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CASE REPORT

Dismal outcome of therapy-related myeloid neoplasm associated with complex aberrant karyotypes and monosomal karyotype: a case report

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Abstract

Introduction: Individuals who are exposed to cytotoxic agents are at risk of developing therapy-related myeloid neoplasms (t-MN). Cytogenetic findings of a neoplasm play an important role in stratifying patients into different risk groups and thus predict the response to treatment and overall survival. *Case report:* A 59-year-old man was diagnosed with acute promyelocytic leukaemia. Following this, he underwent all-trans retinoic acid (ATRA) based chemotherapy and achieved remission. Four years later, the disease relapsed and he was given idarubicin, mitoxantrone and ATRA followed by maintenance chemotherapy (ATRA, mercaptopurine and methotrexate). He achieved a second remission for the next 11 years. During a follow-up later, his full blood picture showed leucocytosis, anaemia and leucoerythroblastic picture. Bone marrow examination showed hypercellular marrow with trilineage dysplasia, 3% blasts but no abnormal promyelocyte. Fluorescence *in-situ* hybridisation (FISH) study of the PML/RARA gene was negative. Karyotyping result revealed complex abnormalities and monosomal karyotype (MK). A diagnosis of therapy-related myelodysplastic syndrome/myeloproliferative neoplasm with unfavourable karyotypes and MK was made. The disease progressed rapidly and transformed into therapy-related acute myeloid leukaemia in less than four months, complicated with severe pneumonia. Despite aggressive treatment with antibiotics and chemotherapy, the patient succumbed to the illness two weeks after the diagnosis. *Discussion and Conclusion*: Diagnosis of t-MN should be suspected in patients with a history of receiving cytotoxic agents. Karyotyping analysis is crucial for risk stratification as MK in addition to complex aberrant karyotypes predicts unfavourable outcome. Further studies are required to address the optimal management for patients with t-MN.

Keywords: therapy-related myeloid neoplasms, complex aberrant karyotypes, monosomal karyotype, acute myeloid leukaemia

INTRODUCTION

Therapy-related myeloid neoplasms (t-MN) is a disease that occurs as a complication in individuals previously exposed to cytotoxic agents and/or radiation for a neoplastic or non-neoplastic disorder. Under the current WHO 2008 classification, t-MN comprises therapy-related acute myeloid leukaemia (t-AML), therapy-related myelodysplastic syndrome (t-MDS) and therapy-related myelodysplastic syndrome/myeloproliferative neoplasms (t-MDS/MPN).[1] t-MN accounts for 10-20% cases of AML, MDS and MPN/MDS.[1] Patients at any age may be affected but the risk seems to increase with age when associated with radiation therapy or alkylating agent while the risk seems to be same across all ages when associated with topoisomerase II inhibitor.[1] Patients with t-MN usually have a shorter median survival when compared to patients with de novo AML, MDS, or MDS/MPN.[2] The incidence of t-MN in patients treated with cytotoxic agents differs depending

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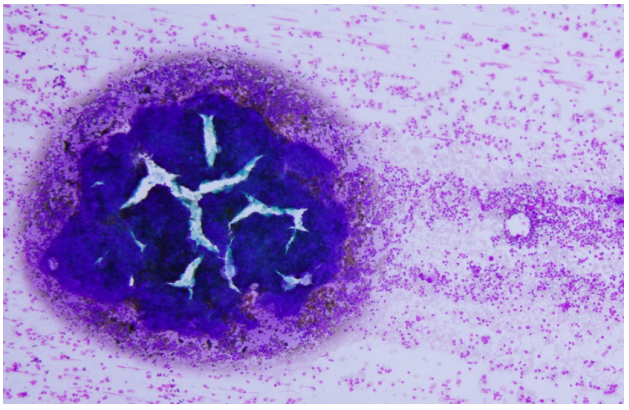

FIG. 1: Hypercellular marrow. (May-Grünwald-Giemsa (MGG) stain, x40)

on the primary disease, specific agents, timing of exposure, and dose.[3] t-MN is believed to be a result of mutational events caused by cytotoxic therapy/ radiation.

