Leukemoid Reaction in Association with Bone Marrow Necrosis due to Metastatic Prostate Cancer

Taichi AZUMA, Ikuya SAKAI, Takuya MATSUMOTO, Akira OZAWA*, Nozomu TANJI*, Akito WATANABE**, Naoyuki UCHIDA, Hiroshi NARUMI, Yoshihiro YAKUSHIJIN, Takaaki HATO***, Masaki YASUKAWA and Shigeru FUJITA

Abstract

An 80-year-old man presented to the internist with fever, fatigue and leukocytosis up to 66.8×10^3/l. Although a chronic myelogenous leukemia was initially suspected, he was diagnosed as metastatic bone marrow tumor with bone marrow necrosis from primary prostate cancer on the basis of the clinical and pathological findings. The serum concentrations of IL-6 and TNF-α were mildly elevated to 65.0 pg/ml and 54.0 pg/ml respectively. It is probable that these humoral factors were partially responsible for the leukemoid reaction although other factors induced by the bone marrow necrosis with bone marrow metastasis of prostate cancer are also likely involved.

Key words: leukocytosis, LAP score, TNF-α, IL-6

Introduction

Leukemoid reaction is defined as a reactive leukocytosis in excess of 7.5×10^3/l. It is caused by an exaggerated myeloid response to several stimuli including infections, allergies, burns, intoxications, acute hemorrhage, malignant neoplasms and certain drugs including corticosteroids and lithium. In the absence of lymphadenopathy, organomegaly, basophilia, or eosinophilia, a high leukocyte alkaline phosphatase (LAP) score initially favored the diagnosis of a leukemoid reaction. LAP is an enzyme present in the cytoplasmic microsomes of neutrophils, bands, metamyelocytes and myelocytes but not of lymphocytes or monocytes. A LAP score is usually requested in cases of neutrophilia (1). While immature neutrophils such as chronic myeloid leukemia (CML) have decreased LAP, stimulated neutrophils such as in a leukemoid reaction or infection have increased LAP scores. We report here a case of marked leukocytosis with bone marrow necrosis in a patient with prostate cancer, who was initially suspected as CML because of a decreased LAP score.

Case Report

An 80-year-old man with fever, anorexia, and general fatigue had a medical examination at a regional hospital. CML was suspected because of marked leukocytosis. He was referred to our hospital for additional investigation and treatment. On admission, physical examination showed mild swelling of prostate with digital rectal examination. No lymphadenopathy or hepatosplenomegaly was detected. Hematological findings were as follows: white blood cells, 66,800/l (1.5% myeloblasts, 24.5% myelocytes, 4.5% metamyelocytes, 54% neutrophils, 2% eosinophils, 4% basophils, 3% monocytes, 6% lymphocytes, 0.5% atypical lymphocytes); hemoglobin, 10.4 g/dl; platelets, 32.4×10^4/l. In addition, 1.5 erythroblasts per 100 white cells were counted on smears of the peripheral blood. Coagulation test revealed elevated fibrin degradation products and D-dimer. Lactate dehydrogenase (LDH) level and alkaline phosphatase (ALP) level was 1,028 IU/ml (normal: 85–253) and 965 IU/ml (normal: 104–338), respectively. LAP score was 130.0 (normal: 169.5–335.0). A bone marrow aspirate from the sternum showed myeloid hyperplasia without abnormal morphological appearance. Neither excess of blasts nor abnormal cells was found. Cytogenetic studies were normal karyotype and bcr/abl fusion transcript was not observed by reverse transcription-polymerase chain reaction. Diagnosis of a leukemoid reaction was established. In the absence of infection, a
search for an occult malignancy was mandatory. The serum level of prostate-specific antigen (PSA) was elevated to 330.2 ng/ml (normal: less than 4 ng/ml). A bone scintigraphy showed multiple uptakes, which suggested bone metastases. A bone marrow aspiration and biopsy from the posterior iliac crest showed bone marrow necrosis (Fig. 1) and invasion by a small round tumor, positive for PSA staining, respectively (Fig. 2). On the basis of these clinical and pathological findings, we diagnosed the case as metastatic bone marrow tumor with bone marrow necrosis from primary prostate cancer. To examine the cause of leukocytosis, multiple cytokine levels in serum were measured. The serum concentrations of cytokines, including interleukin (IL)-1α, IL-1β, IL-3, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony-stimulating factor (GM-CSF), were unremarkable. In contrast, the serum concentrations of IL-6 and tumor necrosis factor (TNF)-α were elevated to 65.0 pg/ml (normal level, 8.0 pg/ml) and, 54.0 pg/ml (normal level, 5.0 pg/ml), respectively. Antiandrogenic therapy with oral chlormadinone acetate following subcutaneous injection of goserelin acetate as luteinizing hormone releasing hormone (LH-RH) analogue was started. The clinical course is shown in Fig. 3. After the above hormone therapies were administered, he was afebrile and progressed favorably. Leukocyte count of peripheral blood and PSA level declined to the normal range immediately and remained stable over the subsequent 4 months.

