Laboratory and Bone Marrow Evaluation in Patients With Cancer

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Anemia in patients with cancer has multiple causes. Since establishing a diagnosis can be difficult, evaluation via laboratory findings and bone marrow histopathology is often necessary. Cytopenias can result either directly or indirectly from the malignancy, or they occasionally are the result of other causes, such as AIDS or infection.

Introduction

Patients with cancer frequently have anemia, with or without other associated cytopenias. Cancer-related anemia can be a direct result of tumor invasion of the bone marrow, an indirect result of tumor therapy or systemic symptomatology, or an “incidental” finding resulting from other pathology in the patient. In many cancer cases, anemia may cause the presenting symptoms, and hematologic abnormalities can contribute to the overall morbidity of the tumor. Identification of the pertinent clinical and laboratory abnormalities and correlation with bone marrow histopathology are often essential in establishing an accurate diagnosis and in developing an appropriate treatment plan.

Noninvasive Laboratory Evaluation

The initial evaluation of anemia in the cancer patient should be noninvasive and should include pertinent findings from the peripheral blood smear, blood chemistries, and some specialized tests. These should always include a complete blood count (CBC), a peripheral blood smear examination, and a reticulocyte count. In most institutions, reticulocyte counts are performed by flow cytometry and are reported as an absolute or “corrected” reticulocyte count. (In the event that a percentage is given, manual correction for the level of hemoglobin is necessary.) Additional testing may include, but will not necessarily be limited to, serum lactate dehydrogenase (LDH), serum iron studies, direct antiglobulin test (DAT), or erythropoietin (EPO) levels.

Automated hematology results can be a key component in deciding the direction in which an anemia workup should proceed. It is important to ascertain the degree and number of cytopenias present (anemia, neutropenia, or thrombocytopenia) in order to gauge the reticulocyte response (an elevated reticulocyte count suggests red cell destruction with an intact bone marrow capable of responding to the anemia) and to identify the red cell size (macrocytic anemias are frequently associated with marrow failure, while microcytic anemias are most commonly associated with hemolysis or abnormalities in iron metabolism).

Evaluation of the peripheral blood film by a trained individual will further aid in delineating the most probable causes for the anemia and will indicate the need for additional or ancillary laboratory testing. Specific red cell abnormalities, when present, can suggest a mechanism for red cell destruction (schistocytes and red cell fragments in microangiopathy, and spherocytes in autoimmune red cell hemolysis). Target cells and burr cells are frequently found in metabolic disorders (liver and renal disease), and teardrop cells may be seen in bone marrow and splenic infiltration by malignant cells. Caution is needed, however, regarding these latter three abnormalities, which are relatively less specific than the finding of true spherocytes and schistocytes and can be observed in variable numbers in association with antibiotic therapy and chemotherapy, as well as after splenectomy. The presence of nucleated red cells and/or immature myeloid cells may suggest bone marrow infiltration (leukoerythroblastosis) or a primary hematologic disorder such as myelodysplasia or a chronic myeloproliferative disorder. Rouleaux and red cell agglutination may suggest a diagnosis of multiple myeloma or the presence of cold agglutinins.

Frequently performed and helpful ancillary studies include flow cytometry for immunophenotyping or DNA ploidy analysis, immunohistochemistry (some antigens do not survive processing conditions well), molecular diagnostics (including polymerase chain reaction, fluorescence in situ hybridization, and Southern blot analysis), and cyto genetics.

Bone Marrow Evaluation

Direct evaluation of the bone marrow can be of value when the cause of the cytopenias is suspected to be marrow failure, either secondary to infiltration by tumor or as a result of antitumor therapy, or when definitive diagnosis requires tissue to be obtained for cytology or special studies. These findings can yield a multitude of morphologic or cytologic abnormalities related to causative mechanisms for hematologic compromise (Table 1). However, specific morphologic findings may be more visible on one or the other of these specimens (Table 2), and it is important to understand the contributions and limitations of each. Cytology is better visualized on well-stained Wright-Giemsa smears, and anatomic abnormalities or disorders associated with fibrosis are best identified on thinly cut, well-fixed decalcified core biopsy sections. While techniques may be available in specialized institutions to handle core biopsy specimens, most ancillary studies will require additional anticoagulated marrow aspirate. In general, cell yield and viability also will be improved when aspirate is submitted.

