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CASE HISTORY

The patient is a 71-year-old female recently diagnosed with malignant lymphoma of the stomach [extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT)]. The bone marrow is performed for staging.

Laboratory data include: WBC = 10.2 x 10⁹/L; HGB = 9.7 g/dL; HCT = 30.2%; MCV = 69.8 fl; RDW = 14.5; PLT = 229 x 10⁹/L

INTRODUCTION

In patients newly diagnosed with malignant lymphoma, examination of the bone marrow, along with the performance of routine laboratory testing, is among some of the tests needed to determine extent of disease prior to initiation of therapy. A bone marrow examination can also be performed in patients in whom a clinical suspicion of lymphoma is present, but cannot be confirmed due to nondiagnostic lymphoid infiltrates in other sites, inaccessibility for biopsy in extramedullary locations, or to assess response to therapy if the marrow was initially involved. The marrow can often be the site of primary diagnosis in a patient with unexplained cytopenias. When a bone marrow examination is performed for staging of the patient, a complete blood count, along with a white blood cell differential, is also typically ordered. An absolute lymphocytosis may be present in the peripheral blood, such as with chronic lymphocytic leukemia/small lymphocytic lymphoma. Morphologic examination of the peripheral blood smear can also be useful in identifying atypical lymphoid cells in patients without an absolute lymphocytosis; this may be indicative of peripheral blood involvement by lymphoma. Malignant lymphoma cells in the peripheral blood can be seen in about 10% of all patients with non-Hodgkin lymphoma (NHL) at diagnosis, and careful review of the nuclear characteristics, cell size, and cytoplasm of lymphoid cells in the peripheral blood smear is required in these patients. Splenic marginal zone lymphoma cells can often be present in the blood at the time of diagnosis; therefore, it is important to be familiar with the type of lymphoma to determine the likelihood of blood or marrow involvement. The presence of circulating lymphoma cells can also occur in patients with a longstanding history of lymphoma and can be indicative of extensive marrow involvement and disease progression. Flow cytometry studies on the peripheral blood can be useful in confirming a morphologic impression of lymphoma in the blood.

EVALUATION OF BONE MARROW

The evaluation of a bone marrow specimen for the presence of lymphoma should include examination of the bone marrow aspirate, touch imprint, core biopsy and/or clot section. Information concerning the type of lymphoma from the diagnostic specimen should be obtained as bone marrow findings can be
cytologically discordant. A follicular lymphoma diagnosed in a lymph node can demonstrate mostly large cells (centroblasts), while the marrow may demonstrate only a small cell component (centrocytes). The type of lymphoma can also determine which ancillary studies may be needed. The integration of ancillary studies, such as flow cytometric immunophenotyping (Figure 1 below), cytogenetic as well as genotypic studies if indicated, can allow for a comprehensive assessment of the lymphoma and can provide information that can be used in initial and post therapy marrow specimens, such as Cyclin D1 immunohistochemistry for mantle cell lymphoma or trisomy 12 determination in atypical chronic lymphocytic leukemia. The percentage of lymphoid cells should be included in the differential count of the bone marrow aspirate and compared to established normal ranges for lymphocytes in the marrow. Lack of increased or atypical lymphoid cells in a marrow differential may not be indicative of an uninvolved marrow due to factors such as sampling or fibrosis associated with lymphoma in the biopsy.

Figure 1.

Flow cytometry histograms of a bone marrow specimen involved by B-cell lymphoma indicate B-cells that are kappa positive and CD19 positive.

Patterns of marrow involvement in the core bone marrow biopsy include the following: diffuse solid, focal paratrabecular, focal nonparatrabecular, diffuse interstitial and intrasinusoidal (Figures 2, 3, 4, 5, and 6, respectively, on the following page); the intrasinusoidal pattern can be highlighted with immunohistochemical staining for CD20 (Figure 6 on the following page) or other B-cell stains. The pattern of marrow involvement can be associated with different subtypes of NHL. Lymphoplasmacytic lymphoma or small lymphocytic lymphoma demonstrates mostly interstitial and diffuse patterns of marrow involvement, while follicular lymphoma demonstrates mostly a paratrabecular pattern of infiltration. Intrasinusoidal infiltration can be seen in splenic marginal zone lymphoma. It should be noted that lymphomas can display mixed patterns of marrow infiltration.
Figure 2. Diffuse Solid

Figure 3. Focal Paratrabecular

Figure 4. Focal Nonparatrabecular

Figure 5. Diffuse Interstitial

Figure 6. Intrasinusoidal
The Ann Arbor staging system (Table 1 below), originally developed for Hodgkin lymphoma, along with the Cotswold modification, is used to determine the number of sites of involvement by lymphoma, their location, and the presence or absence of clinical, systemic symptoms (known as B symptoms). The presence of bone marrow involvement would be considered Stage IV, which can be an adverse prognostic factor depending on the type of lymphoma.

