Atlas of Genetics and Cytogenetics in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Case Report Section

Paper co-edited with the European LeukemiaNet

Homogeneously Staining Region (HSR) harboring CMYC amplification in a patient with primary plasma cell leukemia

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Published in Atlas Database: June 2013

Online updated version : http://AtlasGeneticsOncology.org/Reports/CRMYCampMohamedID100068.html
DOI: 10.4267/2042/51823

Clinics

Age and sex
36 years old female patient.

Previous history
No preleukemia, no previous malignancy, no history of plasma cell myeloma or other malignancy, no inborn condition of note main items patient had solvent and formaldehyde exposures.

Organomegaly
No hepatomegaly, no splenomegaly, no enlarged lymph nodes, no central nervous system involvement.

Blood

WBC: 14.4 X 10^9/l
HB: 11.1g/dl
Platelets: 74,000 X 10^9/l
Bone marrow: Hypercellular marrow 100% with near-total replacement by sheets of malignant plasma cells ranging from small uninuclear to very large multinucleated cells with prominent nucleoli, and high mitotic activity (Figure 2A).

Note
At time of presentation her blood work up revealed hypercalcemia; 14.9 mg/dl, BUN; 19 mg/dl; creatinine; 1.5 mg/dl, total protein; 13 g/dl, albumin; 5.09 g/dL, and LDH; 196 units/L. Serum protein electrophoresis and immunofixation demonstrated IgGlambda.

WBC: 14.4x10^9/L 40% plasma cells with atypical features, Hb; 11.1g/dl, hematocrit of 33.5%, platelets; 74,000x10^9.

Cyto-Pathology Classification

Immunophenotype
Flow cytometry on peripheral blood showed an abnormal clonal plasma cell population expressing CD38, CD138, and dim CD45, with lambda chain restriction.

Rearranged Ig Tcr
Not performed.

Pathology
CT scan, MRI and bone scan revealed T5 soft tissue mass, multiple osteolytic lesions in skull, ribs, vertebra and iliac crest.

Electron microscopy
Not performed.

Diagnosis
Plasma cell leukemia (PCL).

Survival

Date of diagnosis: 05-2008

Treatment: Steroid, Zometa, radiation, stem cell transplant.
Complete remission: No short remission.
Treatment related death: No.