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<th>Table 1. -- Bone Marrow Findings Directly Related to a Diagnosis of Anemia</th>
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<td>Cellularity and distribution</td>
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<td>Absolute numbers of hematopoietic precursors</td>
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<td>Iron-deficient, megaloblastic, or sideroblastic erythropoiesis</td>
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<td>Hemophagocytosis</td>
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<td>Fibrosis, necrosis, and marrow damage</td>
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<td>Evidence of infection (parvovirus or granulomas)</td>
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<td>Presence of malignant cells (metastatic or primary hematopoietic)</td>
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<th>Table 2. -- Contributions of Aspirate Smears and Core Biopsies to Diagnosis in the Anemic Cancer Patient</th>
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Cytopenias as a Direct Result of the Malignancy

Malignant tumors, especially hematopoietic malignancies, can be the primary cause of one or more cytopenias. In patients with myelodysplasia, an abnormal clone of hematopoietic stem cells replaces normal hematopoiesis in the bone marrow. This clone has frequent alterations in karyotype, with deletions, additions, and translocations of multiple chromosomes. These chromosomal aberrations are associated with abnormalities in both cellular cytology and function, often producing dyspoietic marrow precursors with decreased maturation ability and diminished survival. The resultant cytopenias can be severe and are often trilineal. The anemia that is present is usually macrocytic and associated with a reticulocytosis and clonal erythropoiesis. While the diagnosis is often suspected after examination of the peripheral smear, confirmation requires evaluation of bone marrow aspirate smears and biopsy sections.

Other hematopoietic neoplasms can also directly cause anemia by suppression of the normal bone marrow. Acute leukemia, regardless of whether it produces a hypercellular or hypocellular infiltrate, directly suppresses normal erythropoiesis and causes an anemia of marrow failure. As in the myelodysplasias, anemia caused by acute leukemia is also frequently macrocytic and associated with a decreased reticulocyte count.

Cytopenias Indirectly Resulting From the Malignancy

While infiltration of the bone marrow is the central mechanism leading to anemia in some cancer patients, it is predominantly associated with the hematopoietic malignancies. The majority of anemic cancer patients will present with cytopenias arising as an indirect result of the tumor. Autoimmune hemolytic anemia (AIHA) has been described in association with a number of tumors, although it is most frequently noted in patients with chronic lymphocytic leukemia. In a recent study of 130 patients with cancer and AIHA, the associated tumors included: chronic lymphocytic leukemia (79), non-Hodgkin’s lymphoma (13), Hodgkin’s disease (12), carcinoma (10), multiple myeloma (5), Waldenström’s macroglobulinemia (4), acute myelogenous leukemia (3), angioimmunoblastic lymphadenopathy with dysproteinemia (2), acute lymphoblastic leukemia (1), and myelodysplasia (1). Warm-reacting antibodies are more common than cold agglutinins. The characteristic schistocytic anemia is associated with bone marrow erythroid hyperplasia, variable nuclear dysmorphism, and a reticulocytosis. Bone marrow examination reveals a picture identical to that seen in patients with autoimmune hemolytic anemia.

Another anemia related to red cell destruction in patients with cancer is characterized by microangiopathy. Most cases of cancer-associated microangiopathic hemolytic anemia are seen in patients with known tumors, although occasionally, this anemia may be the presenting feature of the tumor. Gastric carcinoma is the most frequent coexisting cancer (52% of cases), followed by breast cancer (13%), and lung cancer (10%). The syndromes identified are frequently resistant to traditional therapeutic interventions and show considerable overlap with classic cases of disseminated intravascular coagulation (DIC), thrombotic thrombocytopenia purpura (TTP), and hemolytic-uremic syndrome (HUS). The peripheral blood contains variable numbers of true schistocytes associated with nucleated red cells and a reticulocytosis. Bone marrow examination reveals a picture identical to that seen in patients with autoimmune hemolytic anemia.

