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Leukemoid reaction in malignant bone tumor patients – a retrospective, single-institution study

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Abstract. – BACKGROUND: To the Authors' knowledge, the literature regarding leukemoid reaction in patients with malignant bone tumor is sparse, and most of patients with leukemoid reaction have poor prognosis.

AIM: To study the leukemoid reaction in malignant bone tumor patients.

MATERIALS AND METHODS: A total of 105 consecutive malignant bone tumor patients with a white blood cell count > 50,000/microL were retrospectively identified over a 4-years period (2007-2010). Those patients without a secondary cause of their leukocytosis were defined as having a paraneoplastic leukemoid reaction.

RESULTS: Three etiologies of the leukocytosis were found in those 105 patients: the major one was paraneoplastic leukemoid reaction which accounted for 56%; the second one was hematopoietic growth factors defect accounting for 30%; 14% patients were caused by infection and Tumor bone marrow involvement. The patients diagnosed with a paraneoplastic leukemoid reaction typically had neutrophil predominance (94.8%) and radiographic evidence of metastatic diseases (78%). They were clinically stable, but had a poor prognosis. 95% either died or were discharged to hospice within 12 weeks of their initial extreme leukocyte count. Both of the 2 (2%) patients who survived over 12 weeks received effective antineoplastic therapy.

CONCLUSIONS: Patients with typical paraneoplastic leukemoid reaction were clinically stable despite having large tumor burdens. However, clinical outcomes were poor unless receiving an effective antineoplastic treatment.

Key Words:
Leukocytosis, Leukemoid reaction, Malignant bone tumor.

Introduction

Leukocytosis exceeding 50,000/μL is referred to as a leukemoid reaction and is characterized by a significant increase in early neutrophil precursors in the peripheral blood. The differential count has a marked "left shift," evidenced by the presence of myelocytes and metamyelocytes, and increased numbers of band forms in the peripheral blood. Promyelocytes and myeloblasts may occasionally be found in peripheral blood in severe reactions. Proliferation of all the normal myeloid elements is observed in the bone marrow in leukemoid reactions, in contrast to acute leukemia, in which the immature elements predominate. It is reported that a leukemoid reaction is associated with a variety of infections, intoxications, malignant diseases, hemorrhage and sudden hemolysis[1]. Nevertheless, the exact mechanism of leukemoid reactions still remains unclear. A genetic defect or abnormal cytokine production has been suggested to be the potential cause of the extremely high leukocyte count[2]. Leukemoid reaction in malignant tumor patients has been associated with poor outcomes[3]. Nonclonally derived mature neutrophils usually drive the leukocytosis. To our knowledge, its frequency in patients with malignant bone tumor remains unclear, having been reported to range from 1% to 4% in small case series[4]. Paraneoplastic leukemoid reaction (PLR) remains a diagnosis of exclusion, because of the need to rule out secondary causes such as infections, newly developed hematologic malignancies, use of corticosteroids or hematopoietic growth factors, severe hemorrhage, and metastases to bone with necrosis.

To the best of nowadays knowledge, PLRs have been insufficiently characterized. Affected patients typically appear clinically stable despite having metastatic tumor or a large tumor burdens. Elevated serum cytokine levels have been reported in these patients, chiefly granulocyte-colony-stimulating factor (G-CSF)[5], although elevated serum levels of granulocyte-macrophage-colony-stimulating factor (GM-CSF), interleukin (IL)-1α, and IL-6 have also been measured[6]. Elevated serum levels of multiple cytokines have also been documented[7]. These cytokines may also promote tumor growth in a

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paracrine manner[8]. In addition, the transplantation of tumor cells into mouse models can induce neutrophilia driven by leukogenic cytokines produced by tumor cells[9]. However, there are reports in which no serum cytokines are found to be increased in patients with a PLR. PLRs typically occur late, usually a few weeks or months before death[10]. There are, however, a few case reports of patients achieving resolution of their leukocytosis with the initiation of effective antineoplastic therapy and surgery[6]. In this study, we reviewed our recent case load with leukemoid reaction in a large number of patients with malignant bone tumors.

