CASE REPORT

Therapy Related Acute Myeloid Leukemia with t(8;16) Mimicking Acute Promyelocytic Leukemia

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Abstract Acute myeloid leukemia (AML) with t(8;16)(p11;q13) is a distinct clinical and morphological entity with poor prognosis, which is characterized by a high frequency of extramedullary involvement, most commonly leukemia cutis; association with therapy related AML; frequent coagulopathy and morphologic features overlapping acute promyelocytic leukemia (APL). Herein, we present a case of 47 year-old post-menopausal woman developing secondary AML with t(8;16)(p11;q13) after 1 year of completion of therapy for breast carcinoma. Blasts were granulated with few showing clefted nucleus resembling promyelocytes and immunophenotyping showed high side scatter with MPO positivity and CD 34 and HLA-DR negativity. In view of promyelocyte like morphology and immunophenotyping of blasts, possibility of APL was considered but, reverse transcription polymerase chain reaction (RT-PCR) for PML-RAR α fusion transcript came out to be negative. Conventional cytogenetics showed t(8;16)(p11;q13). So, we should keep possibility of t(8;16) (p11;q13) in therapy related acute myeloid leukemia in patient showing clinical and morphological features of acute promyelocytic leukemia.

Keywords Therapy related AML · t(8;16) · Secondary AML

Introduction

The balanced translocation between the band 11 of the short arm of chromosome 8 and band 13 of the short arm of chromosome 16 [t(8;16)(p11;q13)] is a rare chromosomal abnormality detected in 0.5 % Acute myeloid leukemia (AML). AML with t(8;16)(p11;q13) is a distinct clinical and morphological entity with poor prognosis and characterized by a high frequency of extra-medullary involvement, most commonly leukemia cutis; frequent coagulopathy and morphologic features overlapping acute promyelocytic leukemia (APL). Translocation (8;16) AML blast cells mostly exhibit a myelomonocytic stage of differentiation and frequently associated with hemophagocytosis [1, 2]. It is more frequently presented in therapy related secondary AML than de novo AML [3]. Due to clinical presentation of coagulopathy and morphological features, it can be confused with APL. Herein, we present a case of 47 year-old post-menopausal woman developing secondary AML with t(8;16)(p11;q13) after 1 year of completion of therapy for breast carcinoma, presented with coagulopathy and showed morphologic and immunophenotypic features mimicking APL.

Case Report

A 47-year old post-menopausal woman diagnosed with right-sided breast cancer (T3N0M0), underwent modified radical mastectomy followed by radiotherapy and 6 cycles of adjuvant chemotherapy with FEC (5 Fluorouracil, Epirubicin and Cyclophosphamide). Histopathological examination of resected breast specimen revealed infiltrating ductal carcinoma which was ER+, PR+, HER 2/neu—on immunohistochemistry. Patient was put on oral Tamoxifen

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(20 mg daily). After 1 year of completion of chemotherapy, she developed cutaneous lesions over anterior abdominal wall and chest wall (Fig. 1a). On examination, she had pallor, multiple macular, papular and nodular lesions on neck, chest and abdomen. No lymphadenopathy, gum hypertrophy, organomegaly or ascites was noted. Haemoglobin was 49 g/L, total leukocyte count of $3.5 \times 10^9/\text{L}$, platelet counts of $6 \times 10^9/\text{L}$ and lactate dehydrogenase 2182 u/L. Peripheral blood smear and bone marrow aspiration showed 20 and 80 % myeloperoxidase positive

blasts, respectively. Blasts were granulated with few showing clefted nucleus resembling promyelocytes (Fig. 1b, c). On flowcytometric immunophenotyping, the blasts showed high side scatter with immunopositivity for cMPO, CD45, CD33, CD64, CD36, CD14, CD65, CD9, CD15, CD56, CD4, CD38; and negativity for HLADR, CD34, CD117, CD11b, CD19, CD7, CD2, cCD3 and cCD79a (Fig. 1e). Biopsy from skin lesion showed infiltration by blasts which were myeloperoxidase and leukocyte common antigen (LCA) positive. Conventional cytogenetics showed t(8;16)(p11;q13) (Fig. 1d). In view of promyelocyte like morphology of blasts and lack of expression of CD34 and HLADR, reverse transcription polymerase chain reaction (RT-PCR) for PML-RAR α fusion transcript was done which came out to be negative. Based on above findings, a diagnosis of acute myeloid leukemia with leukemia cutis was made. Echocardiography performed at baseline to rule out epirubicin toxicity, was within normal limits. The feature of coagulopathy in base line is due to low platelet count with deranged coagulation profile which was subsequently managed with platelet transfusion and fresh frozen plasma. After a final diagnosis, daunorubicin and cytosine arabinoside-based 3+7 induction chemotherapy was started. On day 18 of induction, the patient developed sepsis and fungal infection which lead to multi-organ failure, without evidence of disease. The patient succumbed on the same day to the above complications.

Fig. 1 a Cutaneous lesions over anterior abdominal wall and chest wall. b Bone marrow aspiration showing granular blasts, some of which have clefted nuclei (Jenner and Giemsa, $\times 100$) c Blast are myeloperoxidase positive. d Conventional cytogenetics showing t(8;16)(p11;q13) e Immunophenotyping of blasts showing high side scatter with cMPO, CD 45, CD64 and CD14 positivity and cCD3, CD34 and HLA-DR negativity

Discussion

AML with t(8;16)(p11;p13) is uncommon entity with a distinct clinical, morphological and immunophenotypic features [2]. A few cases of AML with t(8;16) and only 3 cases of prior breast cancer were described so far in the literature [4–6]. AML with t(8;16) defined by a unique gene expression signature and distinct clinical features, frequently associated with therapy-related AML, coagulation disorder, frequent extramedullary involvement and poor prognosis. Blasts exhibit a myelomonocytic differentiation and show frequent hemophagocytosis, mostly erythrophagocytosis. On immunophenotyping, blasts frequently express monocytic markers like CD14 and CD11b and show negativity for CD34 and CD117. Lack of CD34 expression suggests that the blasts have a relatively mature granulocytic phenotype [4, 7, 8]. In our case, blasts were granulated with high side scatter and immune-negative for CD34 and HLA-DR, all of which favour a diagnosis of APL. But in contrast to the characteristic APL immunophenotype, the blasts were positive for monocytic markers like CD14 and CD64 and negative for CD117. Translocation (8;16) is characterized by disruption and

fusion of MYST3(8p11) and CREBBP(16p13) gene. MYST3 encodes the monocytic leukemia zinc finger protein, a histone acetyltransferase of the MYST family that activate the AML1 transcription factor complex. CREBBP encodes the cAMP response element-binding protein CBP, another histone acetyltransferase. CREBBP modulates gene transcription by histone acetyltransferase activity and by binding to several proteins with central cell-cycle functions [1]. The exact molecular pathogenesis of this AML subtype has not yet been defined, but this fusion protein has been suggested to play a role. The outcome of patients with t-AML compared with that of de novo AML has been historically poor, with a higher frequency of poor-risk cytogenetics and shorter survival times. AML with t(8;16) is further associated with very poor survival [4].

In conclusion, AML with t(8;16) is a distinct clinicopathological entity which may mimic APL and therefore, immunophenotyping and cytogenetic study is required for a definitive diagnosis. As it is associated with poor outcome, MYST3-CREBBP fusion gene should be evaluated further to yield new effective therapies specific to this subtype that may improve survival.

Informed Consent Informed consent was obtained from the patient.

Conflict of Interest All the authors declared that they have no conflict of interest.

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