

동종골수이식 후 재발한 급성골수성백혈병에서 항암화학요법으로 장기간 관해가 지속된 1예

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A Case of Long-term Complete Remission Following Chemotherapy in Acute Myelogenous Leukemia Relapsed after Allogeneic Bone Marrow Transplantation

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Abstract

Disease recurrence following successful bone marrow transplantation (BMT) remains a major impediment in the management of patients with acute myelogenous leukemia (AML). Approaches to treat patients in relapse after allogeneic BMT including rapid tapering of immunosuppressive agents, donor lymphocyte infusion (DLI), second BMT, immunotherapy, and reinduction chemotherapy can be considered as treat modalities.

We report a case of AML M2 in relapse 35 months involving testis and bone marrow after sibling allogeneic BMT. Second remission was achieved with one cycle of reinduction chemotherapy using cytarabine, 100 mg/m² for 7 days and idarubicin, 12 mg/m² for 3 days.

Annual bone marrow study confirmed sustained complete chimeric status and molecular remission by fluorescence in situ hybridization (FISH) and AML1/ETO RT-PCR. The patient has remained in complete response (CR) with good performance status for 66 months after reinduction chemotherapy.

Key Words: AML, Sibling Allogeneic BMT, Relapse, Reinduction, Chemotherapy

INTRODUCTION

Approaches to treat patients in relapse after allogeneic BMT include rapid tapering of immunosuppressive agents, DLI, reinduction chemotherapy and secondary transplantation.¹⁾

Survival in patients with AML not receiving further treatment after relapse is approximately 3 months

compared to a mean survival of 12.3 months in patients treated with chemotherapy and achieving CR. The use of combination chemotherapy including cytosine arabinoside and anthracyclines can produce a higher CR rate (35-60%). Time to relapse from BMT seems to be the most reliable factor in predicting outcome after chemotherapy. In fact late relapsers have a greater chance to achieve CR than early relapsers.²⁾

Recent studies on DLI showed considerable effect on the patients with chronic myelogenous leukemia, but limited

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effect in the patients with AML.³⁾ Transplantation of hematopoietic stem cells is an increasingly important approach in the management of AML and immunotherapy is currently under investigation in relapsed AML.⁴⁾

We report a case of AML M2 in relapse after allogeneic BMT, presenting with testis and bone marrow involvement. The reinduction chemotherapy successfully induced CR, and the remission sustained with good performance status for 66 months after reinduction chemotherapy. To confirm the remission status, RT-PCR, FISH, and WT1 gene transcript monitoring were performed.

CASE

A 17-year-old male, suffering from fever, chilling, cough and general weakness lasting for 20 days, visited outpatient clinic in May 1995. The chest film appeared normal and there was mild hepatosplenomegaly on abdominal ultrasonography. Laboratory findings were as follows: white blood cell $8,470/\text{mm}^3$, hemoglobin 4.1 g/dL, and platelet $29,000/\text{mm}^3$. On peripheral blood smear, red blood cells were normocytic and normochromic, white blood cells were adequate in number with some blasts, and blasts have Auer rod in their cytoplasm. Immunophenotyping with bone marrow aspiration and biopsy material showed positive in CD13 (48.8%), HLA DR (61.5%), and 65% in overall cellularity. The patient was diagnosed as AML with maturation, AML-M2, but was unchecked with AML1/ETO RT-PCR.

In June 1995, he had an induction chemotherapy with cytarabine and daunorubicin. Cytarabine was administered as a continuous intravenous infusion, $100 \text{ mg}/\text{m}^2$ for 7 days and daunorubicin, $45 \text{ mg}/\text{m}^2$ intravenously on days 1 to 3, and first CR was achieved after one cycle of chemotherapy.

In October 1995, he was treated with HLA-matched, sex-mismatched sibling allogeneic BMT without clinically significant early or late complications. Follow-up chromosomal study showed normal female chromosome in

complete chimeric status (Fig. 1).