Materials and Methods

Using the medical records of Shanghai tenth people's Hospital, we identified all the patients treated in our bone and soft tissue sarcoma Center who had a leukocyte count ≥ 50,000/μL from February 1, 2007 to October 1, 2010. If a patient had multiple high leukocyte counts, only their first high count was considered. After excluding all patients with a known pre-existing hematologic malignancy by bone marrow biopsy or puncture, we retrospectively collected vital signs and clinical data and made a determination of the etiology of the leukemoid reaction. A patient's leukocytosis was determined to be due to the use of CSFs if these agents had been used within the prior 10 days. Leukocytosis was attributed to infection when there was a positive culture from a normally sterile body site or a chest radiograph suggestive of pneumonia and clinical improvement along with reduction of leukocytosis as a response to appropriate antimicrobial therapy. A high leukocyte count was attributed to the use of high-dose corticosteroids and/or vasopressors if the patient had not recently received CSFs and had no radiographic or microbiologic evidence of infection and if the leukocytosis improved with tapering of the above-mentioned agents. All the remaining patients were defined as having PLRs. Tumor burden was indicated by diagnostic imaging, but we did not independently stage the different tumor types. Patient outcomes were dated starting from the first extreme WBC count.

Results

The etiology of leukemoid reaction includes tumor infiltration, infections, hematopoietic growth factors defect, intoxication, severe hemorrhage and hemopathy. Of them, hematopoietic growth factors defect could be caused by multiple factors, thus, we suggested it resulted from mixed factors. In our study, leukemoid reaction was identified in bone tumor cases of our Center, in which severe hemorrhage and intoxication were extremely rare. Therefore, in the 105 consecutive malignant bone tumor patients with a leukocyte count >50,000/μL, leukocytosis was attributed to three etiologies: PLRs in 59 (56%) patients, hematopoietic growth factors defect in 31 (30%) patients, and infection in 15 (14%) patients.

The PLRs progressed quickly, occurred within 3-6 months of tumor metastasis, and it would invade bone marrow, with higher white blood cell count (WBC > 80,000/μL). The short-term prognosis of the patients with a PLR was poor. Four (3%) patients were discharged to hospice and were lost to follow-up. Of the 58 patients for whom data were available, 55 patients died within 12 weeks. A 61-year-old woman died from lung metastasis from malignant fibrous histiocytoma of the distal femora 7 weeks after finding the leukemoid reaction (Figures 1 and 2). Of the 2 (2%) patients who survived over 12 weeks after their initial presentation, both had resolved leukocytosis after aggressive chemotherapeutic or surgical interventions (Table I).

The infection-associated leukemoid reaction progressed more quickly, and the white blood cell count increased one month after infection, with the total WBC > 50,000/μL. Of the 15 patients with documented infections, 8 were diagnosed with pneumonia (Table II). Bloodstream infections were documented in 3 patients. Two

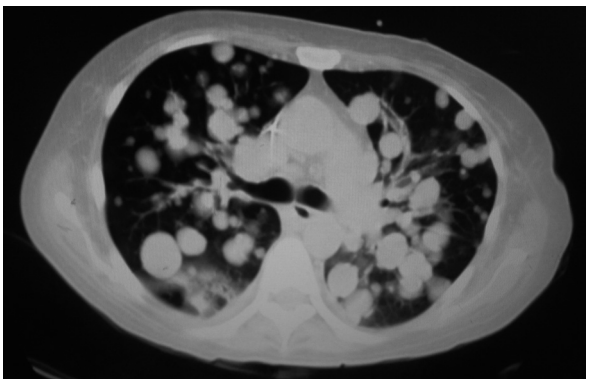

Figure 1. 61 year-old woman die from lung metastasis from malignant fibrous histiocytoma of the distal femora 7 weeks after finding the leukemoid reaction. Chest CT scan shows innumerable pulmonary nodules with "cannonball" morphology.

