Contents lists available at ScienceDirect

Acta Haematologica Polonica

journal homepage: www.elsevier.com/locate/achaem

Original research article/Praca oryginalna

Metastasis of solid tumors into bone marrow – Single center experience

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ARTICLE INFO

Article history:
Received: 15.06.2016
Accepted: 15.05.2017
Available online: 31.05.2017

Keywords:
- Bone marrow
- Solid tumor
- Hematological malignancy
- Metastasis

ABSTRACT

Introduction: Metastases of solid tumors to the bone marrow are rarely reported. Clinical manifestation and laboratory findings remain uncharacteristic and lead to misdiagnosis. Detection of bone marrow metastases may have an impact on therapeutic decisions and is usually associated with poor prognosis. **Aim:** To characterize clinical picture and hematological findings in patients with bone marrow metastasis. **Material and methods:** We retrospectively reviewed medical records of patients with bone marrow metastases who were primary misdiagnosed with hematological malignancies. **Results:** Ten patients at median age of 51 years at diagnosis were included. There were following findings on admission: duopenia ($n = 7$), pancytopenia ($n = 1$), anemia ($n = 1$) and skeletal lytic lesions ($n = 1$). The diagnosis of prior cancer was reported in 3 patients and included multiple myeloma, breast cancer and oligoastrocytoma. Clinical manifestations were hepatomegaly ($n = 4$), lymphadenopathy ($n = 4$), skin pallor ($n = 3$), cachexia ($n = 2$) and hemorrhagic diathesis ($n = 2$). Imaging studies revealed diffuse bone lesions ($n = 5$), pulmonary infiltrates ($n = 2$) and liver masses ($n = 2$). Leukoerythroblastosis was demonstrated in 4 cases. Bone marrow aspirate detected the presence of abnormal cell population in 4 patients. In all studied patients a final diagnosis was established by immunohistochemistry of bone marrow biopsy. The following malignancies were detected: prostate adenocarcinoma ($n = 2$), anaplastic microcellular carcinoma of unknown origin ($n = 2$), adenocarcinoma of unknown origin ($n = 2$), Ewing's sarcoma ($n = 1$), breast cancer ($n = 1$), clarocellular renal cancer ($n = 1$) and neuroendocrine tumor ($n = 1$). Nine out of the 10 metastatic patients died shortly after chemotherapy. **Conclusions:** Unexplained hematological abnormalities should arise the suspicion of bone marrow metastases.

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http://dx.doi.org/10.1016/j.achaem.2017.05.001

Introduction

Data on solid tumors metastasis into the bone marrow are scarce. Patients characteristics comes from small case series or single case reports [1–5]. Carcinomas of breast, prostate, lung and gastrointestinal tract in adult and Ewing's sarcoma and neuroblastoma in children are the most frequent neoplasms infiltrating the bone marrow [3]. Clinical manifestations and laboratory findings remain uncharacteristic and may mimic common myeloid or lymphoid malignancies and often lead to misdiagnosis. Detection of bone marrow metastasis may have an impact on therapeutic decisions and is usually associated with poor prognosis [6, 7]. It was found that bone marrow has unique environment rich in factors facilitating the growth of circulating tumor cells and cancer progression. However, the mechanisms of this process have not been completely defined and any risk factors associated with cancer metastasis into the bone marrow have been established so far [8–11].

Herein, we retrospectively investigated the clinical characteristics of ten adult patients with bone marrow metastasis of solid tumors.

Material and methods

We retrospectively analyzed medical records of patients with bone marrow metastasis who were suspected to have a hematological malignancy and were referred to our Department between years 2002–2014. Patients' medical records included clinical history, physical examination, laboratory and radiological findings. Moreover, the results of blood and bone marrow aspirates smears, histopathological examinations of trephine biopsies as well as their immunohistochemical (ICH) stainings were evaluated in details. The following set of antibodies was initially used to rule out the hematological malignancy on bone marrow aspirate ($n = 7$): CD14, CD34, CD36, CD45, CD64, CD117, IREM-2 and HLA-DR. After the final diagnosis of solid tumor metastasis had been established, these patients were referred to Oncology Unit for further evaluation. Their follow-up data were obtained after contacting the treating oncologist.

Results

Ten patients at median age of 51 years (range 26–75) at the time of first hospital admittance were included in this analysis. Female to male ratio was 1:1.5. There have been the following reasons of their referrals to hematology unit: bicytopenia ($n = 7$), pancytopenia ($n = 1$), anemia ($n = 1$), skeletal lytic lesions ($n = 1$). Three patients had prior history of neoplasm: (1) a 66-year old female was diagnosed with hormone-dependent breast cancer four years before and underwent right-side mastectomy followed by combination of chemotherapy (4 cycles of AC regimen: doxorubicin, cyclophosphamide), radiotherapy and hormones (detailed data on doses and treatment duration were not available), (2) a 44-year old female with non-secretory multiple myeloma received chemotherapy consisting of 4 cycles of CTD regimen (cyclophosphamide, dexamethasone thalidomide), 4 cycles of VTD (bortezomib, thalidomide, dexamethasone) and 1× VAD (vincristine, doxorubicin, dexamethasone) and finally (3) a 39-year old male patient with glioma mixtum oligosarcoma who underwent partial resection of his tumor and received radiotherapy (detailed information were not available) along with chemotherapy with PCV protocol (lomustine, procarbazine, vincristine). The remaining 7 patients had no prior cancer history.