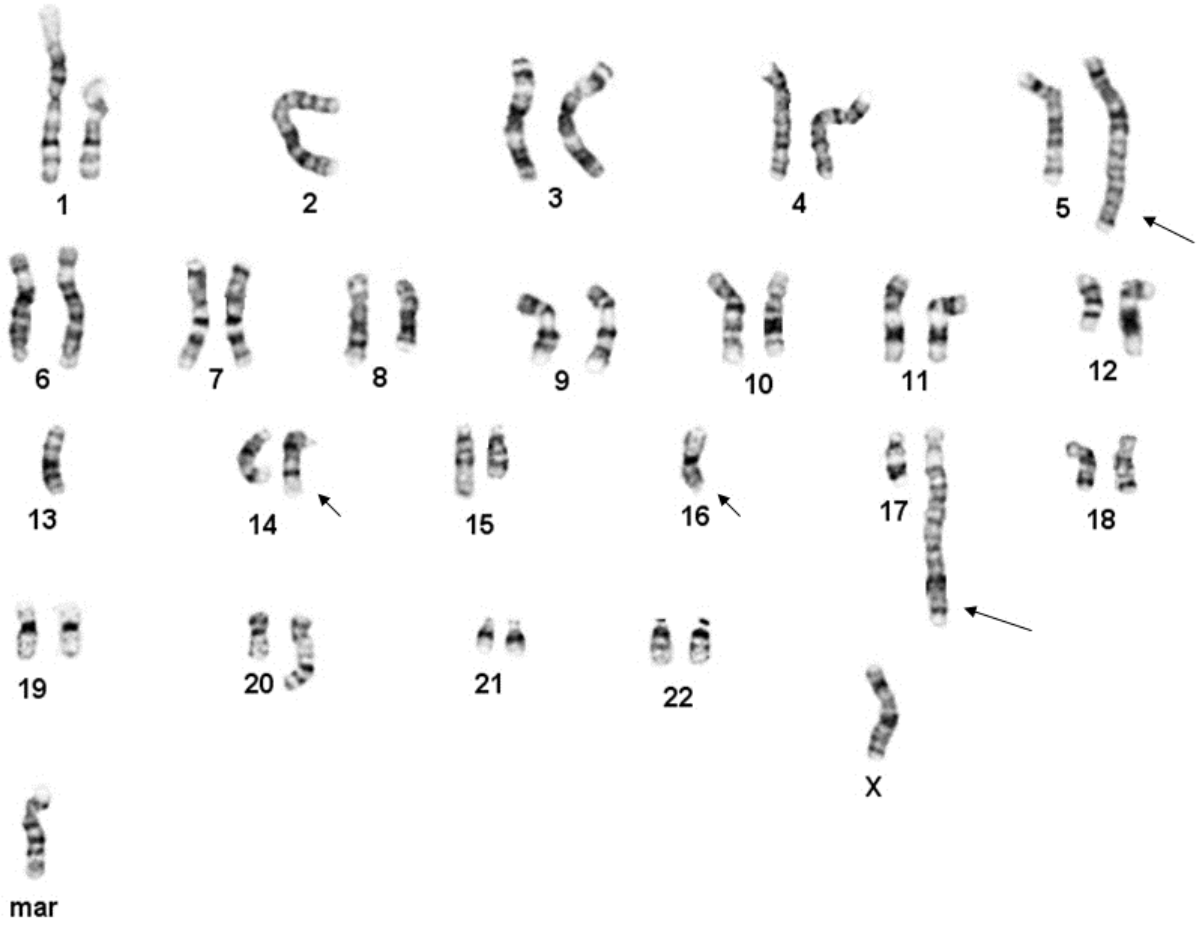

Figure 1. G-banded karyotype showing two hsr regions (long arrows), t(14;16)(q32;q23) (short arrows) as well as other abnormalities.

Relapse: Her disease recurred and spread to extramedullary sites spleen and lymph nodes; expired 5 months after diagnosis.

Status: Death

Last follow up: 10-2008

Survival: 5 months from initial diagnosis

Karyotype

Sample: peripheral blood

Culture time: 24 and 48 hours unstimulated cultures

Banding: GTG

Results

43,X,-X,del(1)(p13p36.1),-2,hsr(5)(q31),del(8)(q22q24.1),del(12)(q14q24.1),-13,t(14;16)(q32;q23),del(15)(q22),-16,del(17)(p11.2),hsr(17)(q24),add(20)(q13.3),+mar[cp14]/46,XX[6] (Figure 1).

Other Molecular Studies

Technics:

Fluorescence in situ hybridization using LSI D13S319/LAMP, TP53 and IGH/MAF DNA probes (Abbott Molecular) revealed loss of chromosome 13, deletion of p53 and IGH-MAF/t(14;16) in approximately 60% of interphase cells.

Results:

Furthermore, hybridization with LSI IGH/CMYC/CEP-8 probe set showed that the two copies of hsr were entirely labeled with CMYC (Figure 2B).

Comments

We report a case of primary PCL admitted to the hospital due to severe diarrhea and a history of 2 months of bone pain.

She was found to havehypercalcemia, and at that time her peripheral blood showed 40% abnormal plasma cells.

Cytogenetic analysis revealed a hypodiploid karyotype with complex abnormalities including monosomy 13, deletion 17p/p53, t(14;16)/IGH-MAF and two copies of hsr indicating a high risk disease (Figure 1). Metaphase FISH revealed that the hsr were positive for CMYC sequences (Figure 2B).

In leukemia, double minute (dmin) and hsr are signs of gene amplification, most often represent the CMYC oncogene or drug resistance genes.

