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Two cases of extramedullary myeloid tumor in patients with continuous remission of acute myeloblastic leukemia

V. Slavcheva[1], Tz. Lukanov[2], N. Tzvetkov[1]
[1]Clinic of Hematology and [2]Laboratory of Immunology, University hospital, Pleven, Bulgaria

Summary

Myeloid sarcoma is described as tumor mass consisting of myeloblasts or immature myeloid cells, involving extramedullary tissues. It can be initial manifestation of myeloproliferative disorders or relapse of previously treated acute myeloblastic leukemia (AML).

We present two patients, one with AML-M2 and the other with acute promyelocytic leukemia (APL)-M3. After remission induced by conventional chemotherapy, which continued for 3 and 10 years respectively, a myeloid sarcoma was diagnosed. Biopsy of a retroauricular tumor formation was made in the first case. The second one was diagnozed after biopsy of a supraclavicular lymph node. In both cases complete laboratory investigation including blood smear, differential counting and flow cytometric analysis of bone marrow were normal. Despite this, the patients received chemotherapy. The APL-M3 patient was treated with radiotherapy to the involved supraclavicular lymph node which was followed by chemotherapy. Three months after radiotherapy bone marrow infiltration and blast cells in the peripheral blood were found. Two years after the diagnosis of myeloid sarcoma the patient died of haemorrhagic stroke. The patient with AML-M2 continued treatment with polychemotherapy.

Key words: genetic, leukemia, myeloid tumor, relapse, sarcoma

Introduction

Myeloid sarcoma, also known as extramedullary myeloid tumor, granulocytic sarcoma or chloroma, frequently involves subperiosteal bone structures of the skull, paranasal sinuses, sternum, ribs, vertebrae, lymph nodes, skin, mediastinum, small intestine and the central nervous system [1-6].

The term granulocytic sarcoma (GS) has been suggested in 1966 by Rappaport to describe extramedullary myeloid tumors consisting of early myeloid precursor cells [7]. In 1903 Turk reported the first case of myelocytic leukemia associated with chloroma and suggested that the tumor cells were the same as the leukemia cells [8].

GS is associated with every FAB cytologic subclass, but is seldom found with APL [7,9].

AML with maturation (FAB classification M2) is the most common morphologic type correlating with translocation (8;21)(q22;q22). Rarely, AML with this translocation shows a bone marrow blast percentage of < 20%. Myeloid sarcomas (chloromas) may be present and be associated with a bone marrow blast percentage of < 20% [9].

Case presentations

Case 1

A 34-year-old female with diagnosis of acute AML-M2 was admitted in May 2007 complaining of a progressively increasing retroauricular mass on the right, painful spontaneously and on palpation. Blood cell count was normal: Hb 13.2 g/ dl, RBC 3.14×10^{12}/l, WBC 6.9×10^{9}/l (segmented neutrophils 72%, monocytes 4%, lymphocytes 24%), and PLT 214×10^{9}/l.

The diagnosis of AML was established for the

Correspondence to: Vanya Slavcheva, MD. Clinic of Hematology, University hospital, 8 A "G. Kochev" blv, Pleven 5800, Bulgaria.
E-mail: slavcheva@abv.bg

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first time in June 2003, when she had symptoms of fatigue, weakness and fever. Antipyretic and antibiotic therapy proved ineffective and the patient consulted a hematologist. After diagnostic procedures including full blood count, bone marrow biopsy, flow cytometric and cytogenetic analysis, the diagnosis of AML–M2, t(8;21)(q22;q22) was established. After 3 induction courses (two courses with cytarabine, epirubicin and one with mitoxantrone and cytarabine), clinical and hematological remission was achieved, proved by flow cytometric analysis in September 2003. This was followed by consolidation therapy with higher doses of cytarabine and maintenance treatment (mitoxantrone plus cytarabine or cytarabine and epirubicin). Three years after remission (June 2006) before the last reinduction therapy, the disease relapsed in the bone marrow. Flow cytometric analysis of bone marrow showed: blast cells 67.5%, which expressed CD45(+); CD14(+low); CD64(+); CD11c(+); HLA-DR(+); CD34(-); CD15(+); CD11b(+); CD13(+); CD33(+); CD117(+) immunophenotypic markers indicative of acute monoblastic leukemia. Two courses with mitoxantrone, cytarabine and etoposide were administered, which induced disease remission till May 2007, when the patient was hospitalized for the above mentioned complaints.

