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Chronic myelogenous leukemia exhibiting trisomy 14 due to a Robertsonian translocation with philadelphia chromosome

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To the Editor

Chronic myelogenous leukemia (CML) is a genetically heterogenous disease that is frequently associated with cytogenetic abnormalities [1]. A second philadelphia (Ph) chromosome, trisomy 8, isochromosome 17q and trisomy 19 are the most common karyotypic abnormalities found in CML patients [2]. Trisomy 14 is a rare chromosomal aberration that is usually observed in myelodysplastic syndrome, myeloproliferative disorders, atypical chronic myeloid leukemia and acute myeloid leukemia which is associated with old age, thrombocytosis and poor prognosis [3–6]. Robertsonian translocations are rarely reported in hematological malignancies and the incidence is estimated to be 1/10.000 [7]. However, trisomies resulted from robertsonian translocations are extremely rare [8]. In the literature there is only one CML patient diagnosed in blastic phase carrying both Ph chromosome and translocation (14;14) who has a similar disease progress as in our case [9].

A 55-year-old man was admitted to our hospital with fatigue, weakness, weight loss, night sweating, abdominal pain, dry cough and fever of more than 39°C for 10 days. On physical examination, there was echymosis along the skin of the extremities, hepatomegaly and massive splenomegaly. The complete blood count showed white blood cells (WBC) 213×10^9/L, hemoglobin (Hb) 8.1 g/dl, hematocrit (Hct) 27.6% and platelets (PLT) 137×10^9/L. Biochemical parameters were within normal limits except lactate dehydrogenase (LDH) 1794 U/L. Peripheral blood smear (PS) revealed the leukocytosis and the presence of 60% of myeloloblastic cells where 3% of them were peroxidase positive. Bone marrow aspiration and biopsy specimen were consistent with the diagnosis of acute myeloblastic leukemia FAB myelomonocytic type (AML-FAB4) showing 60% of myelomonoblastic infiltration with CD34+, MPO+, Lyzozyme+, CD68+ and CD3−, CD79a−, TdT- by immunohistochemical staining. Broad spectrum antibiotherapy was started for the febrile status and cytarabine and idarubicine were given as a remission induction chemotherapy. One month after the chemotherapy, his hematological parameters improved to WBC: 3.1×10^9/L where 65% of them were neutrophils, Hb: 9.4 g/dl, Hct: 29.8%, PLT: 370×10^9/L. However, bone marrow aspiration showed 50% myeloblastic cell infiltration. After the salvage therapy with fludarabine plus cytarabine, a hematological remission was not achieved. At diagnosis, the karyotype obtained from unstimulated culture of bone marrow showed trisomy 14 due to Robertsonian translocation, a philadelphia chromosome and was reported as 46,XY,t(14;14)(q10;q10),t(9;22) (q34;

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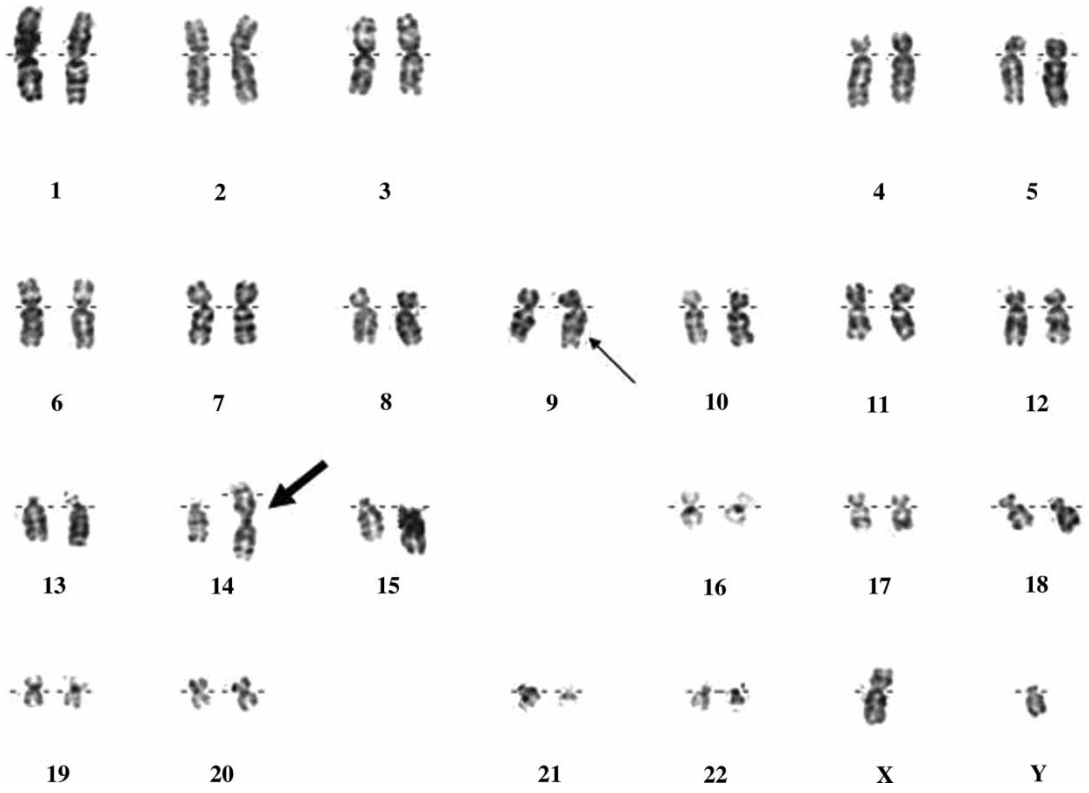

