Nonhepatosplenic Extramedullary Hematopoiesis: Associated Diseases, Pathology, Clinical Course, and Treatment

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• **Objective:** To define associated clinical conditions, pathology, natural history, and treatment outcome of nonhepatosplenic extramedullary hematopoiesis (NHS-EMH).

• **Patients and Methods:** We retrospectively reviewed the medical charts of all patients identified as having NHS-EMH from 1975 to 2002. Diagnosis was made by tissue biopsy, fine-needle aspiration biopsy, or radionuclide bone marrow scanning.

• **Results:** We identified 27 patients with antemortem diagnosis of NHS-EMH. The most common associated condition of NHS-EMH, and disease site were myelofibrosis with myeloid metaplasia (MMM) (in 18 patients [67%]) and the vertebral column (in 7 patients [26%]; all involving the thoracic region), respectively. At the time of diagnosis of NHS-EMH, concurrent splenic EMH (in 22 patients [82%]; 15 [56%] had undergone splenectomy) and red blood cell transfusion dependency (in 12 patients [44%]) were prevalent. Of the 27 patients, 9 (33%) required no specific therapy. Specific therapy was radiation (in 7 patients with a 71% response rate) and surgical excision (in 6 patients with a 67% response). Treatment-associated complications were limited to surgery. Radiation therapy was not used in the non-MMM group, but low-dose radiation therapy was used in the MMM group for paraspinal or intraspinal EMH (median dose, 1 Gy; range, 1.00-1.50 Gy), pleural or pulmonary disease (median dose, 1.25 Gy; range, 1.00-1.50 Gy), and abdominal or pelvic disease (median dose, 2.02 Gy; range, 1.50-4.50 Gy). Median survival after the diagnosis of NHS-EMH was 13 months in the MMM group and 21 months in the non-MMM group.

• **Conclusions:** This retrospective study suggests that NHS-EMH is rare, is often associated with MMM, and preferentially affects the thoracic spinal region. Asymptomatic disease may require no specific treatment, whereas symptomatic disease is best managed with low-dose radiation therapy.


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velopment and growth of hematopoietic tissue outside of the bone marrow is termed _extramedullary hematoPoiesis_ (EMH). Although the particular process is essential in fetal life, its occurrence after birth is usually considered abnormal. As is the case with physiologic EMH in the fetus, the liver and spleen are the usual sites of pathologic EMH. However, nonhepatosplenic EMH (NHS-EMH) has been reported in a myriad of other tissues and organs, including the mediastinum,1 central nervous system,2 peripheral nerves,3 middle ear,4 pancreas,5,6 urethra,7 pharynx,8 pleura and lungs,9,10 pericardium,11 heart,12 gastrointestinal tract,13 peritoneum,14 thyroid gland,15 skin,16 kidney,17,18 adrenal gland,1 prostate gland,19 breast,20 epididymis,5 and endometrium.21 Although NHS-EMH is often associated with myelofibrosis with myeloid metaplasia (MMM)22 or thalassemia,2 it can also accompany other disorders, including hereditary spherocytosis,23-25 sickle cell anemia,26,27 congenital dyserythropoietic anemia,28 immune thrombocytopenic purpura,29 chronic myeloid leukemia,30 polycythemia vera,31,32 myelodysplastic syndrome,33 Paget disease,34 osteopetrosis,35 and Gaucher disease,36 and treatment with myeloid growth factors.37-39 Occasionally, an associated disease is not identified.40,41

Clinically, NHS-EMH may present as an incidental finding or with a symptomatic disease or condition, including pleural effusion,42 ascites,43 neurologic deficit,44 cardiac tamponade,11,45 chronic renal failure,46 acute respiratory failure,48 orbital proptosis,49 and subglottic stenosis.8 Antemortem diagnosis can be made by tissue biopsy, fine-needle aspiration (FNA) biopsy, or radionuclide scanning. Although some of these methods provide a definitive diagnosis, a presumptive diagnosis can be made under the auspices of hematologic disease and characteristic findings on computed tomography or magnetic resonance imaging (MRI).50 Specific treatment may not be required unless

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NHS-EMH is accompanied by symptoms. Previous reports of successful treatment have included red blood cell transfusions,\textsuperscript{51} surgical excision,\textsuperscript{52} decompressive laminectomy,\textsuperscript{53} and chemotherapy including hydroxyurea.\textsuperscript{54,55} However, the extreme sensitivity of hematopoietic tissue to radiation has made low-dose radiotherapy the treatment of choice.\textsuperscript{56,57}

The English literature contains hundreds of reports of NHS-EMH; however, most describe cases discovered post-mortem and provide little information that can be extrapolated to antemortem cases. Additionally, the rarity of NHS-EMH has prevented the description of a large series of patients evaluated and treated at a single institution. We describe the experience at our institution with patients in whom NHS-EMH was diagnosed antemortem by biopsy, FNA biopsy, or radionuclide scan during a 27-year period. To our knowledge this is the largest report of its kind; it includes descriptions of the clinical course, pathology, associated diseases, and treatment as well as a discussion of the possible pathophysiology leading to the development of EMH.

