A 28-Year-Old Man With Leukocytosis and Anemia

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INTRODUCTION

A 28-year-old man was transferred to our hospital for evaluation of hemoptysis and epistaxis in the setting of anemia, thrombocytopenia, and an elevated white blood cell count. The patient was in his usual state of health until four weeks prior to admission when he developed a sore throat. His symptoms resolved after taking two days of an unknown antibiotic provided by a friend. He then developed left upper quadrant abdominal pain not associated with nausea, vomiting, or change in bowel habits; there was no hematemesis, melena or hematochezia. He reported a few episodes of coughing up small amounts of blood and an approximate 20-pound weight loss over three weeks. There was no history of human immunodeficiency virus infection, syncope, chest pains, palpitations, dizziness, shortness of breath, or skin rash. He was not taking any prescribed or over-the-counter medications.

Vital signs on presentation revealed a temperature of 99.8°F, pulse of 108 beats per minute, blood pressure of 139/73 mm Hg, and a respiratory rate of 14 per minute. Pertinent physical findings on presentation included petechiae on the oral mucosal surfaces, gingival hyperplasia, and a spleen tip that was palpable 4 cm below the left costal margin.

His admission laboratory values showed a white blood count (WBC) of 24.5 X 10^3/µL (4.5-11 X 10^3/µL) with a differential of 2% neutrophils, 2% bands, 15% lymphocytes, 2% atypical lymphocytes, 7% monocytes, and 72% immature mononuclear cells. Peripheral blood smear showed blasts containing cytoplasmic inclusions consistent with Auer rods (Figure 1). The hemoglobin and hematocrit were 9.6 gm/dL.
Figure 3. Karotyping showing 46, XY, t(8;21)(q22;q22), del(9)(q12q22)

(13.5-17.5 gm/dL) and 26.9% (40%-51%); platelet count was
7 X 10^3/µL (130-400 X 10^3/µL). Flow cytometry of peripheral
blood showed 80% of the white blood cells to be myeloblasts
consistent with a diagnosis of acute myeloid leukemia. A
basic metabolic panel and liver function test were normal;
an acute hepatitis panel and HIV test were negative. The
prothrombin time was 15.1 sec (9.5-12.5 sec), with an INR
of 1.4 (0.9-1.1) and a normal partial thromboplastin time
of 27.3 sec. The haptoglobin was 314 mg/100mL (33-213
mg/100 mL); lactate dehydrogenase was 885 U/L (0-250
U/L); D-dimer was 485 ng/mL (0-300 ng/mL); uric acid was
3.9 mg/dL (3-7 mg/dL); and fibrinogen was greater than
700 mg/dL (250-650mg/dL). Bone marrow biopsy showed
90%-95% cellularity with nearly complete involvement by
myeloblasts. Cytogenetic evaluation of the blast population
demonstrated an (8;21) translocation (Figures 2 and 3).

The patient was started on allopurinol for tumor
lysis prophylaxis before initiating chemotherapy. He was
enrolled in a treatment protocol employing three days of
daunorubicin, seven days of continuous infusion cytarabine,
and one dose of gemtuzumab ozogamicin (Mylotarg®). The
patient tolerated induction chemotherapy well, though he
did develop chemotherapy-induced pancytopenia for two
weeks which necessitated periodic transfusion of blood
and platelets. Bone marrow biopsy and aspirate performed
upon full recovery of his white blood cell and platelet counts
showed an 80% cellular marrow with no morphologic
evidence of leukemia. The patient remains in remission and
has successfully completed three cycles of consolidation
with high dose cytarabine.

DISCUSSION

Acute myeloid leukemia (AML) is a disorder of
differentiation and maturation of myeloid progenitors in
the bone marrow. While AML can develop in children, it is
a disease primarily of adults, with a median age at diagnosis
of 67 years. The annual incidence in the United States is
approximately 13,000 new cases per year. With current
therapy, the cure rate approaches 40%.