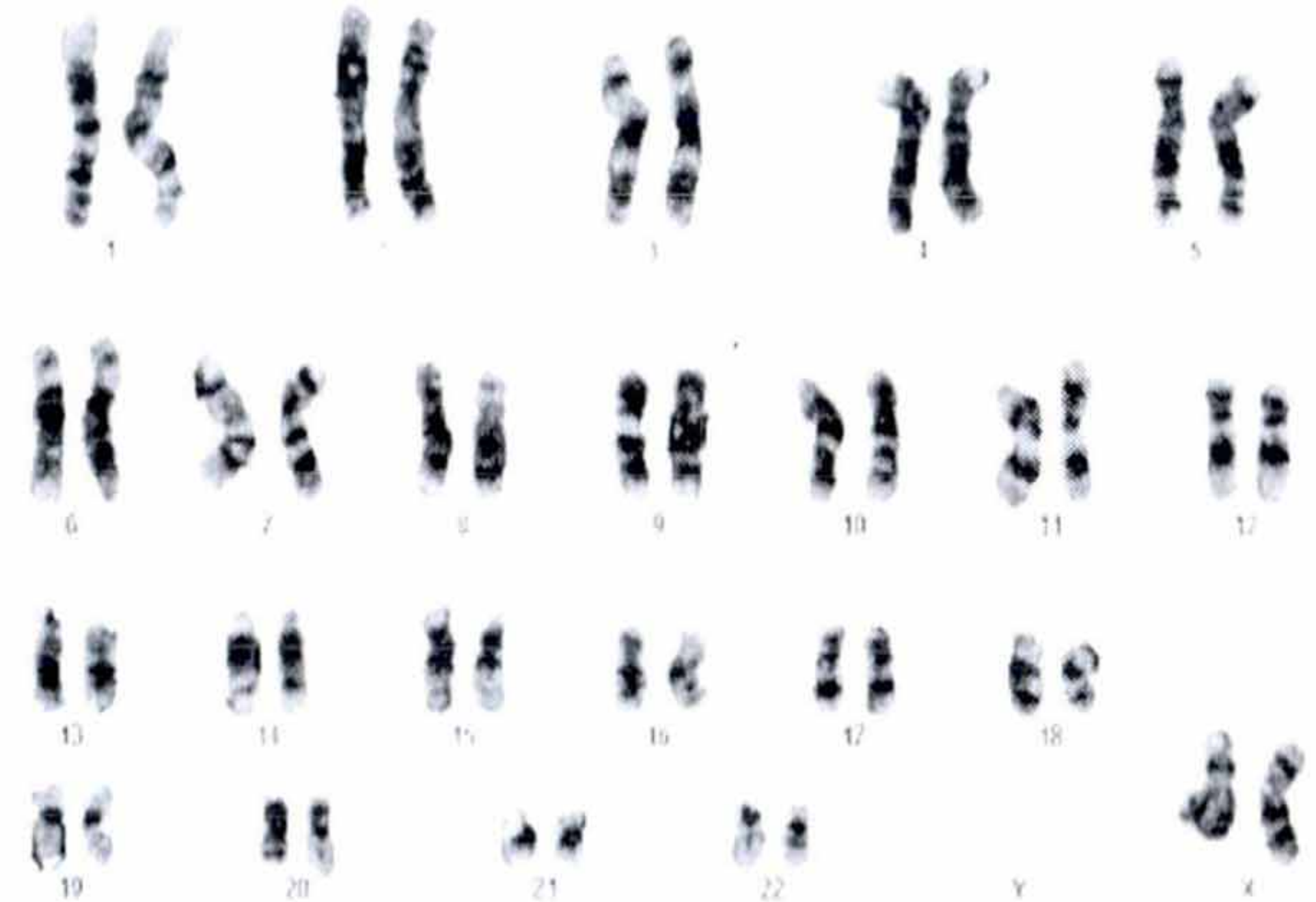


Fig. 1. Chromosome analysis with bone marrow aspirates in first remission showed a normal female chromosome with complete chimeric status.

In September 1998, testicular swelling was developed and the ultrasonography of the left side testis showed about $8 \times 7 \text{ mm}$ sized focal hypoechoic nodular lesion near the mediastinum testis, and about 11 mm sized hyperechoic nodular lesion and small amount of fluid collection with debris in the right side testis (Fig. 2).