PATIENTS AND METHODS
After approval of this study by the Mayo Foundation Institutional Review Board, we comprehensively searched the institutional database of medical diagnoses and procedures to identify patients diagnosed with any form of EMH from 1975 to 2002. A retrospective chart review was conducted on all patients identified, focusing on those with NHS-EMH diagnosed antemortem by biopsy, FNA biopsy, or radionuclide bone marrow scanning. Patients diagnosed with NHS-EMH by computed tomography or MRI without biopsy or radionuclide scan were excluded. Also excluded were biopsy-proven cases of NHS-EMH found incidentally at splenectomy or other unrelated operation. Available archived biopsy specimens from patients included in the study were reviewed and characterized by an experienced hematopathologist (C.-Y.L.).

RESULTS
Associated Diseases
We identified 510 patients as having been diagnosed with EMH. Twenty-seven patients (5.3%) were diagnosed with NHS-EMH and met inclusion criteria: 18 (67%) had MMM (Table 1) and 9 (33%) had no evidence of MMM (non-MMM) (Table 2). The MMM group consisted of 12 patients (67%) diagnosed with agnogenic myeloid metaplasia (AMM) and 6 (33%) diagnosed with post-polycythemic myeloid metaplasia (PPMM) having progressed from polycythemia vera. The non-MMM group consisted of 3 patients with congenital anemia, 2 with chronic lymphocytic leukemia (CLL), 1 with chronic myeloid leukemia, 1 with pachydermoperiostosis, 1 with a cerebrovascular malformation, and 1 in whom no underlying disease could be identified.

In all patients, the median time from diagnosis of the underlying disease to diagnosis of NHS-EMH was 51 months (range, 0-413 months). Patients in the MMM group were diagnosed with NHS-EMH a median of 46 months (range, 0-413 months) after diagnosis of their underlying disease compared with a median of 78 months (range, 0-407 months) for patients in the non-MMM group.

Location of EMH
The most common site involved by NHS-EMH in all study patients was in or surrounding the vertebral column. In 7 (26%) of 27 patients, EMH involved the vertebral column (Figure 1 and Figure 2, right). All 7 cases of intraspinal or paraspinal EMH involved the thoracic region. Four cases (15%) of EMH were discovered in the inguinal, para-aortic, cervical, or paratracheal lymph nodes, and 4 (15%) involved the retroperitoneum (Figure 3). Three cases (11%) involved the lungs, pleura, or both (Figure 2, left); 2 (7%) involved the genitourinary system (Figure 4). There were 2 cases (7%) of cutaneous EMH and 1 case each in the right thalamus, right atrium of the heart, oral mucosa, and rectus femoris muscle.

Clinical Presentation
Most patients diagnosed with NHS-EMH presented with symptoms related to the location of their EMH. Seventeen patients (63%) presented with site-specific symptoms; 4 (15%) had generalized symptoms such as fatigue, weakness, and night sweats or symptoms related only to their underlying disease; and 6 (22%) were asymptomatic at the time NHS-EMH was discovered. Nonhepatosplenic EMH was more likely to be discovered incidentally in patients in the non-MMM group than in those in the MMM group. Of 9 patients in the non-MMM group, 4 (44%) were asymptomatic when their NHS-EMH was discovered compared with 2 (11%) of 18 patients in the MMM group.

Paraspinal and Intraspinal EMH—Patient 2 presented with bilateral lower extremity edema and radicular pain from an intraspinal mass of EMH extending from T3 to T12 as well as left parapelvic and paraurethral EMH. Patient 11 had an acute progressing myelopathy, including lower extremity weakness, paresthesia progressing to the level of the umbilicus, and urinary incontinence as a result of intraspinal EMH extending from T3 to T9. Patient 14 presented with left lower extremity pain and edema, ascites as a result of prevertebral masses of EMH extending from C6 to L2 and L5 to S5, and masses in the superior inguinal region involving the renal pelves bilaterally. Patient 23 had intrascapular pain that became worse with movement due to paraspinal EMH at the level of T10. Patient 25 had been...
Table 1. Patients With Nonhepatosplenic EMH and Myelofibrosis With Myeloid Metaplasia