CASE REPORT

A 59-year-old man was diagnosed with acute promyelocytic leukaemia (APML). He underwent ATRA-based chemotherapy and achieved complete remission (CR). Four years later, the disease relapsed and he was treated with a regimen consisting of idarubicin, mitoxantrone and ATRA and successfully attained a second CR. He did not have a human leukocyte antigen (HLA)-matched donor for an allogeneic haemopoietic stem cell transplant. Therefore, he was put on maintenance chemotherapy consisting of ATRA, mercaptopurine and methotrexate for two years. He remained in CR for the next 11 years.

During a routine surveillance, the patient's full blood picture showed leucocytosis ($21.4x10^9$/L) with predominantly neutrophilia (absolute neutrophil count: $12.7x10^9$/L), anaemia (Hb 8.4g/dL), normal platelet count ($372x10^9$/L) and leucoerythroblastic picture. Bone marrow examination showed hypercellular marrow (Fig. 1) with trilineage dysplasia (Fig. 2), presence of 3% blasts but no abnormal promyelocyte. FISH study of PML/RARA gene was negative; thus excluding the diagnosis of relapsed APML. Karyotyping of bone marrow revealed complex abnormalities and

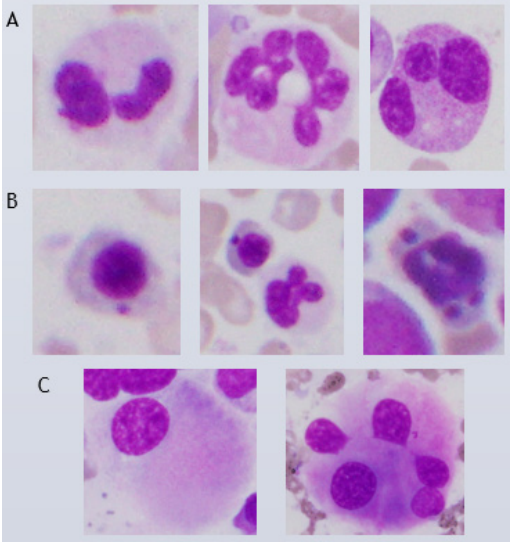

FIG. 2: Trilineage dysplasia. A-dysplastic neutrophils with pseudo Pelger-Huet nucleus and irregular nuclear segmentation. B-dysplastic erythroblasts with nuclear fragment, nuclear budding and multinuclearity. C-dysplastic megakaryocytes with nuclear hypolobation and multiple, separated nuclei. (MGG stain, x600)