On clinical examination, a swelling of semi-elastic consistency around the right retroauricular region was found. Otoscopy showed that the tumor was extending from the inner wall of the external auditory canal and was causing partial obstruction to the ear opening. A biopsy taken from the right retroauricular region showed a tumor with lustrious surface imitating fish meat. Histological examination showed massive infiltration of soft tissues by immature monotonous cells (most likely monoblasts) with round, oval and bean-shaped nuclei and regularly distributed chromatin. The whole picture was interpreted as acute monoblastic leukemia i.e. myeloid sarcoma (Figure 1). Further testing with trephine biopsy (which was inconclusive because of the low quality of the examined material) and molecular analysis (PCR) of bone marrow revealed t(8;21)/AML1–ETO(+) positive transcripts. Because of the insufficient quantity of the isolated RNA marker, the characterization of the investigated marker was inconclusive. Flow cytometric analysis was carried out and existence of blast cells in the bone marrow was not proved (Figure 2).

Twenty metaphase plates with aberrant clonal karyotype were analyzed using classical genetics analysis that found 45, XX, -21, der (8) t(8;21)(q22;q22) [2]/46,XX.

Treatment was started with etoposide and cytarabine in conventional doses. No response was seen after this course, so the patient was advised to have local radiotherapy. One month after the end of radiotherapy (total dose 26 Gy) reduction of the tumor mass was obtained, but both-sided cervical lymphadenopathy, leukocytosis, thrombocytopenia and presence of blast cells in the bone marrow (83%) appeared (Figure 3). Bone marrow immunophenotyping identified AML M0-M1. Chemotherapy was restarted.

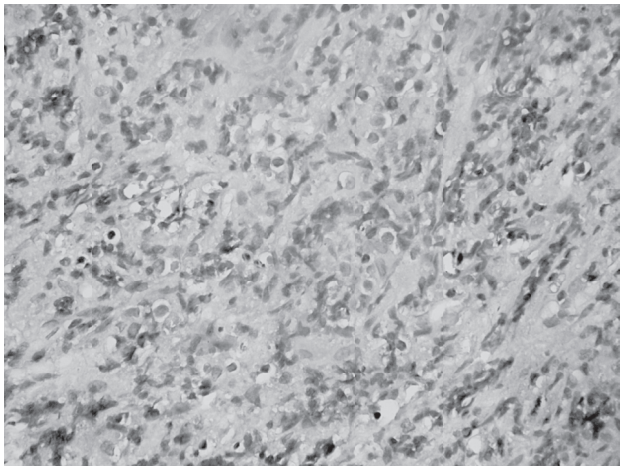

Figure 1. Soft tissue with diffuse infiltration of undifferentiated tumor cells (H&E ×100).

Case 2

A 47-year-old woman with APL (February 2006) came to the clinic complaining of permanent pain in the lumbosacral area, radiating to the right leg. She was first diagnozed with APL in January 1995 and because of pancytopenia on the blood film, bone marrow biopsy was done which showed hypoplastic bone marrow-about 90% of the cells had morphological characteristics of promyelocytes. Immunophenotypic analysis of the blast cells showed CD7(-); HLA-DR(-) 93%, CD15(+); CD13(+) 75%; CD11b(-) 78%; CD 34(-); CD33(+) 79%. In over 50% of the blasts the phenotype was as follows: CD45(+); CD34(-); CD14(-); CD15(+); CD11b(-); CD13(+); CD33(+); HLA-DR(-), characteristic of APL. Cytogenetic analysis was carried out but the material was not enough for interpretation. After two courses with tretinoin, epirubicin and cytarabine, in March 1995, disease re-evaluation was carried out by means of flow cytometric and cytogenetic analysis of bone marrow, which showed disease remission. The patient then received consolidation and maintenance therapy (tretinoin, epirubicin and cytarabine or tretinoin, mitoxantrone and cytarabine) monthly during the first year, every 2 months during the second year and every 3 months during the third year till March 1998. In