<table>
<thead>
<tr>
<th>Patient No./age (y)/sex</th>
<th>Disease</th>
<th>Site of EMH</th>
<th>Presentation</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/66/F</td>
<td>AMM</td>
<td>Lungs</td>
<td>Dyspnea, orthopnea, edema, weight gain</td>
<td>Radiation</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>2/53/M</td>
<td>AMM</td>
<td>Paraureteral; intraspinal T3-T12</td>
<td>Radicular pain, LE edema</td>
<td>Radiation</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>3/69/M</td>
<td>AMM</td>
<td>Posterior cervical lymph nodes</td>
<td>Enlarged lymph node</td>
<td>Removal at biopsy, no treatment</td>
<td>No recurrence</td>
</tr>
<tr>
<td>4/52/F</td>
<td>AMM</td>
<td>Multiple cutaneous lesions</td>
<td>Asymptomatic</td>
<td>Topical corticosteroids</td>
<td>No progression</td>
</tr>
<tr>
<td>5/71/M</td>
<td>AMM</td>
<td>Para-aortic lymph node</td>
<td>Fatigue, early satiety</td>
<td>None</td>
<td>No progression</td>
</tr>
<tr>
<td>6/57/M</td>
<td>AMM</td>
<td>Rectus femoris muscle</td>
<td>Leg pain, weight loss, night sweats</td>
<td>Danazol</td>
<td>No follow-up</td>
</tr>
<tr>
<td>7/53/F</td>
<td>AMM</td>
<td>Cervical lymph nodes</td>
<td>Enlarged lymph node</td>
<td>Removal at biopsy, no treatment</td>
<td>No recurrence</td>
</tr>
<tr>
<td>8/69/F</td>
<td>AMM</td>
<td>Peritoneum and paratracheal lymph nodes</td>
<td>Severe ascites, renal insufficiency</td>
<td>Radiation</td>
<td>Recurrent ascites; refractory to treatment</td>
</tr>
<tr>
<td>9/57/M</td>
<td>AMM</td>
<td>Retroperitoneum</td>
<td>Chills, fatigue, abdominal pain with movement</td>
<td>Danazol</td>
<td>No progression</td>
</tr>
<tr>
<td>10/46/M</td>
<td>AMM</td>
<td>Bladder, renal pelvis, and ureter</td>
<td>Pelvic pain radiating to penis, hydronephrosis, right ureteral obstruction</td>
<td>Ureteral stent; radiation</td>
<td>Improvement; recurrence with bilateral ureteral obstruction</td>
</tr>
<tr>
<td>11/19/M</td>
<td>AMM</td>
<td>Extradural spinal cord T3-T9</td>
<td>Hypermobility, LE weakness, urinary incontinence, paresthesia</td>
<td>Laminectomy; emergency radiation</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>12/61/F</td>
<td>AMM</td>
<td>Lungs and retroperitoneum</td>
<td>Dyspnea, pleural effusion, Pruritus, LE edema</td>
<td>Radiation Removal at biopsy, no treatment</td>
<td>Complete resolution No recurrence</td>
</tr>
<tr>
<td>13/69/M</td>
<td>PPMM</td>
<td>Inguinal lymph nodes</td>
<td>LE pain and weakness, ascites</td>
<td>Radiation</td>
<td>Refractory to treatment; progression</td>
</tr>
<tr>
<td>14/58/M</td>
<td>PPMM</td>
<td>Prevertebral L5-sacrum and C6-L2; superior inguinal region; renal pelvis</td>
<td>Severe abdominal pain, nausea and vomiting</td>
<td>Surgery</td>
<td>Complete resolution</td>
</tr>
<tr>
<td>15/79/F</td>
<td>PPMM</td>
<td>Small bowel mesentery and adhesions</td>
<td>Incidentally discovered</td>
<td>None</td>
<td>No progression</td>
</tr>
<tr>
<td>16/72/F</td>
<td>PPMM</td>
<td>Rectosigmoid</td>
<td>Tricuspid murmur, congestive heart failure</td>
<td>Surgery</td>
<td>Died of complications</td>
</tr>
<tr>
<td>17/49/F</td>
<td>PPMM</td>
<td>Right atrium</td>
<td>Pruritic rash</td>
<td>Topical corticosteroids</td>
<td>No progression</td>
</tr>
<tr>
<td>18/71/M</td>
<td>PPMM</td>
<td>Multiple cutaneous lesions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AMM = agnogenic myeloid metaplasia; EMH = extramedullary hematopoiesis; LE = lower extremity; PPMM = post–polycythemic myeloid metaplasia.

previously diagnosed with pachydermoperiostosis and had clubbing of the digits, pachydermia, periostosis, and generalized pruritus at the time EMH was discovered in the pelvic retroperitoneum and the paraspinal region at the levels of T2-T3 and T9-T10.

