Clinical characteristics and laboratory analyses of acute myeloid leukemia with t(16;21)(p11;q22)

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Abstract. The present study reviewed three patients with acute myeloid leukemia (AML) who had the specific genetic abnormality t(16;21)(p11;q22). To investigate the clinical and laboratory characteristics of AML with t(16;21)(p11;q22) translocation, the similarities and differences of clinical characteristics and laboratory examinations were compared, and a literature review was conducted. According to the French-American-British classification system, patient 1 was M4, patient 2 was M1 and patient 3 was M2. The cytogenetic aberrations were 46, XY, t(16;21)(p11;q22); 47, idem, +21 for patient 1 and 46, XX, t(16;21)(p11;q22) for patients 2 and 3. Cytophagocytosis and cluster of differentiation 56 antigen expression were found in all three cases. The prognosis was poor in all the cases. AML with t(16;21)(p11;q22) is a specific subtype of AML that exhibits unique characteristics of morphology, immunology, cytogenetics and clinical features, as well as a poor prognosis. Stem cell transplantation may be the first and only choice for treatment.

Introduction

Acute myeloid leukemia (AML) is a type of hematologic malignancy. The peak age of onset is >60 years old (1). AML is frequently accompanied by specific cytogenetic aberrations. t(16;21) (p11;q22) is a rare and non-random chromosomal translocation that causes the rearrangement of erythroblast transformation specific-related gene (ERG) on chromosome 21 and translocated in sarcoma/fused in sarcoma (TLS/FUS) on chromosome 16, forming the TLS/FUS-ERG fusion gene. t(16;21) (p11;q22) occurs with an incidence of 1% in AML (2). The morphology, immunology and clinical manifestation of this translocation are distinct from other subtypes of AML. Literature associated with t(16;21) (p11;q22) AML is scarce. The present study reports three patients with AML and t(16;21) (p11;q22) who exhibited unique characteristics compared with other subtypes of AML. Written informed consent was obtained from the family of the patient.

Case report

Patient 1. Patient 1 was a 17-year-old male. Three weeks prior to presentation, the patient exhibited a fever of unknown origin with a peak temperature of 38.5°C. The patient did not exhibit chest tightness, chest pain or a cough. He was administered antibiotics and dexamethasone in a local hospital, and his body temperature returned to normal. The patient was then transferred to the Shandong Provincial Hospital (Jinan, China) for further diagnosis and treatment. Peripheral blood count results showed a hemoglobin level of 77 g/l, a platelet (PLT) count of 14x10^9/l, and a white blood cell (WBC) count of 46.82x10^9/l (10.5% segmented neutrophils, 12% lymphocytes and 77.5% leukemic blast cells). A physical examination revealed an anemic appearance, no skin or mucosal bleeding, no pain at the bottom of the sternum, normal heart and lung exams and no hepatosplenomegaly.

Bone marrow aspirate was stained by Wright-Giemsa stain (Sigma-Aldrich, St. Louis, MO, USA), and showed a hypercellular marrow with 77.5% leukemic blast cells. Hemophagocytosis and vacuolation were observed in the leukemic cells (Fig. 1). Phagocytosed blood cells included WBCs, red blood cells and PLTs. Cytochemical staining of leukemic blast cells included peroxidase, naphthol AS-D chloroacetate esterase and periodic acid-schiff reaction staining (all obtained from Zhuhai Baso Biological Technology Co., Ltd., Zhuhai, China). Morphology and cytochemical staining of leukemic cells are shown in Table I. Blasts were detected using flow cytometry (BD Biosciences, San Jose, CA, USA) for the antigens shown in Table II, including cluster of differentiation (CD)17, CD13, CD34, CD56, CD38, CD33, CD15, myeloperoxidase (MPO) and human leukocyte antigen-DR (HLA-DR) (all purchased from BD Biosciences). Antigens CD19, CD10, CD20, CD7, CD11b, CD64, CD3 and CD138 were all negative (data not shown). Under the French-American-British (FAB) classification system, patient 1 was AML-M4. Bone marrow cells were incubated with RPMI 1640 medium (Biosource International, Inc., Camarillo,
CA, USA) containing 10% heat-inactivated fetal bovine serum for 24 h and chromosomes were analyzed using the Wright-Giemsa stain. VideoTest-Karyo3.1 Chromosome Analysis system (VideoTest, Petersburg, Russia) was used to analyze the karyogram. The karyotypes were described according to the International System for Human Cytogenetic Nomenclature 2009 (3). Patient 1 was 46,XY,t(16;21)(p11;q22)(16)/47, idem,+21(4) (Fig. 2A). Bio-Rad CFX96 fluorescent quantitative polymerase chain reaction (PCR) system (Bio-Rad Laboratories, Hercules, CA, USA) and reverse-transcription PCR kit [Tiangen Biotech (Beijing) Co., Ltd., Beijing, China] were used for detection. The patient was negative for the following fusion genes: AML1-Eight-Twenty-One, promyelocytic leukemia-retinoic acid receptor α (long, short, variant), core binding factor β-myosin 11A, E2A-pre-B-cell leukemia homeobox 1, breakpoint cluster region-Abelson murine leukemia viral oncogene homolog 1 (P210, P190), translocation ets-like gene-AML1, SCL interrupting locus-transcription-activator-like 1, and mixed lineage leukemia-AF4. The TLS/FUS-ERG fusion gene was positive.