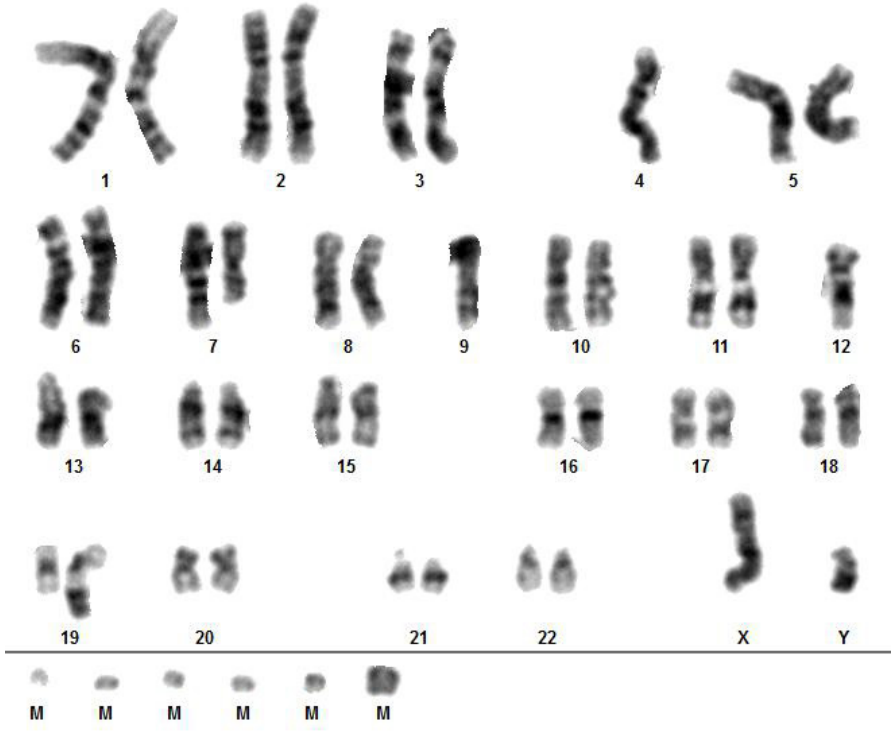

FIG. 3: G-banding of chromosomes showed a complex karyotypes with multiple structural and numerical abnormalities. (49,XY,-4,del(7)(q32),-9,-12,add(19)(q13.3),+6mar)

MK (49,XY,-4,del(7)(q32),-9,-12,add(19)(q13.3),+6mar) (Fig. 3). In view of the previous history of cytotoxic therapy, peripheral blood of leucocytosis, bone marrow morphological findings of trilineage dysplasia, complex aberrant karyotypes and MK, a diagnosis of t-MDS/MPN with unfavorable karyotype and MK was made. The patient subsequently defaulted on his follow-up appointments.

Less than four months later, he returned to hospital with anorexia, weight loss, fever, cough and shortness of breath. Bone marrow examination revealed that his disease had transformed to t-AML (Fig. 4) complicated with severe pneumonia. Despite aggressive treatment with multiple antibiotics and chemotherapy (daunorubicin and cytarabine), the patient succumbed to the illness 2 weeks later.

DISCUSSION

The diagnosis of t-MN is established when assessment of the peripheral blood and bone marrow aspirate shows morphologic,

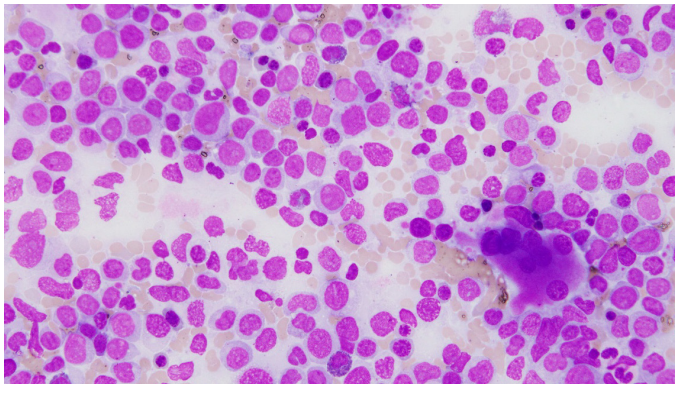

FIG. 4: Bone marrow aspirate showed hypercellular cell trails with 80% blasts indicating transformation to t-AML. (MGG stain, x400)

immunophenotypic and cytogenetic findings consistent with the diagnosis of AML, MDS or MDS/MPN in a patient with prior exposure to cytotoxic agents or radiation. The latency period between first exposures of a cytotoxic agent to the development of t-MN can range between 1 to 10 years.[1] In our patient, the period between first exposure to chemotherapy until the development of t-MN was 15 years although he was treated with cytotoxic agents for the first 6 intervening years for the newly diagnosed and subsequent relapsed APML. The cumulative toxicity of cytotoxic agents is believed to have been contributory to the development of t-MN. With regards to the specific type of cytotoxic agent, it has been reported that alkylating agents-related t-AML are characterized frequently by a preceding myelodysplastic phase, a long interval between cytotoxic treatment and appearance of t-AML, cytogenetic abnormalities involving chromosomes 5 and 7, and complex aberrant karyotypes showing a poor response to chemotherapy, whereas t-AMLs related to therapy with topoisomerase II inhibitors usually presents with overt leukaemia without a myelodysplastic phase, AML M4 or M5 phenotype according to French-American-British (FAB) classification, a short latency period (6–36 months), balanced chromosome aberrations - primarily translocations involving chromosome bands 11q23 and 21q22, and a more favourable response to chemotherapy.[4-6] Despite these, the multi-agent chemotherapeutic regimes commonly used in haematological malignancies have made this discrimination less useful.