**Pulmonary and/or Pleural EMH.**—Patient 1 had dyspnea, orthopnea, bilateral lower extremity edema, and a 6.5-kg weight gain due to diffuse parenchymal involvement of both lungs. Patient 12 had dyspnea and a pleural effusion as a result of bilateral pulmonary and pleural EMH.

**Abdominal and/or Pelvic EMH.**—Patient 8 had recurrent severe ascites and renal insufficiency and had EMH involving the peritoneum and right paratracheal lymph nodes. Patient 9 presented with chills, fatigue, and nonspecific abdominal pain increasing with movement, especially turning or twisting, as a result of a 3-cm mass of EMH in the retroperitoneum near the left kidney. Patient 10 had extensive involvement of the bladder, right renal pelvis, and right ureter causing pelvic pain radiating to the penis, hydronephrosis, and right ureteral obstruction. Patient 15 presented with severe abdominal pain, nausea, and vomiting due to EMH in the small bowel mesentery and intra-abdominal adhesions. Patient 20 experienced fatigue and weakness that could not be directly attributed to EMH found in the retrorectal space and was likely a result of CLL. Patient 27 presented with a peripheral neuropathy as a result of a right suprarenal mass (7 × 9 cm) and a mass (6 × 4 cm) in the retroperitoneum posterior to the inferior vena cava. In addition, patient 27 had multiple other abdominal masses that were suspected, but not confirmed, to be EMH.

**Other Sites of EMH.**—Patient 3 presented with painfully enlarged posterior cervical lymph nodes that were later confirmed to be due to EMH. Patient 5 experienced fatigue and early satiety leading to the incidental discovery of EMH in the para-aortic lymph nodes. Patient 6 experienced radiating left leg pain as a result of EMH located in the left rectus femoris muscle accompanied by an 11-kg weight loss and night sweats. Patients 7 and 13 had EMH involving the cervical and inguinal lymph nodes, respec-
Table 2. Patients With Nonhepatosplenic Extramedullary Hematopoiesis (EMH) Without Myelofibrosis
With Myeloid Metaplasia

<table>
<thead>
<tr>
<th>Patient No./age (y)/sex</th>
<th>Diagnosis</th>
<th>Site of EMH</th>
<th>Presentation</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>19/58/M</td>
<td>Chronic lymphocytic leukemia</td>
<td>Left lung (lower lobe), pleura</td>
<td>Incidental discovery</td>
<td>None</td>
<td>No progression</td>
</tr>
<tr>
<td>20/67/F</td>
<td>Chronic lymphocytic leukemia</td>
<td>Retrorectal space</td>
<td>Fatigue/weakness</td>
<td>None</td>
<td>No progression</td>
</tr>
<tr>
<td>21/69/M</td>
<td>Chronic myeloid leukemia</td>
<td>Oral mucosa, right thigh</td>
<td>Incidental discovery</td>
<td>Surgery</td>
<td>Recurrence in left side of neck</td>
</tr>
<tr>
<td>22/69/M</td>
<td>Congenital hemolytic anemia</td>
<td>Presacrum and paraspinal (T8)</td>
<td>Incidental discovery</td>
<td>None</td>
<td>No progression</td>
</tr>
<tr>
<td>23/34/M</td>
<td>Pyruvate kinase deficiency</td>
<td>Paraspinal (T10)</td>
<td>Intrascapular pain</td>
<td>Transfusion</td>
<td>No response, treatment discontinued</td>
</tr>
<tr>
<td>24/39/F</td>
<td>Congenital dyserythropoietic anemia</td>
<td>Paraspinal (T8)</td>
<td>Incidental discovery</td>
<td>None</td>
<td>No progression</td>
</tr>
<tr>
<td>25/46/M</td>
<td>Pachydermoperiostosis</td>
<td>Pelvic retroperitoneum; paraspinal (T2-T3, T9-T10)</td>
<td>Clubbing, pachydermia, periostosis, pruritus</td>
<td>None</td>
<td>No follow-up</td>
</tr>
<tr>
<td>26/43/M</td>
<td>Vascular malformation</td>
<td>Thalamus</td>
<td>Diplopia, blurred vision</td>
<td>Surgery</td>
<td>No recurrence; serious surgical complications</td>
</tr>
<tr>
<td>27/70/M</td>
<td>None</td>
<td>Suprarenal and retroperitoneum</td>
<td>Peripheral neuropathy</td>
<td>None</td>
<td>No progression</td>
</tr>
</tbody>
</table>

Patient 7 presented with painfully enlarged cervical lymph nodes, whereas patient 13 presented with generalized pruritus and intermittent left lower extremity edema. Patient 17 presented with a tricuspid murmur and congestive heart failure that was discovered to be due to a right atrial myxoma containing foci of EMH. Patient 26 presented with diplopia and blurred vision as a result of a vascular malformation containing foci of EMH in the right thalamus. Patient 18 had a pruritic rash on his back and dorsum of the forearms that was discovered to be cutaneous EMH.

