Thoracic Cord Compression Caused by Epidural Extramedullary Hematopoiesis During Erythroid-Stimulating Agent Therapy in Two Patients With Myelodysplastic Syndromes

Introduction

Proliferation of extramedullary hematopoiesis (EMH) is a rare event that complicates chronic anemic states. The largest series published to date included 24 cases, all of which were reported in association with hematologic disorders, in which compensatory or inappropriate increase of blood formation (eg, thalassemia, myeloproliferative disorders, sickle cell anemia, and so on) can reactivate unusual hematopoietic sites. Abnormal EMH usually occurs in sites that are involved in hematopoiesis during fetal development, such as the spleen, liver, and kidneys; however, even ectopic locations, such as the paraspinal tissue, may be frequently involved, which results in neurologic symptoms, pain, and spinal cord compression. The epidural block has been often described as midthoracic, probably because of the narrow course of the thoracic epidural space at this level. Few patients (Table 1) have been reported to have a spinal block caused by EMH in association with myelodysplastic syndromes (MDSs), but to our knowledge, none of these patients was receiving erythropoietin-stimulating agents (ESAs) when symptoms occurred. ESAs are universally recognized as first-line treatment for patients with low-risk MDSs who are transfusion dependent. Erythropoietin alpha, erythropoietin beta, and more recently, darbepoetin, have been found to increase hemoglobin levels and ameliorate transfusion dependence in 19% to 68% of patients with MDSs. Despite concern of a detrimental effect on tumor progression in patients with solid cancers, in MDSs, several meta-analyses that have included thousands of patients showed only modest increase in cardiovascular complications that were directly related to the drug have been documented. In both patients, ESA withdrawal resulted in rapid relief of symptoms and mass resolution with no need of laminectomy or radiotherapy.

Table 1. Reports of Neurologic Complications As a Result of EMH Cord Compression

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Treatment for MDS</th>
<th>EMH Localization</th>
<th>Treatment for EMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>002&lt;sup&gt;1&lt;/sup&gt;</td>
<td>RARS</td>
<td>72</td>
<td>Male</td>
<td>Transfusion support</td>
<td>T4-T7</td>
<td>Surgery</td>
</tr>
<tr>
<td>001&lt;sup&gt;2&lt;/sup&gt;</td>
<td>MDS</td>
<td>61</td>
<td>Male</td>
<td>None</td>
<td>T3-T4, T7</td>
<td>Surgery</td>
</tr>
<tr>
<td>004&lt;sup&gt;3&lt;/sup&gt;</td>
<td>MDS</td>
<td>78</td>
<td>Male</td>
<td>Transfusion support</td>
<td>Left frontal lobe</td>
<td>Surgery</td>
</tr>
<tr>
<td>003&lt;sup&gt;4&lt;/sup&gt;</td>
<td>RARS</td>
<td>79</td>
<td>Male</td>
<td>None</td>
<td>T5-T8</td>
<td>Corticosteroids, surgery</td>
</tr>
</tbody>
</table>

Abbreviations: EMH, extramedullary hematopoiesis; MDS, myelodysplastic syndrome; RARS, refractory anemia with ringed sideroblasts.

Case Reports

In March 2002, a 69-year-old woman with a diagnosis of anemia was referred to our clinic. Laboratory studies showed leucopenia (WBC count, $3.3 \times 10^3/\text{L}$; absolute neutrophil count, $1.8 \times 10^7/\text{L}$) and normochromic/normocytic anemia (hemoglobin [Hb], 8.0 mg/dL). Bone marrow aspirate showed less than 5% blasts and karyotype was normal. The final diagnosis was refractory anemia (low risk per the International Prognostic Scoring System). Because the decreasing level of Hb required a program of regular packed red cell unit (PRCU) transfusions, in October 2002, we initiated erythropoietin alpha (10,000 UI three times per week). The therapy was administered for 30 months with good tolerance and no relevant adverse effect. In March 2005, because of an increase in the transfusion requirement from two to five PRCU transfusions per month, we incrementally increased the erythropoietin alpha dosage to 40,000 UI twice per week. A significant reduction in transfusion support was gained. In December 2007, the patient reported persistent thoracic pains spreading to the epigastric region. A total-body computed tomography (CT) scan showed an epidural mass at the D8-D9 vertebral level, with no bone erosion. Erythropoietin alpha was stopped and the symptoms subsided within a few days. A CT-guided biopsy was performed and histologic examination revealed EMH. The patient is alive, receives erythropoietin alpha at a dose of 40,000 UI once per week, and is transfusion free.

