

5q- IN A CASE OF CHRONIC MYELOGENOUS LEUKEMIA RELAPSED AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION

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ABSTRACT

Clonal chromosome and/or hematological abnormalities typically observed in myelodysplastic syndromes (MDS) have been described with increased frequency after autologous bone marrow transplantation (BMT) for lymphoma. We report the case of a woman with chronic myelogenous leukemia (CML) allografted with her HLA-identical sibling who, 5 years after the transplant and under immunosuppressive treatment for chronic graft host disease (GVHD), suffered a cytogenetic relapse associated with a 5q- deletion in the host metaphases. These findings suggest that myelodysplastic changes, possibly related to the chemo-radiotherapy conditioning regimen, may also present after allogeneic BMT.

Key words: bone marrow transplantation, chronic myelogenous leukemia, cytogenetics, myelodysplastic syndromes

Myelodysplastic syndromes (MDS) have been reported with increased frequency after autologous bone marrow transplantation (ABMT) for Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). The four largest series¹⁻⁴ reported an incidence from 3 to 7%, with a 5-year actuarial risk up to 14.5%. In addition, clonal karyotypic abnormalities have been reported in a large series of ABMT patients, half of whom subsequently developed MDS or acute leukemia.⁵ These studies highlight the leukemogenic potential of this treatment modality and pose the question of whether these MDS arise from previously damaged cells reinfused with the autograft, or from endogenous bone marrow cells further damaged by the conditioning regimen that persist after the transplant.

We report here a case in which the relative roles of chemo-radiotherapy preparative regimens and prior antineoplastic treatments are discussed.

Case report

The patient was a 29-year-old female with CML showing the standard t(9;22)(q34;q11) in 100 % of bone marrow metaphases; she was treated with hydroxyurea alone and allografted with her HLA-identical sister after a one-year chronic phase. She was conditioned with cyclophosphamide 60 mg/kg and total body irradiation 1000 cGray, and received conventional cyclosporine (CSA)-methotrexate graft-versus-host disease prophylaxis.⁶ The patient rapidly engrafted and remained in cytogenetic and molecular remission for 5 years. Ten months after CSA was discontinued the patient developed a fibro-retracting arthropathy of both hands and feet, and a diagnosis of eosinophilic fasciitis (Schulman's disease) was made on an ante-brachial fascia biopsy. The patient was initially treated with methylprednisolone and azathioprine (100 mg/day) and subsequently with azathioprine alone for 3 years with slow clinical improvement. At her last follow-up,

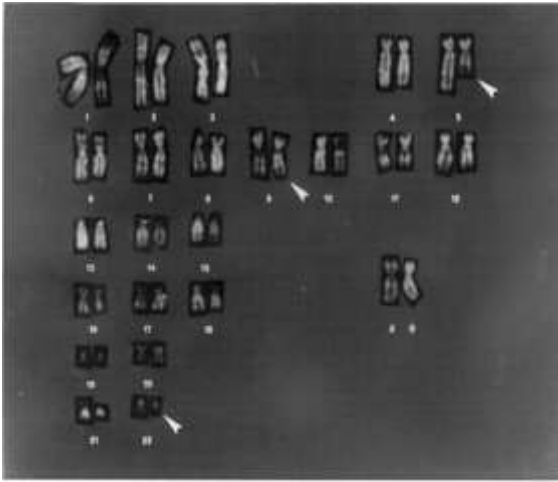


Figure 1. Karyotype of the patient using Q-bands. Arrows indicate the deletion of chromosome 5 and chromosomes 9 and 22 involved in the translocation

although the bone marrow was still in complete remission, there was evidence of a cytogenetic and molecular relapse (bcr-abl message with b3a2 junction by RT-PCR).

Chromosome studies were carried out in a 24-hr bone marrow culture by means of QFQ banding. A total of 160 metaphases were analyzed: seventy-five showed a normal karyotype; the t(9;22)(q34q11) was present in the remaining 85 metaphases, 49 of which showed a clonal evolution with an additional del(5)(q12q22) (Figure 1). An analysis of chromosome polymorphisms⁷ revealed the host origin of the Ph⁺ positive metaphases and the donor origin of the normal metaphases.

The patient was treated with alpha-interferon (α -IFN) at increasing doses for 6 months and then with hydroxyurea and α -IFN, but no change in her hematological picture has been noted. The patient is now under consideration for a second transplant.

Discussion

Clonal chromosome abnormalities other than t(9;22)(q34q11) have been described in large series of patients who relapsed after allogeneic bone marrow transplantation.^{8,9} However, the majority of these were in advanced phases of disease and generally showed complex karyo-

typic structural rearrangements; chromosome 5 and 7q deletions, commonly observed in therapy-related myelodysplastic syndromes,¹⁰ were very infrequent. On the other hand, 5q deletions have been described in only two cases of CML in blastic crisis,^{11,12} and the 5q- breakpoints were different from those identified in our case.

Clonal chromosomal abnormalities, whether associated or not with morphologically recognizable MDS, are a recently described but not uncommon complication of ABMT;¹⁻⁵ however, the relative contributions of pre-transplant treatments and ABMT conditioning regimens to the development of clonal hematopoietic alterations are difficult to establish in these patients. The presence of the 5q deletion, generally associated with MDS, suggests that this may also be a late complication of allogeneic BMT.¹³ The fact that this karyotypic abnormality is observed in Ph⁺ host metaphases further emphasizes the leukemogenic potential of the conditioning regimen *per se*. In fact, our patient's bone marrow cells were exposed to a short course of pre-transplant cytotoxic drugs (hydroxyurea) and to chronic post-transplant immunosuppression with azathioprine, which has been associated with the development of lymphoproliferative disorders, mainly non-Hodgkin's lymphomas,^{14,15} but whose mutagenic potential has not been clearly established.

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