Relationship to Splenic EMH and Red Blood Cell Transfusion.—Of the 27 patients, 22 (82%) had splenic EMH before NHS-EMH was diagnosed. Fifteen (56%) of the patients had severe splenic EMH requiring splenectomy. Of 18 patients in the MMM group, 17 (94%) had splenic EMH before NHS-EMH was diagnosed, with 13...
Figure 2. Left, Whole-body scan with technetium Tc 99m shows diffuse radionuclide uptake in the lungs bilaterally in a patient with pulmonary extramedullary hematopoiesis (EMH). Right, Computed tomogram reveals bilateral heterogeneous paraspinal soft tissue masses of EMH.

(72%) having undergone splenectomy. Of 9 patients in the non-MMM group, 4 (44%) had splenic EMH with only 1 (11%) requiring splenectomy.

Of the 27 study patients, 12 (44%) were transfusion dependent at the time NHS-EMH was diagnosed. Of 18 patients in the MMM group, 10 (56%) were transfusion dependent compared with 2 (22%) of 9 patients in the non-MMM group.

Laboratory Findings

Patients in all groups presenting with NHS-EMH had a median hemoglobin level of 9.5 g/dL (range, 7.1-14.8 g/dL), a median white blood cell count of 14.9 × 10^9/L (range, 2.0-112.9 × 10^9/L), and a median platelet count of 155 × 10^9/L (range, 28-930 × 10^9/L). The median hemoglobin value in patients in the MMM group was 9.4 g/dL (range, 7.1-14.8 g/dL) compared with 9.5 g/dL (range, 8.0-14.4 g/dL) in the non-MMM group. Patients in the MMM group had a median white blood cell count of 25.4 × 10^9/L (range, 2.0-104.7 × 10^9/L) compared with 10.0 × 10^9/L (range, 3.4-112.9 × 10^9/L) in the non-MMM group. The median platelet count in patients in the MMM group was 125 × 10^9/L (range, 28-823 × 10^9/L) compared with 217 × 10^9/L (range, 34-930 × 10^9/L) in the non-MMM group.

Diagnosis and Pathology

The most common method used to diagnose NHS-EMH was surgical biopsy, performed in 16 (59%) of the 27 patients. Fine-needle aspiration biopsy was used in 7 patients (26%), radionuclide bone marrow scanning in 3 (11%), and paracentesis in 1 (4%).

A review of all available tissue sections from surgical biopsies confirmed EMH. Biopsy specimens from patients with AMM and PPMM were from the extradural spinal T8 level, renal pelvis, rectus femoris muscle, small bowel mesentery, para-aortic lymph node, and right inguinal lymph node. The lesion from the spinal T8 level showed trilineage hematopoiesis similar to normal marrow hematopoiesis (Figure 5). The rest of the lesions showed EMH, primarily consisting of granulopoiesis and occasional megakaryocytes. In the nodal lesions, EMH was seen primarily in the paracortical region of the lymph nodes (Figure 6). A right maxillary lesion from a patient with chronic myelogenous leukemia showed primary granulopoiesis and occasional erythroblasts. Two biopsy specimens (1 from the parietal pleura and 1 from the retrorectal space) from patients with CLL showed trilineage EMH forming irregular aggregates of erythroblasts, immature granulocytes, and scattered megakaryocytes on a background of small lymphocytes (Figure 7). A paraspinal biopsy specimen from a patient with congenital hemolytic anemia showed trilineage EMH with predominantly erythropoiesis (Figure 8).

Treatment and Outcomes

Of 27 patients, 11 (41%) required no treatment and were either observed or lost to follow-up. Nonhepatosplenic EMH requiring treatment was most commonly and most successfully managed with low-dose radiation therapy. Of the 7 patients treated with low-dose radiation, 5 (71%) experienced complete resolution; 2 patients’ symptoms were refractory to treatment. Surgical excision was performed in 5 patients (19%), with 4 (80%) having complete resolution of symptoms. Two patients experienced severe postoperative complications, including permanent neurologic deficit and death. Topical corticosteroids were used to treat cutaneous EMH in 2 patients, whereas hormonal therapy (danazol) was used in 2 patients. One patient’s
EMH mass was removed at biopsy, and 1 patient received multiple blood transfusions.

Patients in the MMM group were more likely to require treatment for NHS-EMH than those in the non-MMM group. Of 18 patients in the MMM group, 13 (72%) required treatment (Table 1), 7 of whom received low-dose radiation treatment for NHS-EMH. The median dose of radiation was 4.25 Gy delivered in a median of 10 fractions.