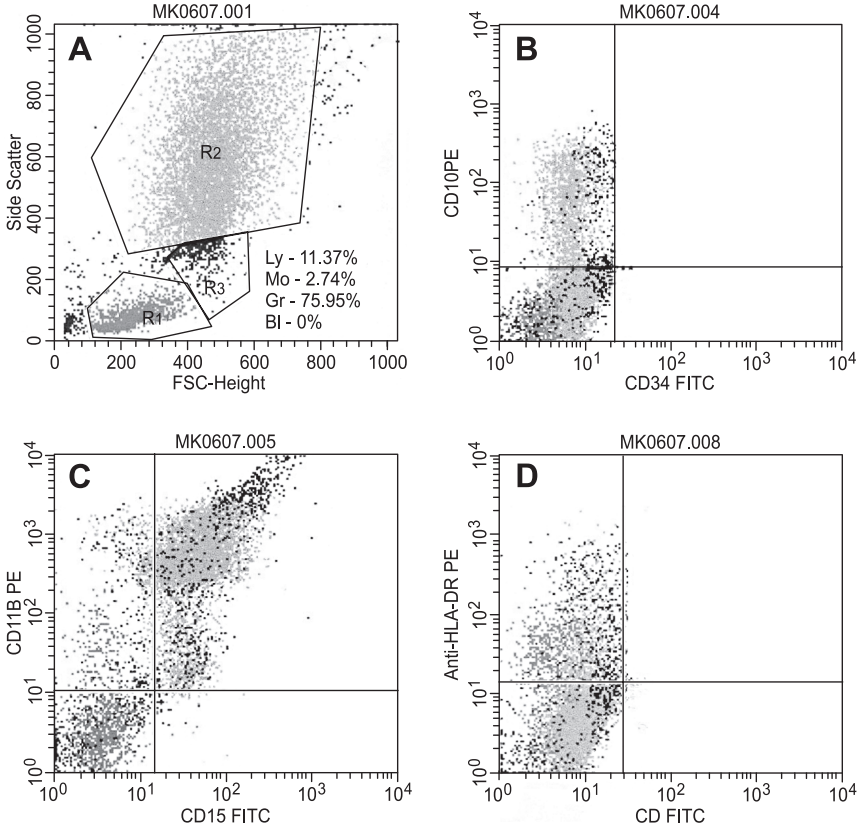

Figure 2. Flow cytometric analysis of bone marrow - May 2007.

A Forward light scatter (FSC)/Side light scatter dot plot picture with three gates set around lymphocytes (Ly) – R_1, monocytes (Mo) – R_2 and granulocytes (Gr) – R_3

B Fluorescence (Fl) 1/Fl2 dot plot presentation of bone marrow cells. The cells are $CD34^-$. No blast cells were found

C Fl1/Fl2 dot plot presentation of bone marrow cells. Monocytes and granulocytes are double-positive $CD15^+/CD11b^+$. No blast cells were found

D Fl1/Fl2 dot plot presentation of bone marrow cells. The cells are HLA DR^-. No blast cells were found.

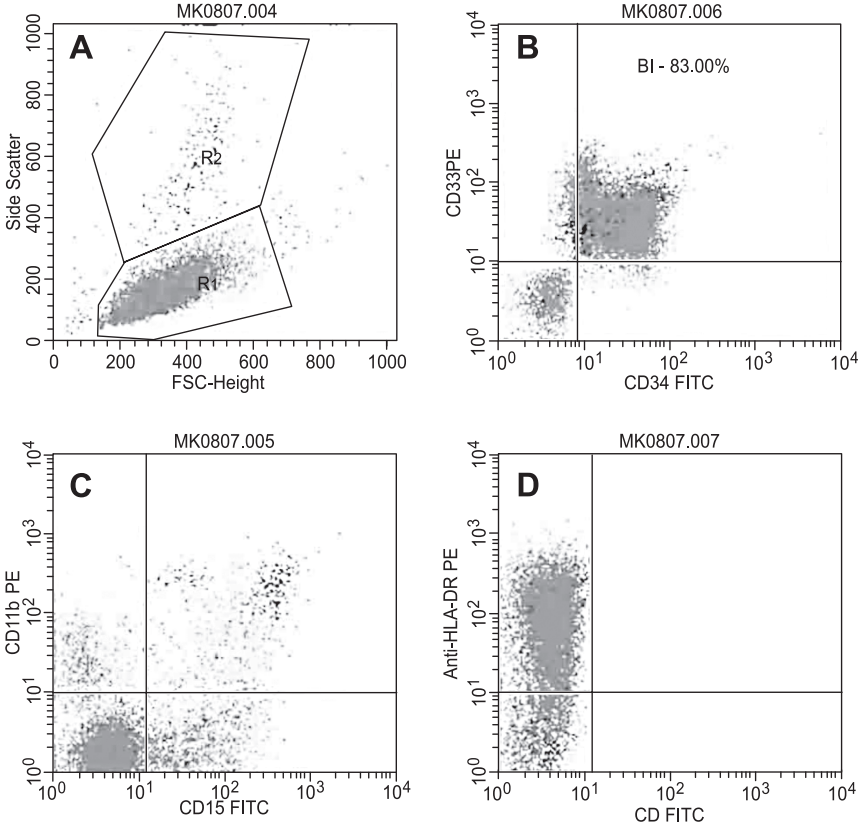

Figure 3. Flow cytometric analysis of bone marrow- August 2007.

