Letter to the Editor
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Concurrent Hematologic and Metastatic Epithelial Malignancies in the Bone Marrow: Report of Three Cases

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Dear Editor

The reported prevalence of multiple primary malignant neoplasms varies from 0.734% to 11.7% [1]. Because adenocarcinomas originate in epithelial cells, the presence of adenocarcinoma cells in the bone marrow (BM) always indicates a primary lesion at another site. Here we describe three cases, in which hematologic and epithelial malignancies coexisted in the BM.

A 70-yr-old woman presented with fever. On the basis of complete blood count (CBC), she was identified to have anemia with leukocytosis (hemoglobin, 7.9 g/dL; leukocyte count, 18.5 $\times 10^9$/L). The BM aspirate predominantly consisted of myeloblasts (81.6%) that were positive for myeloperoxidase (MPO), CD34, CD13, CD33, CD117, and CD15. However, two cytomorphologically distinct subsets of cells were evident (Fig. 1A). In BM biopsy preparations, one population was positive for MPO and CD34, whereas the other was Periodic Acid-Schiff (PAS)-positive with positive immunostaining for cytokeratin (CK) 7 and pan-CK. These findings supported the coexistence of two distinct malignances: AML and metastatic adenocarcinoma. A complex and monosomal karyotype (45,XX,del(3)(p21),del(5)(q13q31),-17,-20,+mar1[9]/45,idem,-22,+mar2[21]) was observed on chromosomal analysis, and radiologic studies revealed the presence of lung cancer with mediastinal invasion. Transbronchial needle aspiration of a mediastinal lymph node confirmed thyroid transcription factor-1-positive metastatic adenocarcinoma, highly suggestive of a lung origin. The presence of MPO-positive leukemic myeloblasts was also observed (Fig. 1B). The patient refused chemotherapy, and instead, she was placed in hospice care.

A 68-yr-old woman with chest pain was diagnosed as having non-ST elevation myocardial infarction (MI). Her CBC revealed bicytopenia (hemoglobin, 8.2 g/dL; platelet count, 40×10^9/L). Predominance of erythroid precursors with features of dyserythropoiesis and clusters of atypical cells were observed on BM aspirates. A hypercellular BM biopsy showed signs of dysmegakaryopoiesis (micromegakaryocytes) and a diffuse infiltrate of malignant cells. The latter was positive for PAS, pan-CK, and CK7 but negative for CK20 (Fig. 1C). Myelodysplastic syndrome, refractory cytopenia with multilineage dysplasia and metastatic adenocarcinoma were diagnosed as concurrent disorders. The patient had a trisomy 9 karyotype (47,XX,+9[8]/46,XX[12]). Based on the staining characteristics (CK7-positive, CK20-negative), the carcinoma could have originated from the lung, breast, ovary, or bile duct [2]. Computed tomography revealed a mass-

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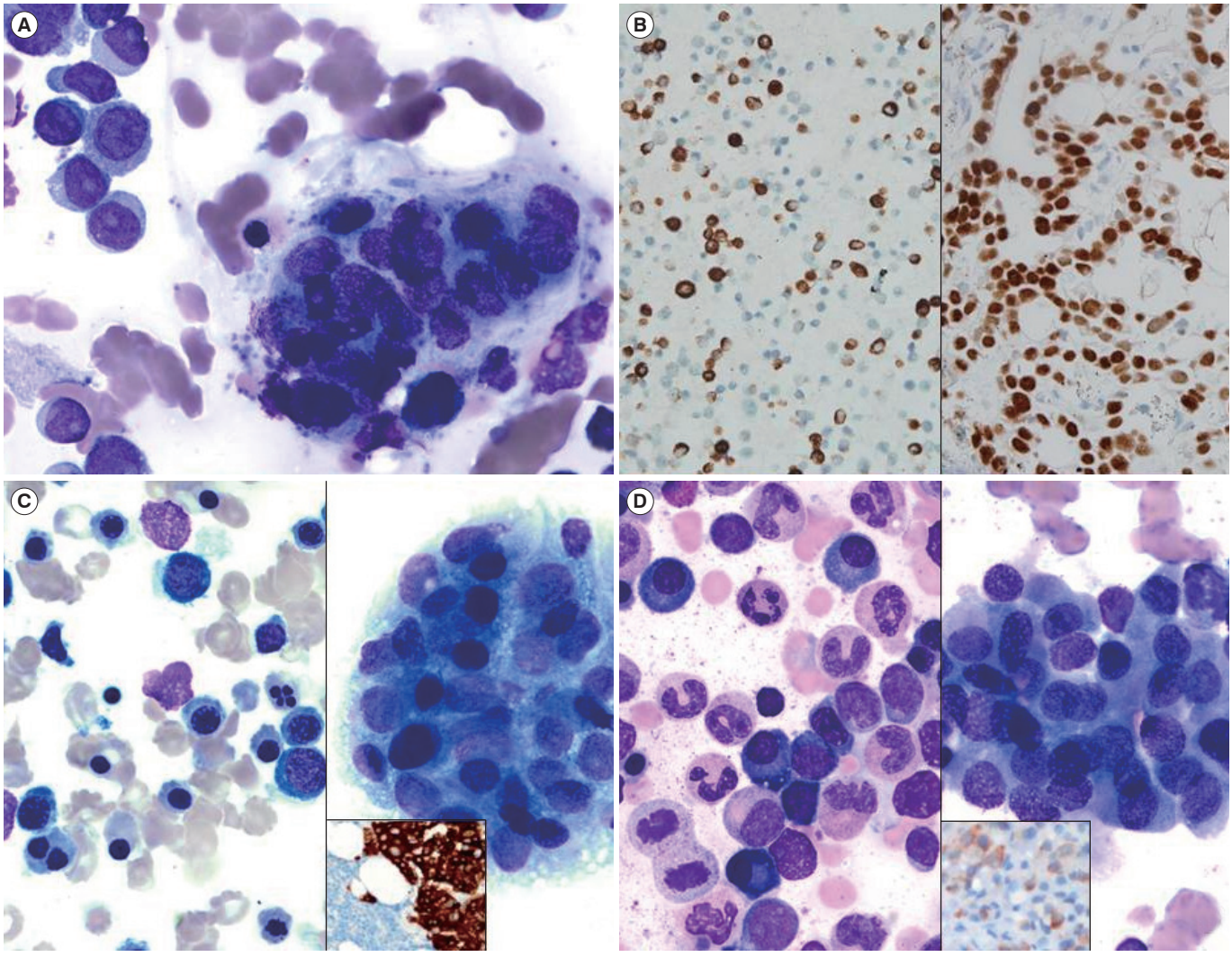

