients with acute neurological deficits that fail to respond to adequate transfusion, hydroxyurea, and radiotherapy.31 Surgery might also have a role in obtaining pathological tissue when diagnosis remains uncertain despite multiple needle biopsies.20 The established risks of a surgical procedure include a high propensity for hemorrhage due to the marked vascularity of EMH masses, which may be significantly aggravated by the inherent risks of performing surgery in anemic individuals.44 Nevertheless, if medical treatment fails to effectively reduce mass compression, resection should be considered. In this setting, an en bloc resection technique should be pursued whenever possible to reduce intraoperative blood loss and ensure total resection of the lesion.33

A recently published treatment algorithm for paraspinal EMH in patients with thalassemia intermedia summarizes the general therapeutic guidelines.22 In fact, we believe that such an algorithm is applicable to patients with ectopic epidural and paraspinal EMH with or without predisposing hematological anomalies (Fig. 4).

In summary, until prospective trials are performed to evaluate the efficacy and outcomes of available treatment options, first-line therapy for EMH at spinal or paraspinal sites must continue to rely on multiple transfusions, radiotherapy, and hydroxyurea (either alone or in combination). Surgery should be reserved for decompression of significant or progressive neurological deficits that do not respond to appropriate initial therapies, or for tissue sampling when the diagnosis remains uncertain.

Conclusions

This is the first reported instance of ectopic EMH occurring as a paraspinal mass with extension to the epidural space in a patient without any predisposing hematological
disorder. Although EMH proliferation in this manner is a relatively uncommon finding in spine surgery practice, recognition of the true nature of this mass lesion is important because radiologists may misinterpret it as a primary bony neoplasm such as osteoblastoma, fibrous dysplasia, aneurysmal bone cyst, or giant cell tumor. The most appropriate and effective first-line therapies for EMH spinal masses are multiple transfusions, chemotherapy, and radiotherapy. Operative intervention risks significant surgical blood loss that is unwarranted unless medical treatment has failed, acute neurological deterioration requires urgent decompression, or tissue diagnosis is necessary after multiple negative biopsies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Joseph, Mendel. Acquisition of data: Higgins, Joseph, Mendel. Analysis and interpretation of data: Higgins, Mendel. Drafting the article: Mattei, Higgins. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Mattei. Study supervision: Mendel.

References


Fig. 4. Recommended treatment algorithm for paraspinal EMH. With kind permission from Springer Science+Business Media: Eur Spine J. Paraspinal extramedullary hematopoiesis in patients with thalassemia intermedia, 19, 2010, pp 871–878, Haidar et al., Figure 4.

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