The prognosis of t-MN is generally poor with shorter median survival when compared to their de novo counterparts;[2,7] evidence-based risk stratification is integral to tailor the most appropriate therapy. Thus, what is the biological basis of the unfavourable prognosis of t-MN compared to its de novo counterpart? Previous study reported a series of 93 patients with *t*-AML and 1091 patients with de novo AML treated uniformly and found that unfavourable cytogenetics were present more frequently in *t*-AML cases (46.2% *vs* 20.4%) and median overall survival was worse (10 *vs* 15 months; $p<0.01$).[8] However, owing to the large impact of karyotype aberrations in patients with *t*-AML, the authors concluded that the unfavourable outcome in the *t*-AML group was more influenced by karyotypic aberrations, rather than the disease per se.[8] The report of German-Austrian AML Study Group (AMLSG) revealed that when compared to 2653 patients with de novo AML, 200 patients with t-AML were shown to have higher rate of unfavourable cytogenetics (39% vs 19%; p<0.0001), lower 4-year relapse free survival (RFS) rate (24.5% vs 39.5%; p<0.0001) and inferior 4-year overall survival (OS) rate (25.5% vs 37.9%; p=0.001).[7] Investigators from the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) also reported outcomes of 38 patients with t-AML in comparison with 144 de novo AML patients treated with standard chemotherapy. No difference was observed with regards to CR rates, disease free survival (DFS) and OS between the two groups,[9] although the unequal comparison arm is notable. Interestingly, in a patient series reported by C Schoch *et al*, the proportion of favourable karyotypes was comparable in t-AML and de novo AML while unfavourable karyotypes and complex aberrant karyotypes in particular, were significantly more frequent in t-AML.[10] There was significant correlation of favourable and unfavourable cytogenetics with OS in t-AML.

Generally, patients may be divided into three categories which are favourable, intermediate and unfavourable according to cytogenetic results.[10] The favourable karyotypes include inv(16), t(8;21) and t(15;17), these patients are likely to achieve complete remission with conventional chemotherapy and the reported median overall survival is 27 months.[8] Unfavourable karyotypes are defined as 3q21q26 abnormalities, del 5, del 7, monosomies 5 or 7, 11q23 abnormalities, 12p abnormalities, 17p abnormalities, or a complex aberrant karyotypes described as at least 3 abnormalities excluding cases with t(8;21), inv(16) and t(15;17).[10] The median overall survival of patients with unfavourable karyotype treated by conventional chemotherapy is only 6 months.[8] Intermediate karyotypes are defined as patients with a normal karyotype or those with other abnormalities not included as favourable or unfavourable.[10] This group of patients has a median overall survival of 13 months with conventional chemotherapy.[8]

Our patient's bone marrow karyotype revealed complex abnormalities (49,XY,-4,del(7)(q32),-9,-12,add(19)(q13.3),+6mar) which fall into the unfavourable group. In addition to that, he has also monosomal karyotype (MK). MK is defined as 2 or more monosomies, or a single monosomy in the presence of structural abnormalities.[11] MK has been described as an important independent risk factor that denotes extremely

