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Review Article

Metastatic tumors in bone marrow: histopathology and advances in the biology of the tumor cells and bone marrow environment

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Abstract The nonhematopoietic tumors most often diagnosed in the bone marrow are metastatic. Currently, accurate diagnosis of tumor metastasis requires integration of the clinical findings; morphological features; and results of immunohistochemical stains, cytogenetics, and molecular studies. This review focuses on a practical approach to the diagnosis of metastatic tumors in the bone marrow according to current standards of practice and discusses recent advances in understanding of tumor metastasis and the interaction between tumors and the bone marrow environment.

Keywords: Bone marrow; Metastasis; Microenvironment; Immunohistochemistry; Cytogenetics; Molecular study

1. Introduction

Bone marrow (BM) biopsy is an invasive procedure used mainly in the diagnosis of diseases of the hematopoietic system, but a significant proportion of biopsies are performed for staging in cases diagnosed with nonhematopoietic tumors. Involvement of the BM by nonhematopoietic lesions can be seen incidentally, and careful examination can result in accurate diagnosis. Most often, nonhematopoietic tumors diagnosed in the BM are metastatic. In children, the most frequently encountered metastatic tumors are neuroblastoma; rhabdomyosarcoma; and tumors of the central nervous system (CNS), such as medulloblastoma and retinoblastoma. In adults, lung, breast, and prostate cancer predominate [1-3]. Other carcinomas, sarcomas, and melanoma are less frequently diagnosed in the BM, mainly because of their lower overall incidence. Still, many of these tumors have a tendency toward bone metastasis. Almost every class of malignant tumor has been shown to metastasize to bone or BM.

2. Systemic manifestations of metastatic disease

The presence of a metastatic process in BM can lead to systemic abnormalities that should trigger a BM biopsy to clarify origin. Bone pain, spinal cord compression, and pathological fractures are among the most frequently described skeletal symptoms of metastatic disease [4]. Abnormalities detectable in the peripheral blood are frequent, and in some studies, most patients with metastatic disease involving BM have hematological abnormalities [5]. Probably the most common hematological finding in the peripheral blood is anemia. The types of anemia observed in patients with metastatic neoplasms include anemia of chronic disease, iron deficiency, and microangiopathic hemolytic anemia (Fig. 1) [6]. The exact cause of anemia is sometimes difficult to establish because many patients have received concomitant treatment or experienced blood loss. Although more frequent in patients with BM involvement by metastatic disease, anemia also occurs in a substantial proportion of patients with tumors that do not involve the BM, and it can be absent in many cases with BM metastases, which makes it a nonspecific finding. Microangiopathic hemolytic anemia has been associated with mucin-producing neoplasms, such as adenocarcinomas of the breast, lung, or gastrointestinal (GI) tract, but it also has been shown in metastatic sarcomas and pediatric tumors [7,8].

The most frequently encountered abnormalities in isolated hematopoietic lineages are thrombocytopenia, the presence of nucleated red blood cells, and anisopoikylocytosis [9]. Those abnormalities are either the result of abnormalities in cell survival (as is the case of platelets in

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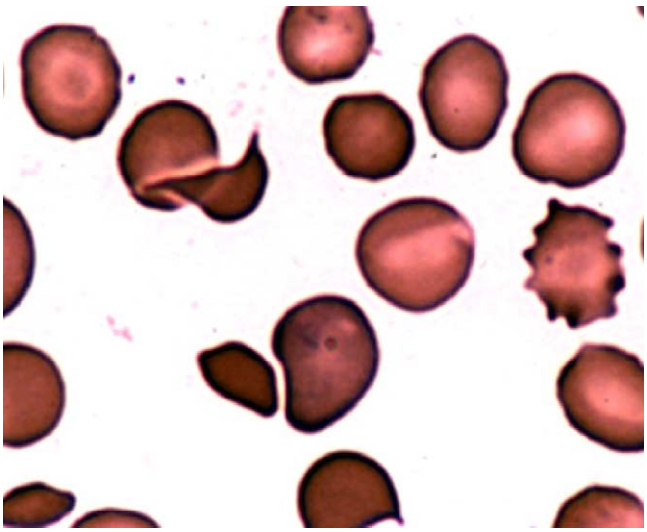

Fig. 1. Microangiopathic hemolytic anemia. Numerous schistocytes are present in the peripheral blood smear (Wright-Giemsa, original magnification ×1000).