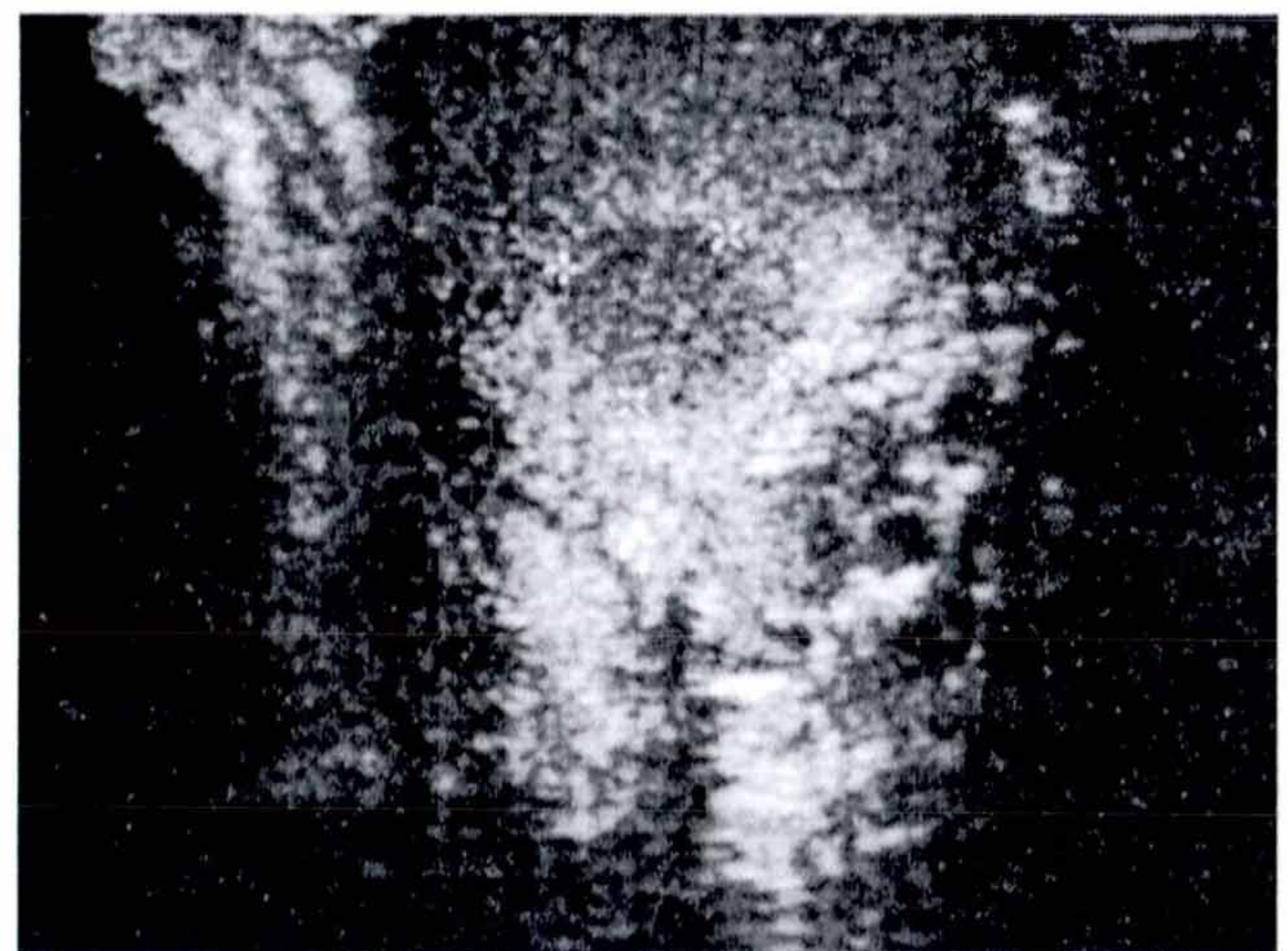


Fig. 2. Left side testis shows about $8 \times 7 \text{ mm}$ sized focal hypoechoic nodular lesion near the mediastinum testis.