Fig. 1. Bone marrow (BM) findings and tissue preparations for patients. (A) Leukemic myeloblasts on BM aspirate smear with clusters of atypical cells from case 1 (Wright-Giemsa stain, ×1,000); (B) Cancerous cells that were positive for thyroid transcription factor-1 (TTF-1) (TTF-1 stain, ×400) and myeloperoxidase-positive myeloblasts of the mediastinal lymph node aspirate in case 1 (myeloperoxidase stain, ×400). (C) Prominent dyserythropoiesis (multinucleation) and atypical cell clusters on BM aspirate smear (Wright-Giemsa stain, ×1,000) and the BM biopsy infiltrated by cytokeratin 7-positive carcinoma cells (inset) in case 2 (cytokeratin 7 stain, ×200); (D) Excess of plasma cells and clusters of atypical cells on BM aspirate smear (Wright-Giemsa stain, ×1,000) and cancerous BM infiltrate with pan-cytokeratin positivity (inset) in case 3 (pan-cytokeratin stain, ×400).

like lesion at the gall bladder neck and multiple hepatic masses. The condition of the patient prohibited decisive therapeutic intervention. She was treated medically but died of an acute MI after 15 days of hospitalization.

A 64-yr-old man presented with Bence-Jones proteinuria. His CBC revealed anemia (hemoglobin, 8.7 g/dL), and serum protein electrophoresis confirmed IgG, lambda monoclonal gammopathy. Multiple osteolytic lesions of the humerus, femur, pelvis, and whole spine were revealed on bone scintigraphy. Excessive plasma cells (15.4%) shown on a BM biopsy were lambda light chain-positive on immunostaining, indicative of multiple myeloma. Clusters of non-plasmacytic malignant cells were also observed providing sufficient immunohistochemical support (pan-CK, positive; CK7 and CK20, negative) for a diagnosis of metastatic adenocarcinoma coexisting in the BM (Fig. 1D). Chromosomal analysis revealed a normal karyotype. The absence of CK7 and CK20 immunostaining suggested a primary carcinoma of the prostate or kidney [2]. Radiography revealed multiple metastases to the liver, retroperitoneum, pleura, and bone. The patient declined further evaluation or chemotherapy, and he was

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Table 1. Cases of hematologic malignancies that simultaneously presented with bone marrow metastatic carcinoma

Case No.	Age (yr)	Sex	Hematologic malignancies	Metastatic carcinoma	Treatment & Outcome	Reference
1	70	F	Acute myeloid leukemia	Lung adenocarcinoma	Transfer to hospice	Present study*
2	68	F	Myelodysplastic syndrome	Adenocarcinoma of unknown origin (CK7+/CK20-)	Supportive care; died after 15 days	Present study*
3	64	M	Multiple myeloma	Adenocarcinoma of unknown origin (CK7-/CK20-)	Transfer to hospice	Present study*
4	63	M	Multiple myeloma	Lung adenocarcinoma	Chemotherapy; not described	Reference 4
5	72	M	Hairy cell leukemia	Gastric signet ring cell carcinoma	Supportive care; died after 2 yr	Reference 5

*These patients were identified in 41,658 bone marrow examinations performed between January 2002 and December 2013.
Abbreviations: F, female; M, male; CK, cytokeratin.

placed in hospice care.

The coexistence of hematologic malignancies and solid tumors is likely coincidental. However, the *IDH1/2* mutations identified through genomic sequencing of various malignancies (AML and cancers of the biliary tract, colon, stomach, lung, and prostate gland) are certainly of note [3]. Because such mutations have been implicated in tumorigenesis, individual malignancies in the proximal microenvironment may possibly interact during tumor initiation and progression. Nevertheless, simultaneous presence of the malignancies in the BM is rare compared with at other sites of origin. In a literature search in the PubMed database, we identified only two reports involving a hematologic malignancy diagnosed concurrently with a metastatic carcinoma in the BM: myeloma and lung cancer in one instance and hairy cell leukemia and gastric cancer in the other [4, 5]. Table 1 summarizes the characteristics of these two patients and the present three cases.

These patient scenarios are at odds with the traditional Osler principle, which stipulates that a constellation of symptoms is caused by a single disease process. However, this tenet may not hold true, particularly in elderly individuals. It is therefore important to closely examine all elements of BM specimens, recognizing the potential for the coexistence of multiple malignancies. Infiltrative patterns typical of metastatic carcinoma were characteristic of each of our patients prior to the immunohistochemical staining results. Therefore, hematopathologists should strongly consider the possibility that multiple disease entities could simultaneously arise in the BM.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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