Discussion

Neutrophilia is frequently seen in large cell lung cancer (2), although it has been reported in association with a variety of tumors (3–7), particularly in the presence of marrow involvement (8, 9). The leukocytosis is usually modest, in the range of 12–30×10⁹/µl, although levels as high as 100×10⁹/µl have been reported (10). It is likely that such leukemoid reactions are mediated by tumor-related cytokines, including GM-CSF, IL-1α, IL-6 and G-CSF (11–14). Nevertheless, the fact that no detectable cytokines can be found in other cases suggests that carcinoma-related neutrophil leukocytosis may be induced by mechanisms other than those described above. Typically, tumor-associated leukemoid reactions reflect an aggressive underlying clinical course and both diagnoses are often established simultaneously (15).

Bone marrow necrosis is defined as the destruction of hematopoietic tissue and marrow stroma with preservation of bone (16, 17). Most frequently, it is caused by failure of bone marrow microcirculation. It is a complication in a wide...
spectrum of diseases, most frequently of malignancies, and is only rarely diagnosed ante mortem. Clinically, it is characterized by fever and bone pain usually located in the lower back. A leukoerythoblastic picture in peripheral blood, pancytopenia and increased levels of LDH and ALP are the most frequent laboratory signs. Bone marrow necrosis is a rare event and is associated mainly with a neoplastic process involving the bone marrow. Hematologic malignancies are the neoplasms most commonly related to bone marrow necrosis (18). As for non-hematologic malignancies, tumors of the stomach are the most often described, excluding tumors of unknown origin (19).

In the present case, the serum concentrations of IL-1α, IL-1β, IL-3, G-CSF, and GM-CSF, were unremarkable. In contrast, the serum concentrations of IL-6 and TNF-α were mildly elevated. TNF, a macrophage secretory protein produced by peripheral blood monocytes from patients with cancer, has been shown to possess cytotoxicity toward tumor cells in vitro (20). The correlation between bone marrow necrosis in patients with cancer and TNF in plasma has been reported (21, 22). On the other hand, it was reported that IL-6 caused leukocytosis related to several malignancies. Leukocytosis is considered the result of elevated IL-6 in connection with parathyroid hormone-related protein secreted primary tumor or with necrotic tissue involved tumor cells (23). It is probable that these humoral factors were partially responsible for the paraneoplastic syndromes induced by the prostate cancer with bone marrow metastasis in the present case.

Assay of LAP is used to differentiate CML from neutrophilic reactions as seen in other myeloproliferative disorders or in infection. Abnormally low LAP scores are preferentially seen in CML and paroxysmal nocturnal hemoglobinuria (24). The reason why the LAP score was decreased in our patient is unclear. In patients with CML, it is regarded that the low LAP activity reflects incomplete maturation of granulocytes, which is related to serum G-CSF levels (25). A negative feedback mechanism exists between peripheral neutrophils and serum G-CSF levels in the chronic phase of CML, and that low levels of G-CSF in the chronic phase of CML might be an important factor in the low LAP score (26). In accordance with this notion, the LAP activity in polymorphonuclear leukocytes from patients with CML is enhanced by the addition of G-CSF in vitro (27). Generally, the LAP activity in cancer patient is varied in the various disease states (28, 29). In the present patient, the low LAP score seems to be caused by the low level of serum G-CSF (14 pg/ml) in comparison with neutrophil counts as well as in CML. To our knowledge, this is the first case of leukemoid reaction with bone marrow necrosis in a patient with prostate cancer.

References