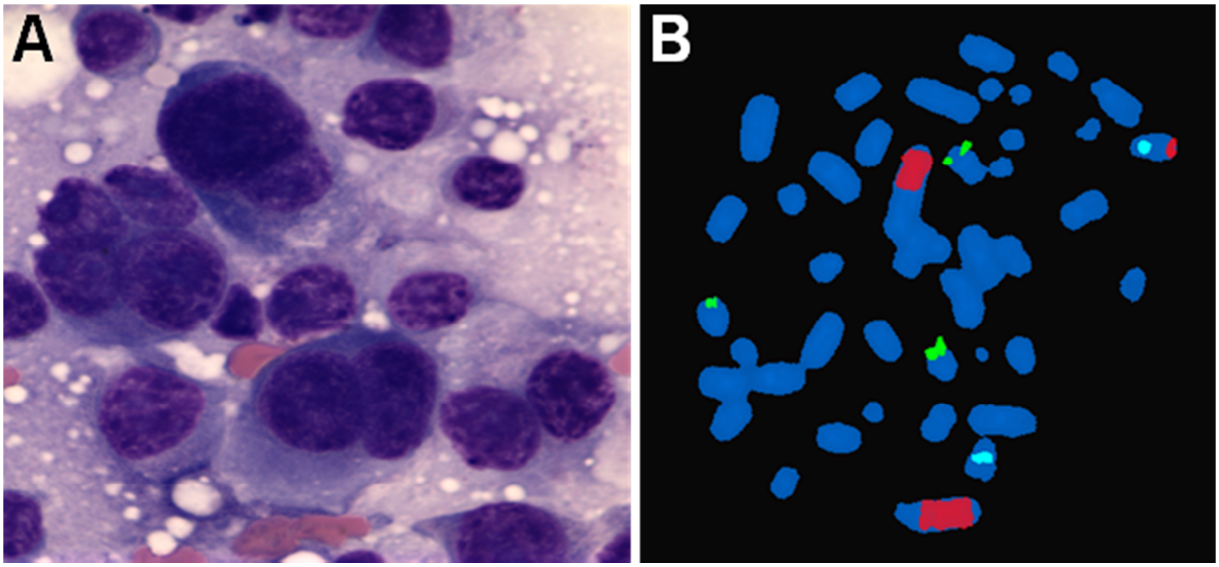

Figure 2. (A) Touch imprint of bone marrow biopsy showing several very large multinucleated as well as small uninuclear myeloma cells. (B) FISH analysis with LSI IGH/MYC/CEP8 tricolor, dual fusion translocation DNA probe set. The IGH is labeled with spectrum green, MYC with spectrum orange, and CEP 8 with spectrum aqua. (B) Hybridization of a metaphase showing 2 hsr regions (arrows), 3 IGH green signals, 1 orange MYC signal, and 2 aqua signals identifying chromosome 8. Notice one chromosome 8 has no MYC signal.

Dmins tend to occur in elderly with a myelodysplastic syndrome and acute myeloid leukemia, and are associated with a rapid and aggressive clinical outcome.

However, an hsr is extremely rare in leukemia and based on our search in the medical literature, the present case is the first report of CMYC amplification in the form of an hsr seen in myeloma. In contrast, development of PCL in this patient at relatively young age is quite uncommon, possibly due to history of exposure to mutagens which initiate a series of DNA mutations.

The presence of an hsr in this case is also associated with a very bizarre plasma cell morphology and dismal clinical course. As seen in our patient, dmin and hsr have been described in association with deletion of 17p13/p53, suggesting that loss of p53 primes leukemic cells by increasing their survival, therefore allowing deregulation of other oncogenes such as CMYC and RAS. Still the molecular events that allow the plasma cells to escape the bone marrow environment are unclear. Sequential involvement and cooperation of multiple oncogenes and tumor suppressor genes, as well as other epigenetic events, are required for plasma cell expansion into the peripheral blood and extramedullary tissues.

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This article should be referenced as such:

Pathan NF, Palutke M, Mohamed AN. Homogeneously Staining Region (HSR) harboring CMYC amplification in a patient with primary plasma cell leukemia. Atlas Genet Cytogenet Oncol Haematol. 2013; 17(11):799-801.