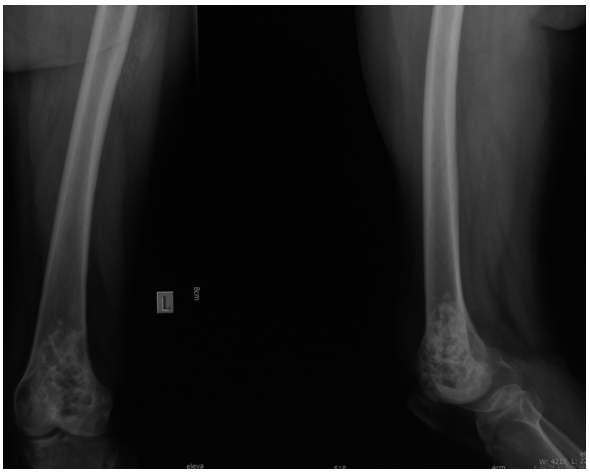

Figure 2. 61 year-old woman with malignant fibrous histiocytoma of the distal femora relapsed after surgery for 2 years.

patients were diagnosed with osteomyelitis and wound infections. Peritonitis and urinary tract infections were noted in 1 patient and 2 (3%) patients, respectively. Three patients presented with apparent septic shock, although their blood cultures were negative. Six patients had multiple sources of infection. The infectious agents were diverse, without one particular species or class of pathogens predominating. The infection-associated leukemoid reaction could gradually stabilize after anti-infection therapy. The number of leukocytes increased owing to infection, with the maximum value of 56.23-182.46×10^9 and mean value of 87.31×10^9, the ratio of neutrophile granulocytes in total leukocyte ranged from 87% to 95% (Table III).

Table I. Outcomes of leukemoid reaction in 105 patients.

Catalogue	Numbers (%)
Died ≤ 1 week	21 (20%)
Died 1 ≤ 4 weeks	26 (25%)
Died 4 ≤ 12 weeks	53 (50%)
Survived > 12 weeks	2 (2%)
Lost to follow-up	3 (3%)

Discussions

In our case load, 58 (55%) of the 105 malignant bone tumor patients with leukemoid reaction had a PLR. We probably underestimated the contribution of PLR to a patient's leukemoid reaction in that our mutually exclusive diagnostic definitions did not take the possibility of multiple etiologies into consideration. For example, patients might have a baseline tumor-associated leukocytosis in the range of 20,000/μL to 50,000/μL that was then increased into the extreme range (WBC >50,000/μL) by a subsequent infection and, therefore, would have been defined as having an infectious etiology. These patients were chronically but not acutely ill, had a neutrophilic predominance (perhaps because neu-

Table II. Demographics and clinical characteristics of leukemoid reaction in 105 patients.

Demographic and clinical characteristics	Result
Median age (range), y	56.3y (28y~67y)
Sex, male/female	59 (56%)/46 (44%)
Paraneoplastic leukemoid reaction (malignant bone tumor)	58 (56%)
Malignant fibrous histiocytoma	23 (21.6%)
Osteosarcoma	13 (12.3%)
Ewing's sarcoma	11 (10.4%)
Chondrosarcoma	11 (10.4%)
Hematopoietic growth factors defect	32 (30.4%)
Infection and tumor bone marrow involvement.	15 (14.3%)
Pneumonia infections	8 (7.6%)
Bloodstream infections	3 (2.8%)
Osteomyelitis and wound infections	2 (1.9%)
Other infections	2 (1.9%)
Tumor involving lung	74 (71%)
Tumor metastases	81.9 (78%)
Mean WBC at presentation (range), K/μL	72.0 (43.7-130.1)
Neutrophils > 65%, no. (%)	99 (94.8%)
Lymphocytes > 40%, no. (%)	3 (3.4%)
Monocytes > 10%, no. (%)	1 (0.9%)

Table III. The number of leukocyte caused by etiology of infection with leukemoid reaction (n=15).