Fine needle aspiration biopsy of the testis and bone marrow revealed relapsed AML-M2, and chromosome analysis showed $45,X,-Y,t(8;21)(q22;q22)$ (Fig. 3).

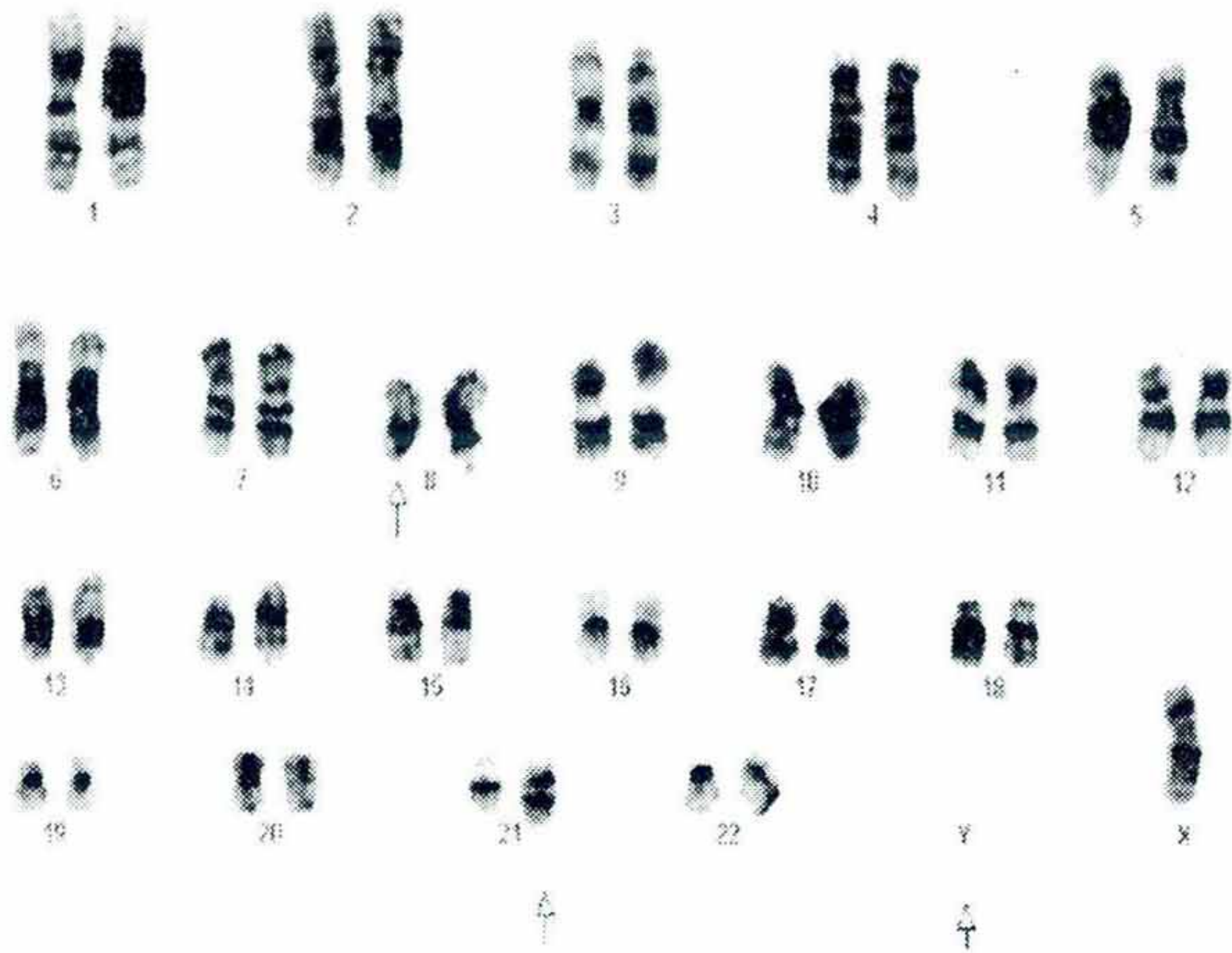


Fig. 3. Chromosome analysis with bone marrow aspirates in relapsed AML-M2 showed 45, X,-Y, t(8;21)(q22;q22).