A Forward light scatter (FSC)/Side light scatter dot plot picture with two gates set around blast cells – R_1 and granulocytes – R_2

B Fluorescence (Fl) 1/Fl2 dot plot presentation of bone marrow cells. The blast cells (83%) are double-positive $CD34^+/CD33^+$. Half of the blast cells are $CD34^+$ with a lower antigen density

C Fl1/Fl2 dot plot presentation of bone marrow cells. The blast cells are double-negative $CD15^-/CD11b^-$

D Fl1/Fl2 dot plot presentation of bone marrow cells. The blast cells are HLA DR^+.

The blast cells are also $MPO^+/CD13^+/CD38^+/CD4^+/CD117^-/CD10^-/CD14^-/CD64^-/CD11c^-$ (data not shown).

December 2004 a biopsy was taken from a newly found tumor in the right supraclavicular region. Histology showed a lymph node with diffuse infiltration of cells with more abundant, light and slightly eosinophilic cytoplasm and ovoid nuclei. The major cell component consisted of promyelocytes (Figure 4). In January 2005 a trephine biopsy showed no bone marrow involvement. However, PCR of bone marrow found the presence of t (15; 17)/PML-RAR α positive transcripts. Chemotherapy with tretinoin, epirubicin and cytarabine in conventional dosage was restarted. In August 2005 local radiotherapy (4 Gy) to the right supraclavicular region was delivered in 5 days because of non response to chemotherapy. Three months later repeat trephine biopsy detected the presence of diffuse proliferation of blast cells compatible with AML. The normal hemopoiesis was significantly reduced. Three induction courses with idarubicin and tretinoin; tretinoin, epirubicin and cytarabine; liposomal doxorubicin plus cytarabine were administered, followed by severe pancytopenia. Two years after the appearance of GS the patient died with clinical manifestation of haemorrhagic stroke.

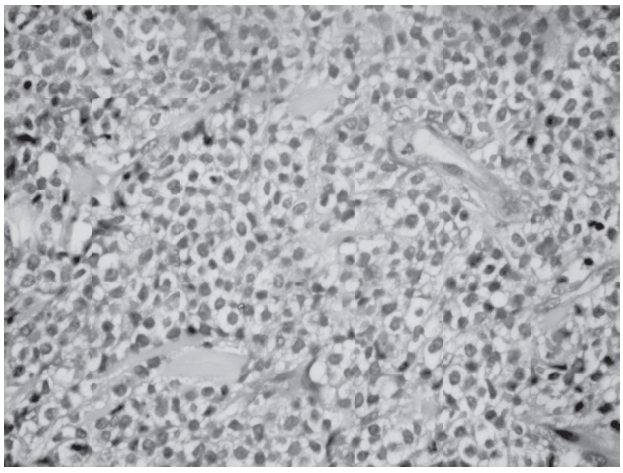

Figure 4. Diffuse infiltration of a lymph node from large cells with ovoid nuclei, immature chromatin and light cytoplasm into the lymph node (H&E ×100).

Discussion

The described cases are of interest because of the unusual manifestation of relapse of the disease, which some authors explain by the specific biological parameters of the blast cells- increased tissue invasion (CD 87) and adherence abilities (CD 138 and CD 54) [4]. In both cases, the flow cytometric analysis of bone marrow did not detect pathological clone at the time of extramedullary relapse. Molecular analysis only registered the presence of positive transcripts. A question arises whether this is minimal residual disease or remission of the disease.

According to the literature, adults with t (8; 21) AML have favorable prognosis and higher doses of cytarabine (HiDAC) as consolidation therapy improve survival [10]. In the first case bone marrow relapse was found 36 months after the diagnosis AML–M2. Eleven months later GS was proved. In both cases remission was achieved with local radiotherapy, followed by chemotherapy. At the end of radiotherapy appearance of blast cells in the bone marrow and blood was proved after one month in the first patient and after three months in the second case.

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