Cancer patients frequently have some degree of immunosuppression, either transiently related to chemotherapy, or more long-term and related to the primary immunosuppressive properties of their tumors. Like other immuno compromised individuals, these patients can develop opportunistic infections or can show unusual manifestations of otherwise common infectious diseases. The infections themselves can produce bone marrow suppression and anemia. Antibacterial, antifungal, and antiviral medications are contributors to this process. One specific infectious agent, parvovirus B19, can produce a syndrome of pure red cell aplasia with a severe anemia. Although ubiquitous in the population, immunosuppressed patients, including those with malignancies, can develop a protracted infection with this virus. In a recent study of serologically confirmed parvovirus B19 associated pure red cell aplasia, patients with both myelodysplasia and lymphoma were identified. Characteristic bone marrow findings include the presence of giant pronormoblasts showing both intranuclear and often cytoplasmic viral inclusions, as well as a profound erythroid hypoplasia with an apparent erythroid maturation arrest. Other cell lineages frequently appear normal.
One of the more common anemias noted in patients with cancer is characterized by a normal red cell size, a low reticulocyte count, and an apparent increase in bone marrow iron storage. This process has been called the "anemia of chronic disease" and is associated with the elaboration of inflammatory cytokines in the host. When anemia of chronic disease is seen in cancer patients, a wide variety of marrow histologies can be seen. Frequently, the marrow is normocellular, with a normal M:E ratio and an increase in histiocyte storage iron (Figs 2A-B). However, variable degrees of myeloid hypoplasia may result in an overall marrow hypocellularity and a decrease in the M:E ratio. Occasionally, erythroid hyperplasia is present. Dyspoiesis, when identified, is generally minimal. These abnormalities may be identified even in the absence of tumor invasion of the bone marrow and may reflect a systemic response to the presence of the malignancy.

In addition to the processes initiated by the presence of tumor in the patient, iatrogenic causes of anemia should be considered. As already mentioned, antibiotics and other medications may cause marrow suppression or red cell destruction. Chemotherapeutic agents, as well as radiation therapy, may cause direct marrow damage and resultant cytopenias. This damage is usually transient, and the degree of marrow toxicity is related both to the drug dose and specific drug type. Chemotherapeutic agents have variable myelotoxic profiles and are administered frequently in combinations. On examination of the peripheral blood smear, it is not possible to distinguish the drug-induced effect from cancer-related causes of marrow compromise. Bone marrow biopsies of chemotherapy patients show variable serofibrinous damage, occasional hemorrhage, and drop-out of hematopoietic precursors. Shortly after the initiation of chemotherapy, apoptotic cells are numerous. High-dose chemotherapy is associated with more stromal damage and more serofibrinous exudate than conventional therapy for solid tumors or lymphoma.

Cytopenias That Are Incidental to the Malignancy

Although the appearance of anemia or other cytopenia in patients with known malignancies is most frequently related to the tumor or its therapy, other causes are occasionally identified. Other hematologic malignancies, including the development of a secondary myelodysplasia or acute leukemia, should be considered when a patient develops cytopenia several years into treatment for a primary solid tumor or lymphoma. Elderly patients may have more than one tumor, and marrow involvement by a second cancer is a recognized phenomenon. Undiagnosed hemoglobinopathies, particularly beta thalassemia trait, may confuse the clinician who is seeing a patient for the first time. Acquired immunodeficiency syndrome (AIDS) or infection with human immunodeficiency virus (HIV) can produce anemia. This infection can be pre-existing and related to the development of the patient's malignancy, or it can occur during the course of therapy as either transfusion-related or associated with other risk factors. Bone marrow evaluation in patients with HIV infections show nonspecific findings, although some degree of marrow suppression, plasmacytosis, and an associated "anemia of chronic disease" is frequently found.11

Conclusions

Cancer can have a major impact on bone marrow function. Anemia in these patients is frequently multifactorial, and arriving at a single diagnosis can be difficult. It is important to have some understanding of the most probable mechanisms operating in any given patient before rational therapy can be initiated. Directed laboratory evaluation and examination of the bone marrow can provide important diagnostic clues in many cases.

References

DR BENNETT

Do you think plastic sections represent an improvement over typical paraffin-embedded material? Is it worth recommending a switch to plastic embedding to have
When I was a resident, we did all plastic sections, and they were beautiful. Much immunohistochemistry and even some cytochemistries could be done directly on plastic sections. Unfortunately, it takes extra time. In this era, we are trying to come up with faster diagnoses and more efficient ways of dealing with things, so plastic-embedding is probably not a great idea.

DR SABA

Your slide of Hodgkin’s disease shows a bone marrow with iron outside of the cell. What does this mean in terms of a mechanism of anemia?

DR MOSCINSKI

The mechanism relates to anemia of chronic disease, which is multifactorial and is still being elucidated. My understanding is that the macrophages themselves are unable to release iron. This is a cytokine-mediated event, so one expects to see iron in the macrophage and not in the red cell precursors.

DR BENNETT

My experience is identical to Dr Moscinski’s. There is a disparity between chronic inflammatory diseases and diseases of malignancy, with either very few sideroblasts, and those present having only occasional single grains of ferritin and iron in them, stained by Prussian blue. I think it would be unusual to see much excess iron in the macrophages and at the same time see sideroblast iron, except perhaps in the myelodysplastic syndromes.