Most patients in the non-MMM group required no treatment (Table 2) and were observed. Six (67%) of 9 patients observed had no subsequent enlargement of their NHS-EMH or progression of symptoms. None of the patients in the non-MMM group received radiation therapy. Surgery was the most common form of treatment for patients with NHS-EMH in the non-MMM group, with 2 of 9 patients having had their NHS-EMH excised surgically.

**Paraspinal and Intraspinal EMH.**—Of 7 patients with paraspinal or intraspinal EMH, 4 required low-dose radiation therapy; the median dose of radiation was 1 Gy (range, 1-10 Gy) delivered in a mean of 1 fraction (range, 1-5 fractions). Patient 2 received 1 Gy of radiation in 5 fractions to the vertebral column from T1 to L4, with complete resolution of symptoms 3 days after treatment; MRI 1 month later revealed no evidence of NHS-EMH. Patient 11 required emergency treatment with 10 Gy of radiation delivered in 5 fractions from T3 to T10 and a laminectomy of the eighth vertebra. The patient experienced complete resolution of neurologic deficit and had no recurrence. Patient 14 received 1 Gy in 1 fraction to vertebral levels C5 to L1 and 1 Gy in 1 fraction to levels L2 to S5. This patient’s NHS-EMH was refractory to treatment, and treatment was stopped at his request, leading to progression of symptoms.

Figure 3. Computed tomograms. Left, Large heterogeneous soft tissue mass of extramedullary hematopoiesis (EMH) displacing the bladder and cecum anteriorly. Right, Heterogeneous soft tissue mass (4 × 4 cm) of EMH in the presacral area.

Figure 4. Computed tomograms. Left, Hepatomegaly and heterogeneous soft tissue masses of extramedullary hematopoiesis (EMH) involving the left proximal ureter and renal pelves bilaterally. Right, Scan with contrast shows heterogeneous soft tissue masses of EMH involving the renal pelves bilaterally.
NHS-EMH. Patient 23 received multiple blood transfusions during a 3-month period with no response. The transfusions were discontinued; the mass was stable for 31 months at which time it began to progress, causing spinal cord compression with right upper and lower extremity weakness and left paraspinous percussion tenderness. The patient received treatment for the recurrence at an institution elsewhere.

**Pulmonary and/or Pleural EMH.**—Of 3 patients with pulmonary and/or pleural EMH, 2 required low-dose radiation therapy; their symptoms resolved completely. The median dose of radiation was 1.25 Gy (range, 1.0-1.5 Gy) delivered in a median of 5 fractions (range, 1-10 fractions). Patient 1 received 1 Gy in 1 fraction to both lung fields, experienced complete resolution of difficulties 2 days after radiation, and had no recurrence. Patient 12 received 1.50 Gy in 10 fractions to the left hemithorax, with complete resolution of the pleural effusion. Images before and after irradiation in a patient with diffuse pulmonary EMH who is not part of the original study population are shown in Figure 9.

**Abdominal and/or Pelvic EMH.**—Of the 7 patients who required treatment for abdominal or pelvic EMH, 4 received low-dose radiation therapy at a median dose of 2.02 Gy (range, 1.50-4.50 Gy) delivered in a median of 7 fractions (range, 4-9 fractions). Danazol, either 600 mg or 800 mg per day, was given to 2 patients, and 1 patient underwent surgical removal of masses of EMH. Patient 2 received radiation at a dose of 1.80 Gy in 4 fractions to the left renal pelvis and ureter, with complete resolution of symptoms (as described previously). Patient 8 received 1.50 Gy of radiation in 6 fractions to the whole abdomen every 6 weeks for 18 weeks with no subsequent improvement of symptoms including ascites. Patient 10 underwent 2.04 Gy of radiation in 6 fractions to the right and left abdomen, 3.06 Gy in 9 fractions to the pelvis, and placement of a right ureteral stent. This patient experienced complete resolution of symptoms, and the right ureteral stent was removed; however, 9 months after treatment, he had recurrent bilateral EMH encompassing both ureters and causing urinary obstruction. The recurrence was successfully treated with 4.50 Gy of radiation delivered in 9 fractions to the bilateral upper urinary tracts, with complete resolution of bilateral ureteral obstruction and no future recurrences. Patient 14 received 2 Gy of radiation to the whole abdomen and pelvis for EMH in the renal pelvis and superior inguinal region, resulting in complete resolution of symptoms (as described previously). Patient 9 received 800 mg of danazol per day for 2 weeks; however, because of adverse effects from the medication, he discontinued treatment. Patient 15 underwent surgery to remove small bowel adhesions containing foci of EMH and experienced complete resolution of symptoms with no evidence of recurrence.

