

Leukoerythroblastosis in castration-resistant prostate cancer: A clue to diffuse bone marrow carcinomatosis

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Abstract

A 66-year-old man with a previous history of advanced prostate cancer failing complete androgen blockade, docetaxel chemotherapy, denosumab, and abiraterone acetate as judged by persistent high serum levels of prostate specific antigen presented with exertional dyspnea, normocytic anemia, and thrombocytopenia. Leukoerythroblastosis was noted in his peripheral blood. Bone marrow examination disclosed diffuse bone marrow carcinomatosis from prostate cancer. Prolonged activated partial thromboplastin time, prothrombin time, and an extremely elevated serum level of D-dimer led to a diagnosis of disseminated intravascular coagulation. Magnetic resonance imaging of spine revealed extensive bone marrow involvement but bone scan showed only scanty bony metastasis. We like to call attention to the importance of prompt bone marrow examination once recognizing leukoerythroblastosis in patients with advanced prostate cancer. Survey of a possible coexistent disseminated intravascular coagulation is as well strongly recommended in this condition.

Introduction

Leukoerythroblastosis is the presence of nucleated red blood cells and early myeloid cells in the peripheral blood with or without anemia. Most common causes of leukoerythroblastosis include bone marrow infiltration by metastatic carcinoma or primary myelofibrosis, severe infection, osteopetrosis, marked bone marrow response to acute blood loss or acute hemolysis and recovery from bone marrow suppression.¹ Appearance of this phenomenon has been recognized as a warning sign of bone marrow involvement by metastatic carcinoma in breast cancer.² We like to present the dis-

mal nature of disseminated bone marrow metastasis in a castration-resistant prostate cancer patient and call attention to the importance of immediate bone marrow examination once recognizing leukoerythroblastosis during care of such patients.

Case Report

A 66-year-old Taiwanese man was admitted to our medical oncology ward with the chief complaint of progressive exertional dyspnea for twenty days in December 2017. He had been diagnosed with bony metastasis from prostate cancer for 8 years and failed various kinds of treatment including luteinizing hormone-releasing hormone agonist (leuporelin), androgen receptor antagonist (bicalutamide), denosumab and docetaxel. He was brought to our hospital after starting on dexamethasone and abiraterone acetate without improvement of serum prostate specific antigen level for two months in a medical center nearby.

There was no obvious bone pain, chills or fever. He denied other major systemic disease except essential hypertension under regular medical control. His chest X-ray film disclosed right side costophrenic angle blunting and a little fluid accumulation in the minor fissure without extensive pulmonary edema. Blood chemistry showed that levels of alanine aminotransferase, gamma glutamyltransferase, blood urea nitrogen and creatinine were within normal ranges. Abnormal results included alkaline phosphatase of 123 iu/L (normal 32 to 91), albumin of 3.2 g/dL (normal 3.5 to 4.8) and calcium of 7.7 mg/dL (normal 8.6 to 10). Serum prostate specific antigen level was 905 ng/mL (normal 0 to 4). Prolonged activated partial thromboplastin time (41.2 sec, control 31.5) and prothrombin time (international normalized ratio 1.23) were noted. Although plasma fibrinogen level was still normal (335 mg/dL, normal 200 to 400), the concentration of D-dimer was extremely high (over 20,000 ng/mL, normal less than 500). Blood routine test revealed hemoglobin of 6.4 g/dL, mean corpuscular volume of 89.4 fl, platelet count of 1,100/ μ L, and white cell count of 7,200/ μ L with extraordinary abnormal differential counts: segments 19%, lymphocytes 35%, monocytes 1%, eosinophils 3%, bands 19%, metamyelocytes 11%, myelocytes 6%, promyelocytes 4%, blasts 1%, and atypical lymphocytes 1%. There were 48 nucleated red cells per 100 white cells. A diagnosis of leukoerythroblastosis was thus established based on morphological evidence (Figure 1).

Bone marrow aspiration from right side

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posterior superior iliac crest gave a smear of full-blown metastatic carcinoma with many clustered, dispersed or microacinar groups of epithelioid malignant cells. Bone marrow biopsy from the same area showed a picture of metastatic adenocarcinoma composed of highly pleomorphic tumor cells with hyperchromatic nuclei, prominent nucleoli, and vacuolated cytoplasm, infiltrating diffusely in the marrow with a sheeted pattern. The carcinoma cells were positive for prostate specific membrane antigen, negative for cytokeratin 7 and cytokeratin 20 on immunohistochemical stains using Bond Polymer Refine Detection Kit (Leica Biosystem, Milton Keynes, UK) performed on automated Leica Bond MAX stainer (Leica Biosystem, Melbourne, Australia) with three primary antibodies (Leica Biosystem) (Figure 2).