Second remission was achieved with one cycle of reinduction chemotherapy using cytarabine 100 mg/m² for 7 days and idarubicin, 12 mg/m² for 3 days.

Annual bone marrow study confirmed sustained complete chimeric status and molecular remission by FISH (Fig. 4) and AML1/ETO RT-PCR. The patient has remained in CR with good performance status for 66 months after reinduction chemotherapy.

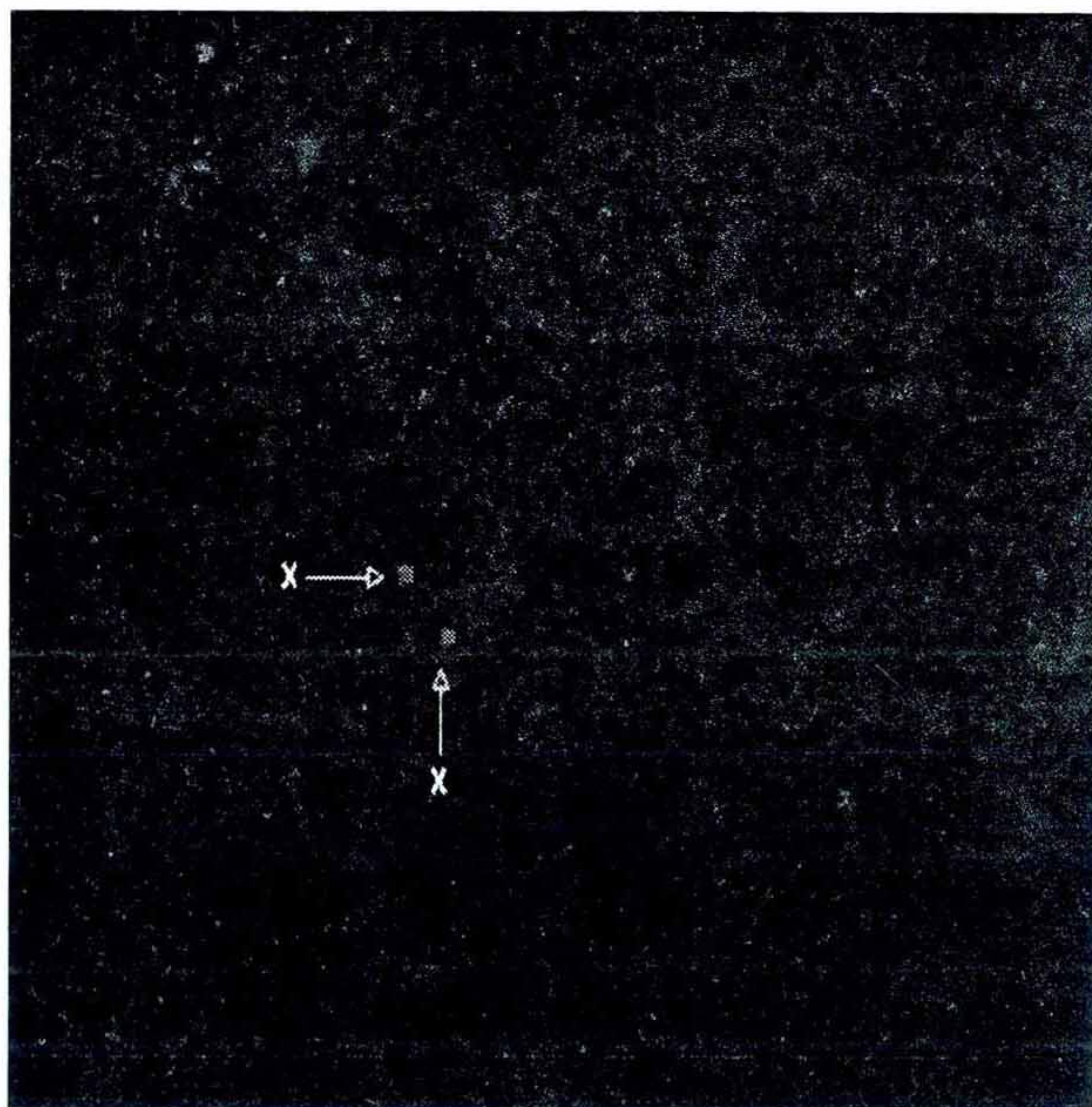


Fig. 4. FISH showed sustained complete chimeric status in second remission.