disseminated intravascular coagulopathy) or of abnormalities in cell production. When the BM involved in a metastatic process is fibrosed, as often occurs with metastatic adenocarcinomas (but not only in adenocarcinomas), peripheral blood smears can show a leukoerythroblastic reaction. That reaction is similar to what is seen in myelofibrosis. It initially was thought to result from hematopoietic progenitors being "squeezed out" from the BM space by the fibrotic process. The current understanding is more complex, as a leukoerythroblastic reaction also is encountered with tumors that do not involve BM or that induce minimal marrow fibrosis, a finding that points to the possible role of as yet unidentified cytokines. Granulocyte colony-stimulating factor is one cytokine that is thought to help mobilize progenitor cells from the BM, and cases of tumors secreting detectable amounts of granulocyte colony-stimulating factor are well documented [10]. When the reaction is severe and skewed toward the myeloid lineage, it mimics a leukemoid reaction, a diagnostically challenging finding. Circulating tumor cells have been described in cases of breast carcinoma, small cell carcinoma, ovarian carcinoma, neuroblastoma, Wilms tumor, and rhabdomyosarcoma, sometimes mimicking the clinical appearance of acute leukemia [5,11-14]. Identification of the tumor cells is more likely if molecular techniques are used or if larger volumes of blood are screened [15].

Detection of tumor cells in circulation is not an absolute indicator of BM involvement, or even of metastatic disease, as they often can be apoptotic [16]. Tumor components or products can be seen either free in the peripheral blood or engulfed by circulating macrophages or neutrophils. In cases of malignant melanoma with large tumor burden and melanin production, histiocytes with melanin granules can be in BM and in peripheral blood. In extreme cases, free-floating melanin granules are seen on the peripheral blood smear. In adenocarcinomas, free mucin or within macrophages, can be an indication of BM involvement [17]. At least 2 reported cases of Wilms tumors involved the secretion of mucin and circulation of mucin in the peripheral

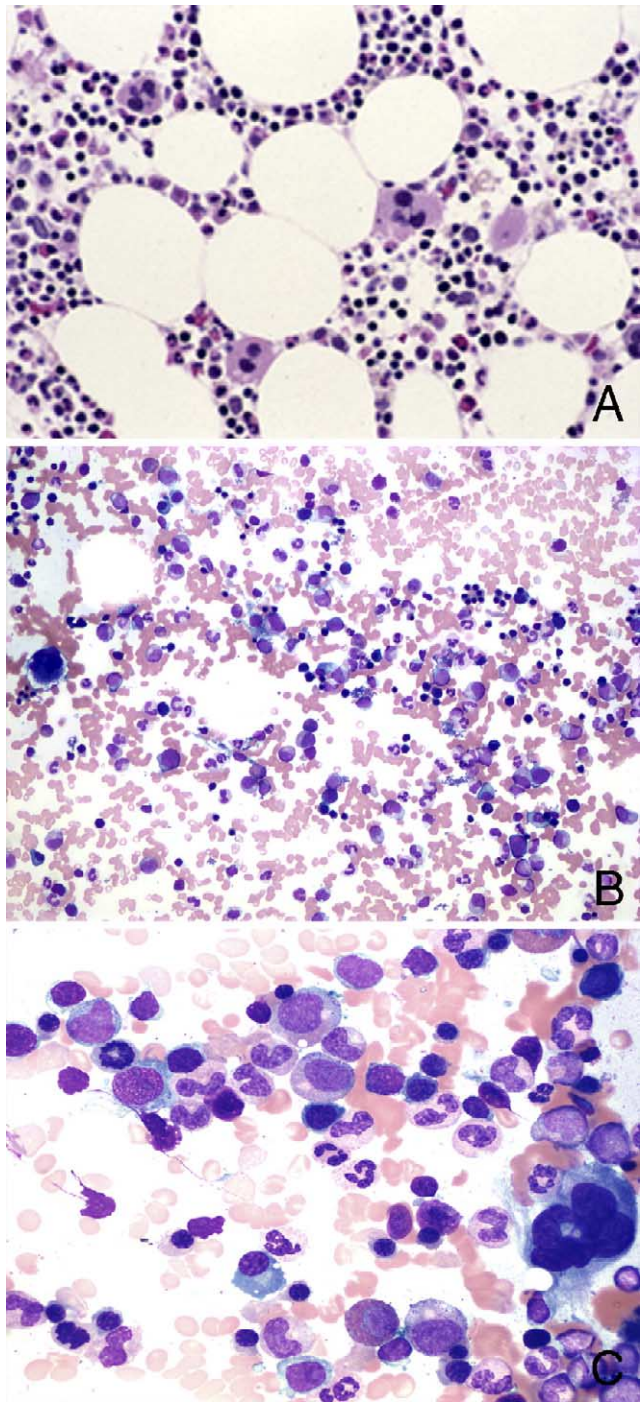

Fig. 2. Normal BM. (A and B) Aspirate smear demonstrates orderly trilineage hematopoiesis; Wright-Giemsa, original magnification ×500 (A) and ×1000 (B). (C) Bone marrow biopsy demonstrates elements of all 3 lineages. Megakaryocytes do not form clusters (H&E, original magnification ×400).