There were only a few small metastatic lesions over skull, manubrium, and ribs in bone scan performed two months earlier but

diffuse bone marrow involvement and destruction could be seen in magnetic resonance imaging of spine done one month prior to the present hospitalization (Figure 3). The patient decided to receive palliative treatment upon knowing his incurable disease status and died of multiple organ failure resulting from fulminant disseminated intravascular coagulation two weeks later.

Discussion

Leukoerythroblastosis has an incidence of about 28.6% in castration-resistant prostate cancer and is associated with severe anemia, thrombocytopenia and disseminated intravascular coagulation.³ The significance of leukoerythroblastosis as a sign of diffuse bone marrow involvement by prostate cancer in patients like ours, although having been reported in the past and familiar to hematologists,^{4,5} might still deserve close attention for general practitioners. Unexpected findings of bone marrow carcinomatosis from a prostate cancer not previously diagnosed, in fact, were occasionally reported in patients initially suspected to have hematologic disorders due to the detection of anemia, thrombocytopenia and immature cells in the peripheral blood.^{6,7}

Disseminated intravascular coagulation is a well-known complication of malignant diseases, especially in mucin-producing adenocarcinoma. Its presentation has been frequently mentioned in metastatic prostate cancer,⁸⁻¹⁰ and even accompanied with enhanced fibrinolysis and extensive hemorrhage.¹¹⁻¹³ Coexistence of bone marrow metastasis and disseminated intravascular coagulation in a metastatic prostate cancer patient similar to ours could be found in the Japanese literature.¹⁴ Overlooking an underlying disseminated intravascular coagulation probably will cause trouble in clinical practice.

Advanced prostate cancer usually has prominent osteoblastic bony metastasis. Progression to terminal stage of this disease was often presumed to take place only in patients with extremely bony metastasis. Nevertheless, as we see in this patient, diffuse bone marrow carcinomatosis can develop silently without striking bony metastasis. There must be a separate pathogenesis to make diffuse bone marrow involvement different from bony metastasis, albeit awaiting further investigation and clarification.

Bone marrow has been identified as a metastatic niche for occult disseminated cancer cells from solid tumors before extensive metastasis to various distant organs.¹⁵

Interaction of dormant cancer cells with bone marrow microenvironment and the final reactivation of the so-called cancer stem cells were found to be a complicated process involving many mediators.¹⁶ Whether the diffuse metastatic prostate cancer cells in this patient's bone marrow still preserve the characteristics of cancer stem cells deserves more intensive study.

Accordingly, leukoerythroblastosis in patients with advanced prostate cancer should definitely be identified as a warning sign of bone marrow carcinomatosis which

could be accompanied by coexistent disseminated intravascular coagulation. Concurrent advanced bony metastasis, to our surprise, is not necessary always present. Overlook of this phenomenon might lead to unfortunate events in regard of patient care.

Conclusions

We recommend that clinicians who treat prostate cancer be familiar with the causes

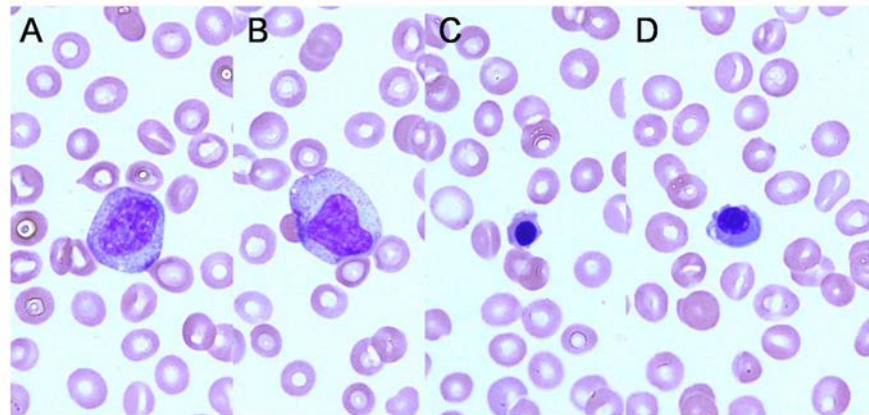


Figure 1. Leukoerythroblastosis: white and red blood cell precursors in peripheral blood. A) Myelocyte. B) Metamyelocyte. C) and D) Nucleated red blood cells.