**Other Sites of EMH.**—Patients 4 and 18 required treatment for multiple cutaneous lesions of EMH. Both patients were treated with topical corticosteroids (triamcinolone), and their EMH remained stable or regressed. Patient 6 received danazol at 600 mg/d to treat NHS-EMH located in the rectus femoris muscle; however, he was lost to follow-up. Patient 17 underwent open heart surgery to remove a right atrial myxoma with foci of EMH; she had a postoperative myocardial infarction and died the following day. Patient 21 underwent surgical excision of a mass in the right maxillary oral mucosa. The mass was successfully excised; however,
18 months after treatment, the patient presented with a 10-cm rapidly growing mass in the left side of his neck, which was diagnosed as NHS-EMH and surgically excised with no further recurrence. Patient 26 underwent surgery to remove a vascular malformation in the right thalamus containing multiple foci of EMH. He experienced no recurrent EMH at that site but had severe morbidity as a result of surgical complications, including myocardial infarction, pulmonary embolus, and permanent neurologic deficit.

Survival
The median follow-up after diagnosis of NHS-EMH was 12 months (range, 0-149 months). Of the 27 study patients, 14 (52%) were dead at last follow-up; median survival was 16.5 months (range, 0-29 months).

In the MMM group, the median follow-up after diagnosis of NHS-EMH was 12 months (range, 0-149 months). Of 18 patients, 10 were dead at last follow-up, with a median survival of 13 months (range, 0-29 months). Patient 2 died of a pulmonary embolus attributed to blast crisis 26 months after the diagnosis of NHS-EMH. Patient 5 died 1 month after NHS-EMH diagnosis; however, the cause of death was not available. Patient 7 died of chronic renal failure and advanced myelofibrosis 10 months after NHS-EMH diagnosis. Patient 8 died of acute respiratory failure and acute myelogenous leukemia transformation of AMM 17 months after NHS-EMH diagnosis. Patient 9 died 14 months after NHS-EMH diagnosis as a result of acute myelogenous leukemia transformation of AMM. Patient 10 died of bronchopneumonia 24 months after NHS-EMH diagnosis. Patient 11 died of diffuse intravascular coagulation, acute renal failure, and bleeding of the upper gastrointestinal tract 27 months after NHS-EMH diagnosis. Patient 14 died of a stroke 5 months after discontinuation of treatment. Patient 17 died at the time of NHS-EMH diagnosis due to complications of open heart surgery to remove a right atrial myxoma containing foci of EMH. Patient 18 died 28 months after NHS-EMH diagnosis because of end-stage congestive heart failure as a result of hemochromatosis due to an extensive history of blood transfusions.

The median follow-up after diagnosis of NHS-EMH in the non-MMM group was 12 months (range, 0-79 months). Of 9 patients in the non-MMM group, 4 (44%) were dead at last follow-up, with a median survival of 21 months (range, 8-34 months). Patient 19 died 21 months after diagnosis of NHS-EMH; however, the cause of death was not available. Patient 20 died of an opportunistic infection related to CLL 8 months after diagnosis of NHS-EMH. Patient 21 died 20 months after diagnosis of NHS-EMH; however, the cause of death was not available. Patient 26 died 34 months after NHS-EMH diagnosis, but the cause of death was not available.

DISCUSSION
The occurrence of NHS-EMH is rare, and to our knowledge, this study is the largest description of patients with NHS-EMH diagnosed antemortem. Most cases of NHS-EMH occurred in the setting of hematologic disease, with MMM being the most frequent diagnosis. Only 2 patients had no evidence of hematologic disease. Most patients with NHS-EMH had chronic anemia, with a median hemoglobin value of 9.5 g/dL at the time of NHS-EMH diagnosis. This supports the theory that EMH might be a compensatory process to combat a chronic anemic state.58

The most frequent site of NHS-EMH in our study was the spinal column, followed by the lymph nodes and
retroperitoneum. In a study of 17 complete autopsies, Pitcock et al found that the lymph nodes were the most common site of NHS-EMH, followed by the kidneys. The discrepancy between their study and ours may be due to the ability to identify all tissues involved with EMH at autopsy vs determination of sites of EMH antemortem by imaging and biopsy only.

Extramedullary hematopoiesis involving the spinal column has been reported previously, and there appears to be a predisposition for EMH involvement at the thoracic levels. In our study, all patients with EMH involvement of the spinal column had at least 1 thoracic vertebral level involved. The reason for the increased frequency of EMH around the spinal column, and more specifically at the thoracic levels, is unknown.

Patients presenting with NHS-EMH usually have symptoms specific to the site of EMH involvement. For example, patients with intraspinal or paraspinal EMH involvement often present with a neurologic deficit related to the level of involvement as well as local tenderness.

