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

Frank Sheng Fan,1 Chung-Fan Yang2
1Section of Hematology and Oncology, Department of Medicine, Ministry of Health and Welfare Changhua Hospital, Chang-Hua County; 2Department of Pathology, Ministry of Health and Welfare Changhua Hospital, Chang-Hua County, Taiwan

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, osteoporosis, 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 dismal 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 (leuprolrelin), 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 1,100,000/μL, and white cell count of 7,200/μL 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 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. 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, 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.

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, and even accompanied with enhanced fibrinolysis and extensive hemorrhage. 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. 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.

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. 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, ×1000). B) Solid nests of highly pleomorphic tumor cells (hematoxylin and eosin stain, ×400). C) A small locus of spindled (sarcomatoid) change of tumor cells (hematoxylin and eosin stain, ×400). D) Tumor cells positive for prostate specific membrane antigen in cytoplasm (×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 leukoerythropo- 
lastosis. Prompt reaction and consultation of hematologists for confirmation of the 
highly suspicious bone marrow involve- 
ment surely can avoid mistakes and make therapeutic plans more accurate and effi- 
cient. Survey of evidence for disseminated intravascular coagulation is highly suggest- 
ed in this condition.

References

1. The Royal College of Pathologists of 
Australasia. Leukoerythroblastic anaemia. RCPA manual. 2019. Available from: https://www.rcpa.edu.au/Manuals/RCPA - Manual/ Clinical Problems/L/Leukoerythroblastic anaemia. Accessed: 21 April 2019.

2. Mahdi EJ, Mahdi AJ. Leukoerythroblastosis and thrombocyto- 
topenia as clues to metastatic malignan- 
cy. BMJ Case Rep 2014;pii: bcr2013202612.

3. Shamdas GJ, Ahmann FR, Matzner MB, Ritchie JM. Leukoerythroblastic anaemia in metastatic prostate cancer. Clinical and prognostic significance in patients with hormone-refractory disease. Cancer 1993;71:3594-600.

4. Solenthaler M, Lämmle B. [Severe hemorrhage, lymphocytosis and leuko- 
erythroblastic blood picture-disseminated intravascular coagulation in metaста- 
tic prostate carcinoma and chronic lymphatic leukemia]. Ther Umsch 1999;56:533-6.

5. Kato T, Yamamoto N, Matsuoka Y, et al. [Disseminated carcinomatosis of the bone marrow in two patients with prostate cancer]. Nihon Hinyokika Gakkai Zasshi 2011;102:28-33.

6. Hiroshige T, Eguchi Y. Prostate cancer with disseminated carcinomatosis of bone marrow: Two case reports. Mol Clin Oncol 2017;7:233-36.

7. Alam R, Tosoian JJ, Okani O, et al. Metastatic prostate cancer diagnosed by bone marrow aspiration in an elderly man not undergoing PSA screening. Urol Case Rep 2017;11:7-8.

8. Duran I, Tannock IF. Disseminated intravascular coagulation as the present- 
ing sign of metastatic prostate cancer. J Gen Intern Med 2006;21:C6-8.

9. Yazdi MF, Malekzadeh G. Search for a cause of disseminated intravascular coagulopathy resulted in finding metastatic prostate cancer. Cent Eur J Urol 2013;66:172-6.

10. Desai M, John B, Evans G, Eddy B. Prostate cancer: beware of disseminated intravascular coagulation. BMJ Case Rep 2015;pii: bcr2014206814.

11. Ong SY, Taverna J, Jokerst C, et al. Prostate cancer-associated disseminated intravascular coagulation with excessive fibrinolysis treated with Degarelix. Case Rep Oncol Med 2015;2015:212543.

12. Palma Anselmo M, Nobre de Jesus G, Lopes JM, et al. Massive bleeding as the first clinical manifestation of metastatic prostate cancer due to dis- 
seminated intravascular coagulation with enhanced fibrinolysis. Case Rep Hematol 2016;2016:7217915.

13. Hamzah AB, Choo YM, Hassali MA, et al. Disseminated intravascular coagulation and excessive fibrinolysis (DIC XFL) syndrome in prostate cancer: a rare complicated disorder. J Clin Diagn Res 2017;11:XD01-2.

14. Minato N, Takada T, Koga M, Sugao H. [Prostate cancer with disseminated carcino- 
matosis of bone marrow initially present- ing with disseminated intravascular coagulation syndrome: a case report]. Hinyokika Kiyo 2012;58:249- 
53.

15. Shiozawa Y, Eber MR, Berry JE, Taichman RS. Bone marrow as a 
metastatic niche for disseminated tumor cells from solid tumors. Bonekey Rep 2015;4:689.

16. Kan C, Vargas G, Pape FL, Clézardin P. Cancer cell colonisation in the bone microenviron- 
ment. Int J Mol Sci 2016;17 pii:E1674.