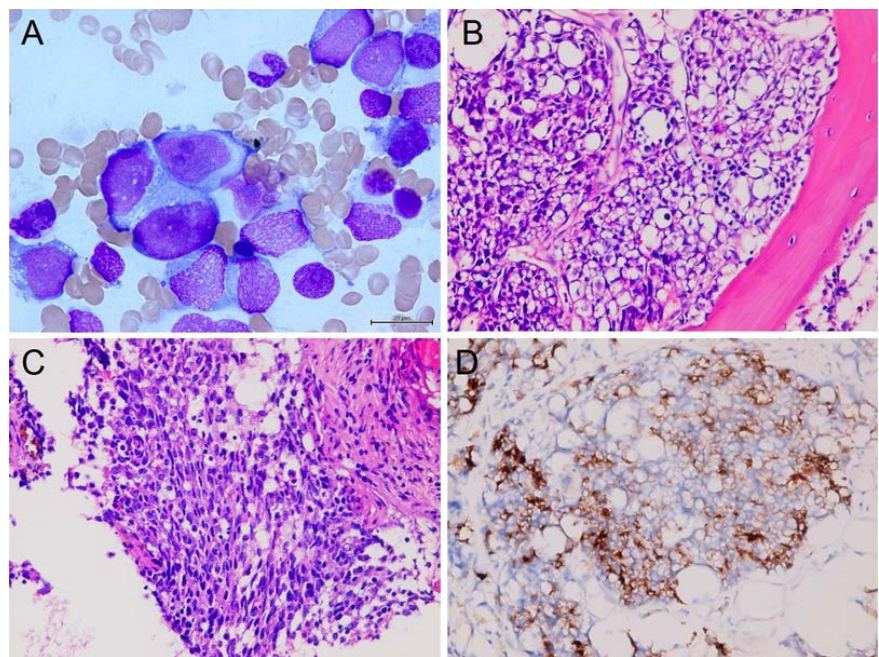


Figure 2. Metastatic prostate carcinoma in bone marrow. A) Clustered and dispersed malignant cells in smear (Wright-Giemsa stain, $\times 1000$). B) Solid nests of highly pleomorphic tumor cells (hematoxylin and eosin stain, $\times 400$). C) A small locus of spindled (sarcomatoid) change of tumor cells (hematoxylin and eosin stain, $\times 400$). D) Tumor cells positive for prostate specific membrane antigen in cytoplasm ($\times 400$).

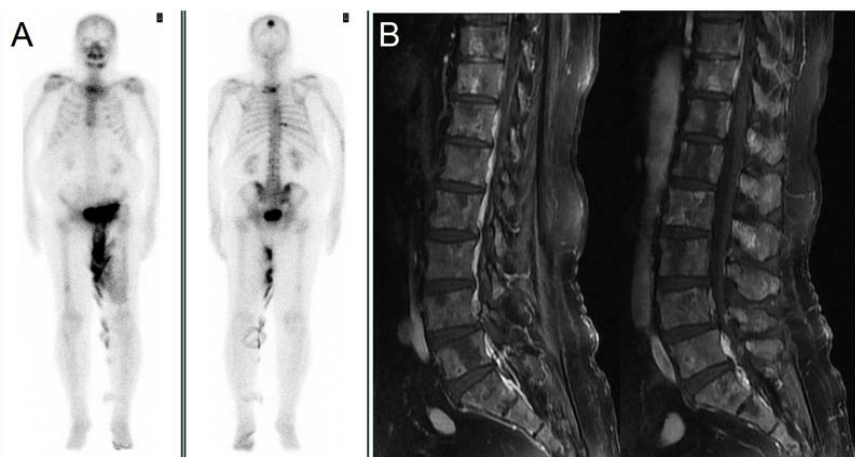


Figure 3. Image studies. A) Bone scan showing a few hot spots over skull, manubrium, and ribs. Also noted are the accumulation of radiotracer in bladder and the urine collecting bag. B) Magnetic resonance imaging revealing diffuse destructive lesions in bone marrow of lower thoracic, lumbar spine and sacrum (T1 fat saturated post-contrast).

and clinical significance of leukoerythroblastosis. Prompt reaction and consultation of hematologists for confirmation of the highly suspicious bone marrow involvement surely can avoid mistakes and make therapeutic plans more accurate and efficient. Survey of evidence for disseminated intravascular coagulation is highly suggested in this condition.

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