The clinical presentation of AML can be highly variable,
but is dictated by marrow replacement with malignant,
marrow progenitor cells (termed blasts) and these cells’
direct influence on the marrow microenvironment. Signs
and symptoms at presentation typically are related to
anemia, thrombocytopenia, or neutropenia. Less common
manifestations include cutaneous extramedullary collections
of blasts, known as chloromas, cranial nerve palsies
from leukemic infiltrates, and hepatosplenomegaly. At
presentation, patients typically have an elevated white blood
cell count (WBC) with myeloblasts seen on the peripheral
smear. Often these myeloblasts are interpreted by automatic
cell counters as “monocytes” or “atypical cells”, and review
of the peripheral blood smear by an experienced practitioner
is recommended. Patients may not present with either an
elevated WBC or circulating blasts. Instead, pancytopenia
is often the only clue to diagnosis.

The differential diagnosis of blasts or pancytopenia
should include several conditions. The myelodysplastic
syndrome (MDS) is a malignant stem cell condition that
results in disordered cellular maturation. Patients with
MDS typically have a period of anemia, leukopenia,
or thrombocytopenia which can ultimately progress to
leukemia. Often, retrospective review of CBCs performed
months-to-years before progression can offer a clue that
leukemia transformed out of MDS. Leukemoid reactions
resulting from systemic infection can result in blasts, or other immature forms, being seen on the peripheral smear. In the leukemoid reaction, immature forms typically constitute less than 10% of the overall white blood cell count (WBC). Therapy with colony stimulating factor (G-CSF), frequently used as a supportive therapy in adjuvant chemotherapy for malignant solid tumors, can cause a transient increase in WBC with immature forms spilling into the peripheral blood. Profound vitamin B12 and folate deficiency can present with pancytopenia resulting from a hyperplastic marrow in arrested metaphase. Finally, AML needs to be differentiated from acute lymphoblastic leukemia or chronic myeloid leukemia. This distinction is critical due to their distinct etiologies and divergent therapies.

The diagnosis of AML is contingent on demonstrating the clonal proliferation of myeloid lineage blasts. At initial clinical presentation, clonality can quickly be established by flow cytometry of circulating blasts. Bone marrow biopsy and aspiration remain critical components of the diagnostic work-up. The traditional French-American-British (FAB) system, established in 1976, classifies AML into eight subtypes (termed M0-M7) based on morphologic and cytochemical features of leukemic blasts. In 1999, the World Health Organization promulgated a system that incorporates cytogenetic characteristics and is now the accepted standard classification system. Consequently, the FAB classification system should no longer be used to characterize AML.

Once the diagnosis of AML has been established, various criteria are used for prognosis including age, WBC count on presentation, and performance status. Ultimately, cytogenetic abnormalities of the leukemic clone are the most powerful tool in predicting long-term outcome at the time of diagnosis and serve as a primary guide for therapeutic interventions. AML cytogenetic abnormalities can be broadly grouped into three risk groups: favorable, standard, and poor (Table). Of good risk patients, 70% can be cured with conventional chemotherapy alone, while those with poor risk cytogenetics have little chance of cure with chemotherapy.

Initial treatment of AML to induce remission is fairly uniform and is generally not dependent on prognostic risk group (with the exception of acute promyelocytic leukemia, which is discussed below). The standard induction regimen employs a continuous seven-day infusion of cytarabine and daily anthracycline, usually idarubicin or daunorubicin, given for three days. This regimen is often referred to as “7+3”. “7+3” requires inpatient hospitalization and results in two to three weeks of pancytopenia requiring frequent transfusions of blood and platelets. Successful remission is defined as less than 5% blasts in a 20% cellular bone marrow biopsy performed at the time of complete count recovery, typically four weeks after “7+3” is initiated. Overall, remission is achieved in 60%-80% of cases. The use of additional chemotherapeutic agents with “7+3” generally results in added toxicity with little enhanced efficacy. In cases of induction failure, reinduction with repeat “7+3” or

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an alternative regimen may be tried. Ultimately, however, initial induction failure implies poor overall survival.12