Patient 1 was treated with DA (administration of 40 mg daunorubicin once a day between days 1 and 3 and 150 mg cytarabine once a day between days 1 and 7) for the first treatment cycle. The next two treatment cycles were administration of HA (3 mg homoharringtonine once a day between days 1 and 3 and 150 mg cytarabine once a day between days 1 and 7). The fourth treatment cycle was administration of 30 mg pirarubicin once a day between days 1 and 3 and 150 mg cytarabine once a day between days 1 and 7. The fifth and sixth treatment cycles were HA, subsequent to which the patient achieved complete remission. The seventh treatment cycle was administration of 100 mg etoposide VP16 once a day between days 1 and 5 and 150 mg cytarabine once a day between days 1 and 7. The eighth treatment cycle was medium cytarabine (administration of 1.0 g twice a day between days 1 and 7). The ninth treatment cycle occurred following admission to the hospital. Bone marrow aspirate showed 30.5% leukemic blast cells. The patient was considered to exhibit a recurrence and was treated with administration of 10 mg idarubicin hydrochloride once a day between days 1 and 3 and 150 mg cytarabine once a day between days 1 and 5). The patient received nine courses of chemotherapy and did not achieve complete molecular and hematological remission. The patient succumbed after 2 years.

Patient 2. Patient 2 was a 10-year-old female who presented with a recurrent fever that lasted >2 weeks and leg pain that lasted 10 days. Two weeks previously, the patient appeared pale and exhibited a fever and a non-productive cough with no evident cause. She did not exhibit nausea, vomiting, abdominal pain or diarrhea. The fever was resolved following drug treatment at a local clinic. A physical examination revealed an anemic appearance, diffuse petechiae and no superficial lymph node enlargement. Peripheral blood count results included a hemoglobin level of 40 g/l, a PLT count of 6x10⁹/l, and a WBC count of 55.59x10⁹/l [2.5% segmented neutrophils, 4% lymphocytes and 93.5% leukemic blast cells (shown in the hypercellular bone marrow aspirate)]. The cytochemical staining and immunological analysis were consistent with AML. The FAB classification M1 was established. Morphology and cytochemical staining of leukemic cells are shown in Table Ⅰ. Hemophagocytosis and vacuolation were observed in the leukemic cells (Fig. 1). Blast antigens are shown in Table II. The karyotype was 46,XX,t(16;21)(p11;q22)(20) (Fig. 2B). The TLS/FUS-ERG fusion gene was positive and the other genes were all negative. The patient received nine days of daunorubicin and etoposide chemotherapy and was in a critical condition from an infection, resulting in mortality after 1 month.

Patient 3. Patient 3 was a 54-year-old female who had a history of epilepsy of >20 years and was on scheduled antiepileptic medications. At 15 days prior to presentation, the patient ceased the use of the antiepileptic medications due to a sustained severe headache. The patient then exhibited weakness, and leg ecchymoses were found. Upon physical examination, the patient was revealed to have clear mental status, normal development, pallor, ecchymoses in the two lower limbs and no superficial lymph node enlargement. Peripheral blood count...
Results included a hemoglobin level of 86 g/l, PLT count of 46x10^9/l, and WBC count of 2.0x10^9/l [18% segmented neutrophils, 13% lymphocytes, 7% monocytes and 62% leukemic blast cells (shown in the hypercellular bone marrow aspirate)]. The cytochemical staining and immunological analysis were consistent with AML. FAB classification M2 was established. Morphology and cytochemical staining of leukemic cells are shown in Table I. Hemophagocytosis and vacuolation were observed in the leukemic cells (Fig. 1). Blast antigens are shown in Table II. The karyotype was 46,XX,t(16;21)(p11;q22) (Fig. 1C). The TLS/FUS-ERG fusion gene was positive and the other genes were all negative. The patient was treated with DA and cytarabine plus mitoxantrone, and subsequently received three courses of chemotherapy, without attaining remission. The patient survived for two years following the initial diagnosis

Discussion

t(16;21)(p11;q22) is a unique subtype of AML. For three patients reported previously, the age at diagnosis had a range of 1-81 years, with a median age of 26 years (1), and had a poor prognosis. t(16;21)(p11;q22) results in the chimeric transcript TLS/FUS-ERG (4). This translocation causes the replacement of the RNA-binding domain of FUS with the DNA-binding domain of ERG (5,6). This fusion gene is thought to be responsible for the leukemogenesis of AML harboring t(16;21) (7). Four transcripts found in AML with t(16;21) have been designated as types A, B, C and D, corresponding to the chimeric products of 255, 211, 179 and 349 bp, respectively. The t(16;21) translocation has been reported in different types of leukemia (5,7). FAB classifications M3, M2 and M5 are the most common, and M1 and M4 are the next most common. These classifications included chronic myeloid leukemia, acute lymphoblastic leukemia and myelodysplastic syndrome (7-10). This result indicates that t(16;21)(p11;q22) and the TLS/FUS-ERG chimeric transcript do not occur exclusively in AML (11).