poor prognosis in patients with haematological malignancies.[11] A recent study conducted on 1344 subjects with previously untreated AML showed that frequency of MK increased with age and accounted for 40% of AML patients with unfavourable karyotype.[11] Interestingly, 98% of MK positive cases exclusively come from AML patients with unfavourable karyotype[11]. Within the group of 440 patients with unfavourable karyotype (176 MK-positive patients vs 264 MK-negative patients), MK-positive patients also have a much lower complete remission rate (18%) than MK negative patients (34%) ($p<0.01$).[11] Furthermore, the 4-year overall survival rate in patients with unfavourable karyotype is reported to be significantly lower in MK positive (3%) when compared to MK negative (13%) ($p<0.01$).[11] Thus, it is important to identify this abnormality during routine karyotyping analysis as this particular subgroup of patients most likely possesses unfavourable karyotype, develops resistance to treatment and has the shortest overall survival. In situation where karyotyping is unsuccessful due to inadequate metaphase spreads, we recommend to use interphase FISH with centromeric probes to look for MK in high risk patients.

Other than cytogenetic aberrations, other explanations for the extremely dismal prognosis of this entity may be the depletion of normal hematopoietic stem cells and damage to bone marrow stroma from previous therapy, leading to impaired haematopoiesis and poor recovery from induction chemotherapy.[12] A study of 277 patients with t-MN also showed that besides adverse cytogenetics, other significant factors that lead to poor prognosis were platelet count $<30x10^9$/L, low Hb level and absence of allogeneic haemopoietic stem cell transplant (HSCT).[13]

Conclusion

Detection of cytogenetic abnormalities at the time of diagnosis represents the single most important prognostic factor in t-MN. Karyotypic analysis of bone marrow is mandatory in all suspected t-MN cases due to the invaluable prognostic information yielded. However, this could be hampered by insufficient cell count, lack of metaphase spreads or poor chromosomal morphology. Since conventional chemotherapy results in poor outcome, patients with unfavourable karyotype and/or MK, may benefit from investigational chemotherapy followed by allogeneic HSCT. Currently, there is scarcity of data on the optimal treatment of t-MN and clinical practice also differs among the clinicians. Further clinical trials and researches are required in order to address the optimal management for this group of patients.

REFERENCES

1. Swerdlow SH, Campo E, Harris NL, *et al*. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2008.
2. Borthakur G, Lin E, Jain N, *et al*. Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared with de novo core-binding factor leukemia. Cancer. 2009; 115: 3217-21.
3. Morton LM, Dores GM, Tucker MA, *et al*. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. Blood. 2013; 121: 2996-3004.
4. Andersen MK, Johansson B, Larsen SO, Pedersen-Bjergaard J. Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. Haematologica. 1998; 83: 483-8.
5. Pedersen-Bjergaard J, Andersen MK, Johansson B. Balanced chromosome aberrations in leukemias following chemotherapy with DNA-topoisomerase II inhibitors. J Clin Oncol. 1998; 16: 1897-8.
6. Pedersen-Bjergaard J, Pedersen M, Roulston D, Philip P. Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. Blood. 1995; 86: 3542-52.
7. Kayser S, Döhner K, Krauter J, *et al*. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood. 2011; 117: 2137-45.
8. Kern W, Haferlach T, Schnittger S, Hiddemann W, Schoch C. Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. J Clin Oncol. 2004; 22: 2510-11.
9. Pulsoni A, Pagano L. Treatment of secondary acute myeloid leukemia. J Clin Oncol. 2005; 23: 926-27.
10. Schoch C, Kern W, Schnittger S, Hiddemann W, Haferlach T. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. Leukemia. 2004; 18: 120-5.
11. Medeiros BC, Othus M, Fang M, Roulston D, Appelbaum FR. Prognostic impact of monosomal karyotype in young adult and elderly acute myeloid leukemia: the Southwest Oncology Group (SWOG) experience. Blood. 2010; 116: 2224-8.
12. Godley LA, Larson RA. Therapy-related myeloid leukemia. Semin Oncol. 2008; 35: 418-29.
13. Fianchi L, Pagano L, Piciocchi A, *et al*. Characteristics and outcome of therapy-related myeloid neoplasms: Report from the Italian network on secondary leukemias. Am J Hematol. 2015; 90: E80-5.