### Table 1. Ann Arbor Staging Classification and the Cotswold Modifications

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer’s ring)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions on the same side of the diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph regions or structures on both sides of the diaphragm</td>
</tr>
<tr>
<td>IV</td>
<td>Involvement of extranodal site(s) beyond that designated E</td>
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**FOR ALL STAGES**

| A | No symptoms (Asymptomatic) |
| B | Fever (> 38°C), drenching sweats, weight loss (10% body weight over 6 months) |

**FOR STAGES I TO III**

| E | Involvement of a single extranodal site contiguous or proximal to known nodal site |

**COTSWOLD MODIFICATIONS**

(i) Suffix X to designate bulky disease as more than one third widening of the mediastinum or > 10 cm maximum dimension of nodal mass

(ii) The number of anatomic regions involved should be indicated by a subscript (e.g., II3)

(iii) Stage III may be subdivided into:

- III1, with or without splenic, hilar, celiac, or portal nodes
- III2, with para-aortic, iliac, mesenteric nodes

(iv) Staging should be identified as clinical stage or pathologic stage

(v) A new category of response to therapy, unconfirmed/uncertain complete remission should be introduced because of the persistent radiologic abnormalities of uncertain significance

Imaging studies in the staging of the patient can include a chest X-ray and computed tomography (CT) scanning of the chest, abdomen, and pelvis. Additional studies, such as magnetic resonance imaging (MRI) and 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) scanning, can be used based on the clinical presentation and sites of disease. PET can provide functional imaging of lymphomas for initial assessment and follow-up. Although PET scanning is commonly used, it does not have an established role in the initial staging of NHL.
The incidence of bone marrow involvement by lymphoma can vary according to the histologic subtype, with more indolent low grade lymphomas, such as nodal marginal zone lymphoma, involving the marrow in approximately 30% of cases to almost 100% of cases of hepatosplenic T-cell lymphoma.

**MALT LYMPHOMAS**

Mucosa associated lymphoid tissue (MALT) lymphomas, as in this case, are extranodal B-cell lymphomas that account for approximately 8% of NHLs. Extranodal marginal zone lymphoma of MALT type is a low grade, indolent lymphoma which commonly involves the gastrointestinal tract in approximately 50% of cases, with the stomach affected most often in about 85% of cases, as in this patient. *Helicobacter pylori* infection has been associated with approximately 90% of gastric MALT lymphomas. MALT lymphomas are thought to arise under conditions of chronic stimulation, such as in chronic infections or autoimmune diseases, which can cause an accumulation of reactive lymphoid tissue and prolonged lymphoid proliferation favoring development of a malignant clone.

Gastrointestinal tract workup and biopsy are indicated in patients with mucosa-associated lymphoid tissue (MALT) lymphomas. Most patients present with Stage I or Stage II disease. Bone marrow involvement is seen in few patients (2-20%) with the frequency of involvement in gastric cases found to be lower than in MALT lymphomas arising in the lung or eye. The median percentage of bone marrow involvement by MALT lymphoma is 10% (3-20% range). The immunophenotype of these cells includes expression of IgM, less often IgA or IgG, light chain restriction, CD19, CD20 and lack of expression of CD10, CD23 and usually CD5. Chromosomal abnormalities associated with MALT lymphomas include t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21) and t(3;14)(p14.1;q32). Peripheral blood involvement is uncommon and occurs more frequently in splenic marginal zone lymphoma.

The lymphoid cells in MALT lymphomas can demonstrate a spectrum of cytologic features which can range from small lymphoid cells with condensed nuclear chromatin to slightly larger cells with irregular nuclei and abundant amounts of cytoplasm (Figure 7 on the following page). Cells with monocytoid features can rarely be seen. Plasma cells may also be admixed.
The bone marrow core biopsy can demonstrate a mixed pattern of involvement including focal, paratrabecular, intrasinusoidal and interstitial patterns. In this case, a lymphocytosis was not identified by manual differential of the aspirate, and lymphoid aggregates were not identified in the bone marrow biopsy. Flow cytometry studies performed on the bone marrow did not demonstrate a clonal B-cell lymphoid population (Figure 8 below). Of note, marrow involvement with MALT lymphoma does not appear to confer a more adverse prognosis.

MALT lymphomas typically follow an indolent course, with high therapeutic response rates, late relapses and long overall survival.

Flow cytometry histograms of a bone marrow specimen indicating polyclonal B-cells.
References

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