DISCUSSION

The most common remission induction regimen used for patients with AML is cytarabine given by continuous intravenous infusion for seven days plus daunorubicin daily for the first three days (the so called "7+3" regimen). Depending upon age and patient selection, 60 to 80 percent of patient achieved CR with this regimen.⁵⁾

BMT using an HLA identical sibling donor is an established post-remission treatment modality in acute leukemia. Long term disease-free survival in adult patients with AML who receive allogeneic BMT while in first CR is approximately 45 to 65 percent.^{6,7)} Relapse after BMT is predicted by the type of leukemia and remission status at the time of transplantation. The relapse rate for patients with AML transplanted in remission is 5% to 21% compared with 55% when transplanted is performed at relapse. The patterns of relapse in AML after BMT are similar to those following chemotherapy.⁸⁾

Optimal management of BMT recipients experiencing relapse is a controversial issue. The median survival of patients relapsing after an allogeneic BMT is only three to four months if no further therapy was given.⁹⁾ Once a patient relapsed, chemotherapy, DLI and second BMT can be considered as treat modalities.¹⁾ Subsequent results appear to be related to the length of the first CR and intensive reinduction therapy, and BMT for second CR are still associated with undoubted treatment-related mortality and morbidity despite improved modern supportive care procedures.⁹⁾

Concerning the use of chemotherapy for leukemia relapse after BMT there are some isolated reports on a small number of patients variously treated and not taking into account leukemia morphology, immunophenotype and cytogenetic abnormalities. Concerning these disparities some considerations can be made: survival in patients with AML not receiving further treatment after relapse is approximately 3 months compared to a mean survival of

12.3 months in patients treated with chemotherapy and achieving CR; the use of combination chemotherapy including cytarabine and anthracyclines can produce a higher CR rate (35-60%); time to relapse from BMT seems to be the most reliable factor in predicting outcome after treatment, using chemotherapy or after second BMT. In fact late relapsers (interval between BMT and relapse more than 9 months) have a greater chance to achieve CR than an early relapser. This is particularly true for patients relapsing within 100 days after BMT in which there is no possibility for further treatment.²⁾ Because these patients were heavily pretreated, chemotherapy for relapsed AML following BMT was not routinely administered. Salvage therapy for these patients may employ effective agents not used as initial induction or as part of the preparative regimen. In a review from the European group for blood and marrow transplantation (EBMT) survey data from 117 patients relapsed from allogeneic BMT were collected. Patients relapsing more than 1 year after BMT were more likely to achieve subsequent CR (46%). No data are available on the type of chemotherapy given.⁹⁾ Studies performed in Seattle confirmed the EBMT data showing a median disease-free survival of 9.7 months in patients with AML relapsed after BMT and submitted to chemotherapy.⁸⁾ An Italian study showed that the aggressive chemotherapy regimen including idarubicin and intermediate dose of cytarabine is well tolerated and can produce long-term survival in patients relapsed BMT provided that the interval between BMT and relapse is more than 9 months.¹⁰⁾ Our experience confirms the above mentioned observations. The patient was treated with aggressive chemotherapy with idarubicin and cytarabine which was very effective and well tolerated even in this heavily pretreated status.

The immune system plays an important role in the control of hematological malignancies. Reversal of the immunosuppression is sometimes sufficient to induce tumor regression. Discontinuation of immunosuppression followed by DLI induces remission in 20 to 35 percent of patients

who relapse after allogeneic BMT.³⁾ Graft versus leukemia (GVL) effects from DLI generally take several weeks to evolve, so it is possible that DLI works poorly in advanced myeloid malignancy, in part because rapid tumor growth rate outstrips the rate at which GVL effects can develop. If so, then debulking tumor with chemotherapy before DLI may be advantageous.