In August 2008, a 75-year-old man with a diagnosis of chronic anemia was referred to our clinic. Laboratory studies showed a WBC count of $3.4 \times 10^3/\text{L}$, absolute neutrophil count of $1.95 \times 10^7/\text{L}$, normochromic/normocytic anemia (Hb, 9.5 mg/dL), and mild thrombocytopenia (platelets, $95 \times 10^9/\text{L}$). Bone marrow aspirate showed less than 5% blasts and cytogenetic analysis demonstrated a chromosome 11 monosomy. The final diagnosis was refractory cytopenia with multilineage dysplasia (International Prognostic Scoring System risk: Intermediate-1). In November 2008, high doses of erythropoietin alpha therapy were initiated (40,000 UI twice per week) because the patient began requiring transfusion support. Erythropoietin alpha treatment was continued for 26 months with good tolerance and no relevant adverse effect. After 8 months of such therapy, the transfusion need decreased from a median number of two to 0.7 PRCU transfusions per month. In January 2011, the patient presented with complaints of persistent, intense pains that spread from the retrosternal to
Inherited hematopoietic disorders such as thalassemia or sickle cell anemia and myeloproliferative disorders such as myelofibrosis or polycythemia vera can render patients prone to develop foci of EMH in the spleen, liver, kidneys, and other sites such as the paraspinal tissue. Reports of such occurrences in MDSs are rare; none of the four previously reported patients (Table 1) who suffered neurologic complications as a result of EMH cord compression were receiving ESA therapy. Conversely, the two patients described here were not only receiving a prolonged ESA therapy, but EMH mass and cord compression–related symptoms rapidly regressed when ESA administration was stopped, which suggests a direct correlation with the stimulation of extrahematopoietic tissue. Our experience raises some relevant questions. First, might development of EMH be a pitfall of ESA treatment in patients with MDSs? Are there any clinical or biologic features that can help predict the development of such a complication? The largest meta-analysis dealing with the use of ESAs in MDSs mentions no warnings about the risk of EMH occurrence. The size and severity of the underlying hematologic disease may represent an additional predisposing cause: 19 of the 24 patients reported by Heffez et al were anemic (Hb < 10 g/dL), and 18 had an enlarged spleen. In line with this observation, both of our patients were anemic and had splenomegaly. In our patients, the masses were studied by MRI. Is this approach the most suitable technique, especially when a bioptic approach is contraindicated? Before the advent of MRI, CT scans were used to diagnose cord compression, and technetium-labeled sulfur colloid–based nuclear scans were specifically indicated to detect ectopic foci of hematopoietic tissue. Currently, MRI seems to offer more robust technical solutions because of the multiplanar capability and excellent soft tissue resolution. Finally, which is the most timely and appropriate approach to treat patients with suspected EMH? High-dose corticosteroids may be used on an emergency basis; however, decompressive laminectomy with or without postoperative irradiation is the suggested approach, even if there is evidence that radiotherapy alone may be sufficient. Not surprisingly, in some patients with EMH, symptoms resolved after the implementation of a hypertransfusion regimen in thalassemia or cytostatic therapy in sickle cell anemia. In our experience, prompt discontinuation of ESAs resulted in a complete resolution of symptoms after regression of the masses.

Therefore, we conclude that in patients with MDSs, the sudden appearance of neurologic symptoms and/or spinal pains or blocks should trigger a proper procedure for the identification of epidural EMH masses. A timely MRI scan must be performed, and laminectomy and/or radiotherapy are the elective therapeutic options for these patients. However, withdrawal of ESAs is strongly recommended, given that this action can potentially promote a spontaneous regression of hematopoietic tissue proliferation.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
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REFERENCES

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