Etiology of Infection	Maximum	Mean	Ratio[a]
Malignant fibrous histiocytoma	79.70-182.46 × 10^9	91.23 × 10^9	77%-96%
Osteosarcoma	78.23-121.46 × 10^9	89.32 × 10^9	79%-93%
Ewing's sarcoma	56.23-131.44 × 10^9	79.32 × 10^9	75%-91%
Chondrosarcoma	81.90-98.43 × 10^9	87.23 × 10^9	72%-87%

[a]Ratio means the number of neutrophile granulocyte taking up in total leukocyte.

trophils are the most responsive to a wider variety of cytokines), and had large tumor burdens[2]. Previous case series described PLRs only in patients with advanced stage malignant bone tumors[11], although there were isolated case reports of occult metastases to the bone marrow inducing a leukemoid reaction[12]. It has been suggested previously that tumor burden correlates with the degree of leukocytosis. The significance of the PLR patients having frequent tumor involvement of the lungs is unclear, although this may be simply a marker of large tumor burdens. In addition, the extensive epithelial linings of the lungs may make tumor involvement there more likely to produce G-CSF.

The clinical outcomes of most of the 58 patients with PLR were poor, with 45 (78%) patients either discharged to hospice or dying within 12 weeks of the first extreme leukocyte count, which is in agreement with previous studies. Exceptions did exist for the subset of these patients (2%) who had resolution of their leukocytosis and survived over 12 weeks after successful treatment of their tumors.

In conclusion, leukemoid reaction in patients with malignant bone tumor is infrequently due to infection. If the patient is clinically stable and has a large tumor burden, PLR should be considered. An effective antineoplastic treatment should be administrated, otherwise clinical outcomes would be poor.

Leukemoid reactions in advanced malignancy are usually myelocytic although eosinophilia, basophilia or monocytosis may also be seen. On the peripheral smear, orderly progressive granulocyte maturation is noted and there are usually no blasts or nucleated red cells. The leukemoid reaction is distinguished from chronic myelogenous leukemia by an inverse correlation between tumor response and leukocytosis, an increased leukocyte alkaline phosphatase (LAP), and generally, lack of thrombocytopenia. The mechanisms of cancer-associated leukemoid reactions are under study. There are various reports in the literature of elevations in GM-CSF, G-CSF, IL-3 or IL-6 in tumors of the nasopharynx, kidneys and bladder[6]. The identification of such factors may have prognostic as well as therapeutic implications.

The mechanism by which certain malignant fibrous histiocytomas produce G-CSF remians unclear. The expression of G-CSF has been suggested to have a corelation with the differentiation state of malignant fibrous histiocytoma cells.Some studies demonstrated GM-CSF was produced in poorly differentiated malignant fibrous histiocytomas at more immature stage. Moreover, paraneoplastic granulocytosis is often associated with rapid tumor growth and poor clinical prognosis and resolves with the treatment of underlying cancers. Paraneoplastic granulocytosis resolves each time after radical resections are performed. Therefore, patients present with unknown etiology of leukocytosis the possibility of tumor origin should be considered especially when infection is not likely[13].

To our knowledge, this is a relative large study of patients with malignant bone tumors with leukemoid reaction so far. The majority of cases (55%) had a PLR. Only a minority (14%) of the patients had an infectious etiology, predominantly pneumonia. Nearly 15% of patients had multiple sources of infection.

Granulocytosis can also be induced by tumor necrosis or glucocorticoid administration. None of these causes were identified in our patients. The other mechanisms causing cancer associated leukemoid reactions are due to cytokines, like G-CSF, GM-CSF or IL-6 in urine and serum that stimulate the proliferation of bone marrow cells in tumors of nasopharynx, kidneys and pancreas. In this case, tumor progression associated elevation in IL-6 and other inflammatory cytokines may result in leucocytosis. Paraneoplastic granulocytosis resolves with the treatment of underlying cancers.

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