The most frequent symptoms presented on admission were as follows: fatigue ($n = 7$) and bone/muscle pain ($n = 6$). Other symptoms included: loss of appetite ($n = 3$), fever ($n = 2$), weight loss ($n = 2$), dysphagia ($n = 2$), hemoptysis ($n = 2$), dizziness ($n = 1$), memory loss ($n = 1$) and nausea ($n = 1$). One patient remained asymptomatic.

Physical examination revealed hepatomegaly ($n = 4$), lymphadenopathy ($n = 4$), skin pallor ($n = 3$), cachexia ($n = 2$), and hemorrhagic diathesis ($n = 2$). Disseminated skeletal lytic lesions ($n = 5$), pulmonary infiltrates ($n = 2$) and liver masses ($n = 2$) were found on imaging studies. All but one patient had anemia and low platelet count was demonstrated in 7 patients. One patient was pancytopenic and no abnormalities on blood test were detected in one.

Peripheral blood smear showed leukoerythroblastosis in 4 cases and left shift was noted also in 4. A normal blood picture was demonstrated in 2 patients. None of the patients had circulating malignant cells. Bone marrow aspirate was successful in 7 patients. Among them 4 patients were found with abnormal cell population, 1 was detected with erythroid dysplasia and 3 patients had no significant abnormalities. Dry tap was present in the remaining 3 subjects. Bone marrow was hypocellular and normocellular in 6 and 4 patients, respectively. Reticulin fibrosis of grade 1–2 was found in the marrow of 4 subjects, but such data were missing for the remaining 6 patients. In all included patients a final diagnosis of solid tumor metastasis was established using a wide panel of immunohistochemical markers (CK, EMA, PAS, PAP, PSA, TTF1, RCC, vimentin, desmin and CD99) on bone marrow biopsies The following neoplasms were diagnosed: renal cancer ($n = 1$; Fig. 1), prostate cancer ($n = 2$; Fig. 2), anaplastic microcellular carcinoma of unknown origin ($n = 2$), adenocarcinoma of unknown origin ($n = 2$), Ewing's sarcoma ($n = 1$), breast cancer ($n = 1$) and anaplastic oligodendroglioma ($n = 1$). Nine out of the 10 patients died shortly after palliative chemotherapy had started.

Discussion

Cancer metastasis is the major cause of death in over 90% of patients with solid tumors [12]. Accordingly, detection of bone marrow metastasis is significant for clinical staging, prognosis and has an impact on therapeutic decisions. The metastatic process is multi-step cascade including local invasion and migration from primary tumor, intravasation into blood capillaries, survival in circulation, extravasation, colonization and proliferation in distant organs [9, 10]. The mechanisms of micrometastasis to the distal tissues are highly regulated and involve numerous intrinsic and