Figure 1. G-banded karyogram from bone marrow cells of the patient showing trisomy 14 due to a Robertsonian translocation, normal and derivative chromosomes 9 and 22. Karyotype of the patient was noted as 46,XY,t(14;14)(q10;q10),t(9;22)(q34;q11.2). The Robertsonian translocation is indicated by the thick arrow and the Ph chromosome was marked with the thin arrow.

q11.2) (Figure 1). Fluorescent in situ hybridisation (FISH) analysis confirmed the Ph chromosome and the Robertsonian translocation in metaphase chromosomes. Together with the philadelphia chromosome positivity, the diagnosis of the patient was considered as CML in blastic transformation and 600 mg/day imatinib therapy was given. Six months after the imatinib treatment, bcr-abl levels decreased from the first level of 0.448 to 0.0074 which was consistent with major molecular response; however there was persistence of 6% blastic cells in bone marrow. The control karyotype performed during this period was also consistent with trisomy 14 and a Ph chromosome. Another tyrosine kinase inhibitor, dasatinib was started and the control bone marrow biopsy after three months revealed 10% blastic cells. The case was considered as drug resistant CML and he does not have a suitable stem cell donor at the moment. Nilotinib therapy has been planned for the future treatment.

Our case was considered to be a blastic crisis of CML by the presence of Ph positivity in all the metaphases obtained from the unstimulated culture of bone marrow at diagnosis and after chemotherapy. Although most of the patients are diagnosed during the chronic phase, less than 10% present with the accelerated or blastic phases as in the presented case [10]. In the literature, there are very few reports about the presence of both Ph chromosome and trisomy 14 in CML. To our knowledge, this is the first case of CML having trisomy 14 due to a Robertsonian translocation. Interestingly a similar disease progress in a 68-year-old CML case with t(14;14)(q11;q32) and Ph chromosome who had B cell phenotype at diagnosis and a biphenotypic (lymphoid-myeloid) expression at relapse was reported [10]. On the contrary of the previously reported case, no complete hematological remission was achieved in our case but major molecular response was obtained. In remission of the previously described case, t(14;14) disappeared but in our patient, trisomy 14 persisted during the molecular response period. Also, therapy with the new and effective tyrosine kinase inhibitors did not alter the prognosis in this patient. This clinical picture may be related to the total trisomy of the chromosome 14 and the Robertsonian translocation may also play a role in the poor prognosis. Further case reports will be needed to confirm these findings. This report reinforces the importance of conventional karyotyping in the diagnosis and prognosis of hematological malignancies and supports the theory that trisomy 14 is a rare cytogenetic abnormality found in myeloid malignancies

and is associated with poor prognosis. This may lead strategies to further increase the understanding of drug resistant CML and may represent next frontier in the targeted therapy of CML patients.

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Hepatocellular carcinoma developing years after extended field radiation for Hodgkin's lymphoma

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To the Editor

Secondary malignancies (SMs) have been described as a complication of radiation therapy (RT) or combined chemoradiation therapy for Hodgkin's lymphoma (HL). In this article, I describe a patient who developed hepatocellular carcinoma (HCC), 34 years after "total lymphoid irradiation" for HL. Review of the literature suggests this to be the first reported case of HCC developing as a probable consequence of RT.

MN is a 49-year-old patient who, at age 14, was treated with total lymphoid irradiation in 1972 for HL. In 2006, she presented with abdominal pain, early satiety, and a 25-pound weight loss over several months. A CT scan revealed a 17 cm mass involving the right and left lobes of the liver. Hepatitis B and C panels were negative. Alphafetoprotein (AFP) was 6.1 (normal). Core needle biopsy of the liver mass was interpreted as showing HCC with a background of only non-cirrhotic liver tissue. The patient had no history of liver disease. The patient was treated with repeated transhepatic artery chemoembolization and later sorafenib after disease progression. Her disease remains stable approximately four months after starting sorafenib.

SMs have been extensively reported as a consequence of radiation therapy. This subject was reviewed in Acta Oncologica [1], wherein the authors described a 20-year cumulative risk of SMs after HL treatment of 15–20%. They also noted a "much longer latent period" for solid tumors com-

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