For those patients who have undergone successful induction therapy, the chance for relapse remains high, and additional therapy is often recommended. Consolidation strategies rest on four important factors: patient preference, age, performance status, and cytogenetic profile. For those patients with good risk cytogenetics the current standard of care is 3 to 4 cycles of high-dose cytarabine (HiDAC).14,15 Use of myeloablative chemotherapy followed by infusion of donor stem cells, termed allogeneic stem cell transplant (alloSCT), is a powerful tool for the cure of leukemia. AlloSCT has two distinct advantages in that it allows for delivery of high doses of chemotherapy along with an immune mediated graft-versus-leukemia effect conferred by the donor stem cells. Transplant does carry substantial complications related to treatment, and mortality can range as high as 30%-50% along with significant infectious and graft-versus-host morbidities.15 As a result, alloSCT is reserved for those patients with poor or intermediate-risk cytogenetics and otherwise good health. The potential complications of transplant need to be balanced carefully with the predicted risk of relapse, requiring an appreciation of the patient’s comorbidities and individual wishes.16

Acute Promyelocytic Leukemia (APML) is a distinct clinical entity frequently presenting with disseminated intravascular coagulopathy, hypofibrinogenemia, and hemorrhage. Meticulous monitoring for coagulopathy along with liberal use of fresh frozen plasma and cryoprecipitate is required at the time of diagnosis, as spontaneous hemorrhage is a frequent cause of death. For this reason, we recommend monitoring a prothrombin/partial thromboplastin time and fibrinogen in all cases of suspected APML. While morphologic examination of peripheral blasts is useful, APML is ultimately defined by the presence of the translocation of portions of chromosomes 15 and 17. APML is unique in responding to all trans retinoic acid and is usually curable without stem cell transplantation.17

Even with optimized intensive therapy, a substantial percentage of patients with AML experience a relapse of disease. Those who relapse can be considered for salvage alloSCT, if not performed as part of initial therapy. Relapse after alloSCT can be treated with infusion of donor lymphocytes in an attempt to induce a graft-versus-leukemia effect. Carefully selected patients can be considered for retransplantation, with cure rates of approximately 30%.15,18

Treatment of acute myeloid leukemia in elderly patients (traditionally defined as patients 65 years or older) is approached differently primarily due to the presence of multiple co-morbidities. The induction regimens chosen, the intensity of treatments, and the choice of transplant itself need to be individualized in this patient subset.16 In the elderly who are not candidates for transplantation, the primary goals often include preserving quality of life. Various options are available such as reduced intensity “7+3” (termed “5+2”), HiDAC, or orally administered hydroxyurea.

Newer agents with unique mechanisms of action have been developed, including the monoclonal antibody gemtuzumab ozogamicin (Mylotarg®), directed against CD33. This agent is approved for use in relapsed AML. While there is no expectation for cure with single agent

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<th>Risk Status</th>
<th>Cytogenetics</th>
<th>Molecular Abnormalities</th>
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<tbody>
<tr>
<td>Good risk</td>
<td>inv(16) t(8;21) t(16;16)</td>
<td>Normal cytogenetics with isolated NPM1 mutation</td>
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<tr>
<td>Intermediate risk</td>
<td>Normal +8 only t(9,11)</td>
<td>c-KIT in patients with t(8;21) or inv(16)</td>
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<tr>
<td>Poor risk</td>
<td>Complex (≥ 3 abnormalities) or any of the following: -5  -7 5q- 7q- t(3;3) t(6;9) t(9;22) inv(3) Abnormalities of 11q23, excluding t(9;11)</td>
<td>Normal cytogenetics with isolated FLT3-ITD mutations</td>
</tr>
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Table. Risk status based on cytogenetics and molecular abnormalities.
gemtuzumab, median survival appears to be improved as compared to best supportive care.\textsuperscript{19} The promising activity of gemtuzumab in the relapse setting has led to its inclusion as part of induction therapy in five ongoing randomized trials.\textsuperscript{20}

In 1966 the median survival of adult patients with AML was 40 days. With the introduction of multiagent chemotherapy regimens, stem cell transplantation, and antibiotic support, five-year survival now approaches 70%.\textsuperscript{21} Despite these promising statistics, survival rates remain poor when compared to survival rates for malignancies such as Hodgkin’s lymphoma or testicular cancer in which cure is the rule. Novel classes of drugs currently in early phase trials hold promise for further breakthroughs in improving survival.\textsuperscript{22-24}

REFERENCES


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