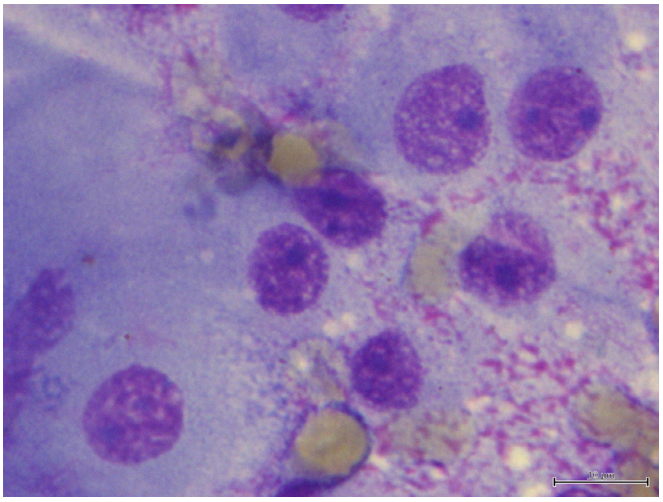

Fig. 1 – Clarocellular renal cancer cells in bone marrow

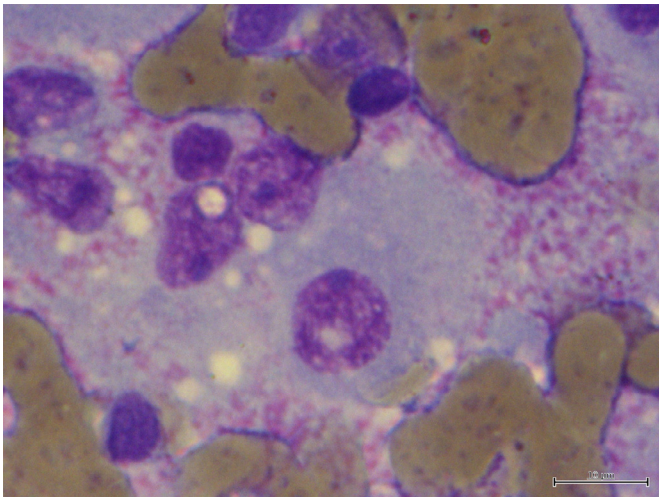

Fig. 2 – Prostate adenocarcinoma cells in bone marrow

extrinsic factors as well as signaling pathways [8–11]. The factors promoting marrow metastasis are poorly defined. However, this process can be explained by the unique marrow environment that is rich in adhesion molecules, cytokines, chemokines and growth factors [9–11, 13, 14]. Cytokines such as IL-6, IL-11, and TNF-α seem to contribute metastasis specifically to the bone and bone marrow. It has been stated that only 0.01% of disseminating tumor cells (DTCs) that enter the circulation will survive and proliferate at distant organs [8]. Factors that decrease the probability of survival of circulating tumor cells (CTCs) include mechanical shear stress, detachment-induced cell death and cell-mediated cytotoxicity. Inflammatory mediators released by cancer cells, physical interaction with leukocytes, endogenous factors present in blood may enhance the ability of CTCs to survive. The activated platelets and fibrin aggregates surrounding CTCs may protect them from NK cell-mediated lysis. Some of these factors and cytokines released into the tumor microenvironment depend on activation of NF-kappaβ and STAT3 and promote the survival of CTCs in circulation [8, 10, 11, 13].

The time needed for activation of DTCs in marrow and transformation into clinically presented macrometastasis is highly variable. There are no characteristic or specific clinical manifestations and laboratory findings which may suggest bone marrow involvement and usually this is present at the late stage of the neoplastic disorder. Bone marrow metastasis is usually accompanied by anemia, thrombocytopenia or both [1, 2, 5]. Anemia was the most common laboratory finding in our study and it was detected in 9 patients while thrombocytopenia was seen in 7. It is important to highlight that unexplained hematologic abnormalities or progressive cytopenia in cancer patients should arouse suspicion of bone marrow involvement. However, the peripheral blood results in patients with marrow metastasis usually remain unremarkable [1–3, 5]. Nevertheless, the detection of leukoerythroblastosis may be suggestive of marrow infiltration and should be further

investigated [2, 7]. Kopp et al. reported that the presence of erythroblasts in the blood smear is highly suggestive of bone marrow infiltration in breast cancer [1]. The current study noted leucoerythroblastic picture only in 4 cases. In our research, the CTCs were not found in blood smear. However, the examination did not encompass newer techniques allowing for detection of tumor cells in the peripheral blood. According to the literature, the detection of the DTCs in bone marrow is associated with the presence of minimal residual disease, clinical relapse or development of metastasis and may serve for follow-up after therapy [15–18]. In this study, abnormal cell population was seen in bone marrow aspirate in 4 patients whilst the trephine biopsy revealed the presence of tumor cells in all 10 cases. Positive results of trephine biopsy for tumor cells are frequently observed while the aspirate remains often negative [19–21]. Both techniques may serve for detection of bone marrow involvement. However, a final diagnosis is rarely based on bone marrow aspirates only and most frequent relies on the trephine biopsy examination confirmed by immunohistochemistry panel. Classically, trephine biopsy is decisive when there is an inability to obtain the sample of the marrow by aspiration. It should be mentioned that identification of marrow infiltration by cancer cells is sometimes difficult and may be overlooked. When the bone marrow metastasis is the first manifestation of cancer, the diagnosis is even more challenging for physicians. In some other cases, metastatic tumor in marrow may mimic hematological diseases and lead to misdiagnosis. The reason for this, among others, is that the bone marrow examination is not a routine procedure in cancer staging. Late cancer diagnosis reduces the chances for survival and makes treatment less likely to succeed. The coexistence of solid tumor and bone marrow metastasis is associated with deteriorating clinical course and poor prognosis. Bone marrow infiltration has an impact on overall survival 9 out of 10patients in this research died shortly after diagnosis, regardless of chemotherapy administered.

Conclusions

To conclude, no single clinical feature is considered to be predictive of bone marrow involvement in cancer patients. Unexplained hematological abnormalities in clinical practice, especially anemia and thrombocytopenia, should arise the suspicion of bone marrow metastases. Trephine biopsy confirmed by immunohistochemistry remains a gold standard in establishing the definitive diagnosis in bone marrow metastasis.

Authors' contributions/Wkład autorów

According to order.

Conflict of interest/Konflikt interesu

None declared.

Financial support/Finansowanie

None declared.

Ethics/Etyka

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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