Ectopic hematopoietic tissue has been shown to be extremely sensitive to low doses of radiation. In the current study, low-dose radiation effectively resolved symptoms in 71% of patients treated. The median radiation therapy of 4.25 Gy delivered in a median of 10 fractions was slightly higher than the 2.77 Gy delivered in a median of 7.5 doses reported in a study by Elliott et al for treatment of splenic EMH and the median dose of 1.50 Gy delivered in a median of 6 doses reported by Tefferi et al for treatment of hepatic EMH. Higher doses of radiation (>10 Gy) have been reported to be successful in the treatment of ascites and pleural effusion caused by EMH. Even at the relatively low doses of radiation used by Elliott et al, 26% of patients treated experienced severe myelosuppression. In light of these results, we advocate the use of radiation therapy for NHS-EMH. To avoid radiation-related adverse effects, the lowest effective dose should be used except in emergency situations, when higher doses of radiation might be warranted. Patient 11 required emergency radiation treatment, and thus a higher dose, in conjunction with laminectomy for rapidly progressing intraspinal EMH causing urinary incontinence.

Most of our patients (82%) had splenic EMH before development of NHS-EMH. Splenectomy was required in 56% of all patients and increased to 72.2% of patients in the MMM group. Of interest, splenectomy might facilitate the development of NHS-EMH. One theory to explain splenic EMH is “splenic filtration,” in which displaced hematopoietic stem cells in the vasculature are filtered by the spleen, accumulate, and establish hematopoiesis. Splenectomy may result in cessation of filtration and allow the hematopoietic stem cells to establish hematopoiesis in other tissues. However, the splenic filtration theory fails to explain the development of EMH in organs and tissues that do not filter the blood, and it does not explain the development of EMH in cases in which hematopoietic stem cells are not displaced from the bone marrow.

Extramedullary hematopoiesis has also been proposed to be a compensatory phenomenon in response to replacement of the bone marrow by fibrosis. The compensatory mechanism is inadequate to explain all cases of EMH because EMH can arise in the absence of fibrosis and anemia. Although the median hemoglobin value in our study was consistent with an anemic state, many patients were not anemic at the time of diagnosis and had no history of anemia. Clearly, another mechanism contributed to the development of EMH in these patients.

Another theory, the myelostimulatory theory, postulates that EMH is the result of aberrant secretion of an unknown myelostimulatory factor that results in up-regulation of hematopoiesis in the bone marrow and embryonic sites of hematopoiesis. The results of our study and others argue against this hypothesis because EMH was discovered in organs not believed to be involved in adult or fetal hematopoiesis.

The 3 proposed mechanisms to date fail to completely explain all cases of EMH. Therefore, we propose the “redirected differentiation theory” to explain how EMH may arise in multiple different organs and tissues. We propose that an as yet unidentified circulating factor(s) induces adult stem cell populations to differentiate into cells of the hematopoietic lineage. Numerous tissues in the body contain stem cell populations capable of repairing damaged tissue and retain...
the capability to proliferate and differentiate into many different cell types. For example, neural stem cells can be induced to differentiate into hematopoietic cells. Hematopoietic stem cells can be induced to differentiate into neurons, cardiomyocytes, and hepatocyte-like cells.

The secretion of cytokines, either aberrantly or in response to chronic anemia, could induce adult stem cell populations to differentiate into cells of the hematopoietic lineage and establish hematopoiesis in organs in which it otherwise would not occur. Candidate molecules causing EMH have been identified in mouse models. For example, administration of interleukin 12 to mice causes splenomegaly and increased production of erythroid, myeloid, and megakaryocytic cells. Interleukin 13 induces EMH when administered to mice. These cytokines have not been shown to redirect stem cell differentiation, but these studies support the role of circulating factors in the induction of EMH.

Self-renewing stem cells directed to produce hematopoietic cells might continue to do so even after the withdrawal of the stimulating factor(s). The dividing pool of stem cells causing EMH has been shown to be highly sensitive to radiation, and the low number of recurrences after radiotherapy in our study might be due to cessation of factor secretion before treatment, preventing restimulation of stem cell populations.

CONCLUSIONS
Nonhematopoietic EMH can arise in a variety of organs, producing various symptoms that are sometimes life-threatening. Although rare, NHS-EMH should be suspected in patients with predisposing conditions such as MMM and PPMM. The etiology of EMH remains to be elucidated. Current theories for the development of EMH fail to account for all cases of EMH, especially those arising outside of the reticuloendothelial system. Therefore, we have proposed that a secreted factor, either aberrantly produced or released in response to anemia, might cause the redirected differentiation of adult stem cell populations to that of hematopoietic cells resulting in the development of EMH in many different tissues. However, we concede the possibility that no 1 mechanism can sufficiently account for all cases of EMH; rather, the development of EMH may “proceed down many different paths.”

REFERENCES