Second allograft offers a chance of long-term leukemia free survival in selected patients. Only a limited portion of patients are well enough for such intensive treatment, and the treatment related mortality is high (25 to 50 percent). The relapse rate is also high. Leukemia-free survivals at three to five years range from 11 to 42 percent.⁴⁾

Although remission induction in patients who relapse after transplantation may be difficult task, the newly developed target therapies provide promise for such patients. CD33 is an attractive antigen to use as a target for treating AML because it is present on most AML cells. Naked antibodies are limited in their ability to kill tumor cells. Calicheamicin, a toxic drug moiety conjugated to anti-CD33 antibody, is currently under investigation in the patients with refractory or relapsed AML¹¹⁾ and also monoclonal antibody-mediated chemotherapy with gemtuzumab ozogamicin has been used for treating patients who relapse after an initial BMT before their second BMT.¹²⁾ Furthermore, small-molecule inhibitors are showing promise in treating patients with refractory relapsed AML.¹³⁾

Our patient had a characteristic sites of involvement, testis, an extramedullary site, in addition to bone marrow at the time of relapse after BMT. Isolated involvement of bone marrow and extranodal site can be seen in approximately 80% and 12.6% of cases, respectively, but mixed involvement of both bone marrow and extramedullary site can be seen in only 7.8% of cases. Testis involvement is especially rare, and is reported to be in 2.1% of cases.⁸⁾

Early recognition of relapse at the molecular level provides a window for therapeutic intervention while the

burden of disease is still relatively low. In acute leukemia, no method for the prediction of relapse following allogeneic BMT based on minimal residual disease levels is established yet. In our patient, annual bone marrow study by the FISH technique for molecular analysis confirmed sustained complete chimeric state, and it seems to provide a useful method for monitoring the disease recurrence. The Wilms tumor gene (WT1) assay is also very useful for the prediction and management of relapse following allogeneic BMT regardless of the presence of chimeric gene markers. WT1 was isolated as a gene responsible for Wilms tumor, a childhood kidney neoplasm, and categorized as a tumor suppressor gene. The WT1 gene is highly expressed in various types of leukemia (AML, acute lymphoid leukemia, and CML) and the expression of the WT1 gene is thus a tumor marker for leukemic blast cells of almost all leukemias. The WT1 expression level, measured by quantitative RT-PCR, significantly increases at relapse compared with that at the time of diagnosis.¹⁴⁾

In conclusion, chemotherapy can cure AML patient who relapsed in long-term first remission duration after allogeneic BMT. The overall survival in the patients achieving CR, excluding patients submitted to a secondary transplant, is encouraging and adds evidence for the role of aggressive chemotherapy in late relapse after BMT. Despite these results, a definitive cure should be considered as an exceptional event; at further relapse, treatment can be reinstituted and an objective response can be obtained but at the cost of excessive life-threatening toxicities and poor quality of life. Nonetheless this approach should be pursued in view of the fate of patients in whom no therapeutic attempt was available.²⁾

초 록

급성골수성백혈병에서 동종골수이식이 성공한 뒤에 생기는 재발은 치료에 있어서 장애요인이다. 동종골수이식 후 재발의 치료에는 면역억제제의 신속한 중단, 공여자 림프구 주입(donor lymphocyte infusion, DLI), 골수이식 재시술, 면역치료, 항암화학요법 재투여 등이 있다.

저자들은 동종골수이식 후 35개월에 골수 및 양측 고환에 재발한 M2 형 급성골수성백혈병 환자를 cytarabine (100 mg/m² 7일간)과 idarubicin(12 mg/m² 3일간)으로 1주기의 재관해 항암화학요법을 시행하여 성공적으로 관해를 유도했다.

이후 매년 시행한 골수의 광동소교잡법(FISH)에서 완전 키메라즘(chimerism), AML1/ETO RT-PCR에서 분자학적 관해를 보였다. 현재 환자는 재관해 항암화학요법 치료 후 66개월로서, 좋은 신체활동도와 완전관해를 유지하고 있다.

중심단어: 급성골수성백혈병, 동종골수이식, 재발, 재관해, 항암화학요법

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