Of the published karyotypes of AML with the TLS/FUS-ERG chimeric transcript, some were t(16;21)(p11;q22), while others had additional abnormalities, including +10, +12, +8, +6, -9, ins (7;2), del(9)(q13;q33), +der (21) and del(15)(q15;q15) (1). In the present report, the karyotype of patient 1 had +21 as an additional abnormality. This combination has not been reported in previous studies. The small chromosome 21, harboring ~300 genes, may be involved in numerous structural aberrations, including translocations, deletions and amplifications in leukemia and lymphoma. Genes located on chromosome 21 have been identified to play important roles in tumorigenesis (12). Trisomy 21 is the most common cytogenetic abnormality at birth and one of the most recurrent aneuploidies in leukemia (13). Constitutional +21 of Down’s syndrome is associated with increased risk for childhood leukemia (14). The elevated incidence of acute megakaryocytic leukemia in young children with +21 is estimated at ~500-fold (13,15).

Immunophenotyping results have been inconsistent for AML with t(16;21). Marosi et al (16) found that the leukemic cells expressed CD7, CD71, CD38, CD15, HLA-DR, CDw65, CD13, CD33 and CD42b (17); however, Nobbs et al (17) reported that the leukemic cells mainly expressed CD34, HLA-DR, CD7, CD13 and CD33, and did not express CD2, CD10, CD19, CD20, CD4 and terminal deoxynucleotidyl transferase. Tan et al (18) reported a 54-year-old man whose leukemic cells mainly expressed CD7, CD13, CD33, CD34, CD17, CD56, CD64, HLA-DR and cytoplasmic (c)MPO, with positive percentages of 89.9, 53.5, 75.8, 96.7, 99.0, 41.4, 19.9, 98.4 and 97.5%, respectively, while CD11b, CD14, CD15, CD19, CD3, CD45e and CD79a were not expressed (19). In the present three cases, the leukemic blast cells all highly expressed CD7, CD13, CD34, CD19, CD20, CD4 and terminal deoxynucleotidyl transferase. Tan et al (18) reported a 54-year-old man whose leukemic cells mainly expressed CD7, CD13, CD33, CD34, CD17, CD56, CD64, HLA-DR and cytoplasmic (c)MPO, with positive percentages of 89.9, 53.5, 75.8, 96.7, 99.0, 41.4, 19.9, 98.4 and 97.5%, respectively, while CD11b, CD14, CD15, CD19, CD3, CD45e and CD79a were not expressed (19). In the present three cases, the leukemic blast cells all highly expressed CD7, CD13, CD34,
Figure 2. Karyograms of patients using Giemsa banding (stain, Wright-Giemsa). (A) Patient 1: 46,XY,t(16;21)(p11;q22)(16)/47,XY,t(16;21)(p11;q22),+21(4).
(B) Patient 2: 46,XX,t(16;21)(p11;q22)(20). (C) Patient 3: 46,XX,t(16;21)(p11;q22)(20).
CD56 and CD38. Additionally, patient 1 expressed HLA-DR and cMPO; patient 2 expressed CD33 and CD15; and patient 3 expressed CD33, CD15 and HLA-DR. This indicates that the blast cells of AML with t(16;21) originate from an earlier stage of myeloid cell differentiation. Granulocytes, mononuclear cells, megakaryocytes and red blood cells may be involved.

Jekarl et al (2) reported that the average percentage of CD56 positive blasts in AML with t(16;21) was 45%. Imashuku et al (9) suggested that the morphology of bone marrow aspirate of patients with AML and t(16;21) was unique. Leukemic cells phagocyte WBCs, red blood cells, PLTs and other leukemic cells. The cytoplasts of leukemic cells have pseudopodia and one or more, occasionally alveolate-like, vacuoles. Increased eosinophilia was observed in the bone marrow or peripheral blood of certain patients, but Auer rods were uncommon. Hemophagocytosis and vacuolation are closely associated with the CD56 expression of blast cells (9). In the present cases, hemophagocytosis and vacuolation of the blast cells were typical, Auer rods were not observed and eosinophilia was absent. These findings were consistent with the reports of Imashuku et al (9), but not with that of Wu et al, who reported that the other five patients in China did not exhibit the aforementioned characteristics (19). Therefore, it has been suggested that heterogeneity exists in the bone marrow aspirate morphology of patients with AML and t(16;21).

The progression of AML is faster in patients with t(16;21)(p11;q22) than in patients with other subtypes of AML. With conventional chemotherapy, complete remission is difficult to achieve, and the duration of remission is short. Early relapse is common, and the median survival time is 16 months (7). Therefore, t(16;21)(p11;q22) can be used as an independent marker for poor prognosis (19). In the present case report, Patient 1 succumbed after 2 years, Patient 2 succumbed after 1 month, and Patient 3 did not sustain remission despite three courses of chemotherapy. Therefore, the treatment results were not adequate compared with conventional chemotherapy regimens, and hematopoietic stem cell transplantation should be performed (7).

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References


