Leukemia Research 73 (2018) 1–4

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Meeting report

"Reversible" myelodysplastic syndrome or ineffectual clonal haematopoiesis? – add(6p) myeloid neoplasm with a spontaneous cytogenetic remission

K. Rady[a,b,*], P. Blombery[b], D.A. Westerman[a,b,c], M. Wall[d,e,f], M. Curtis[d], L.J. Campbell[d], J.F. Seymour[a,c]

[a] Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia
[b] Department of Pathology, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia
[c] University of Melbourne, Parkville, VIC, Australia
[d] Victorian Cancer Cytogenetics Service, Fitzroy, VIC, Australia
[e] Department of Medicine, St Vincent's Hospital, University of Melbourne, Fitzroy, VIC, Australia
[f] St Vincent's Institute of Medical Research, Fitzroy, VIC, Australia

ARTICLE INFO

Keywords:
Therapy-related myeloid neoplasm
Myelodysplastic syndrome
CHIP
MDS
AML
Clonal haematopoiesis
der(6)t(6;13)

ABSTRACT

Cytotoxic chemotherapy has inherent mutagenic potential and alters the bone marrow microenvironment after therapy. In some cases, this potentiates expansion of an aberrant clone and may lead to a therapy-related myeloid neoplasm if the clone overcomes selective pressure. We present the case of a 43-year-old woman diagnosed with an indolent, therapy-related myeloid neoplasm with an isolated chromosome 6p abnormality following treatment for *de novo* Acute Myeloid Leukaemia (AML), who manifest a sustained spontaneous cytogenetic remission two years later, possibly due to an ineffectual or non-dominant founding clone. This case reminds us to be mindful of the possibility that clonal haematopoiesis may not always equate to clinically relevant disease, even in the setting of an abnormal clonal karyotype.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of malignant stem cell disorders characterised by ineffective, dysplastic, clonal haematopoiesis. The acquisition of mutations in a haematopoietic cell, due to aging or secondary genetic insults, drives clonal expansion and confers an increased risk of neoplasia [1,2]. In the premalignant state, this phenomenon is known as clonal haematopoiesis of indeterminate potential (CHIP)2. Subsequent expansion of the founding clone and sequential acquisition of additional driver mutations, typically promoting self-renewal and a proliferative advantage, together with a dysfunctional bone marrow microenvironment contribute to the transition to clinically manifest MDS [2].

Cytotoxic chemotherapy has inherent mutagenic potential and alters the bone marrow microenvironment after therapy which may exert selection pressure on residual haematopoietic populations and confer a competitive advantage for stem cells harbouring certain mutations [2]. Over time, expansion of an aberrant clonal population may lead to therapy-related myeloid neoplasms (t-MN), including AML, or MDS. Clones failing to have an advantage may be weakened by selective pressure, and disappear over time.

We present the case of a 43-year-old woman diagnosed with an indolent t-MN with an isolated chromosome 6p abnormality following treatment for *de novo* AML, who manifest a sustained spontaneous cytogenetic remission 2 years later, possibly due to an ineffectual or non-dominant founding clone.

Following presentation with pancytopenia and circulating blasts in December 2005, the patient underwent bone marrow biopsy revealing acute myeloid leukaemia with maturation (WHO 2017 classification AML not otherwise specified, formerly, M2 subtype under FAB classification [3]) with 45% blasts with an abnormal immunophenotype. Karyotypic analysis revealed a normal female karyotype in 26 metaphases examined. Induction chemotherapy comprised Cytarabine (100 mg/m^2 D1-7 continuous infusion), Idarubicin (12 mg/m^2 D1-3) and Etoposide (75 mg/m^2 D1-7), followed by three consolidation cycles of high-dose cytarabine (3000 mg/m^2 bd D1, 3, 5). Post induction the patient achieved a complete morphologic and immunophenotypic remission.

* Corresponding author at: Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, VIC, Australia.
E-mail address: kirstyrady@hotmail.com (K. Rady).

https://doi.org/10.1016/j.leukres.2018.08.010
Received 11 May 2018; Received in revised form 9 August 2018; Accepted 12 August 2018
Available online 16 August 2018

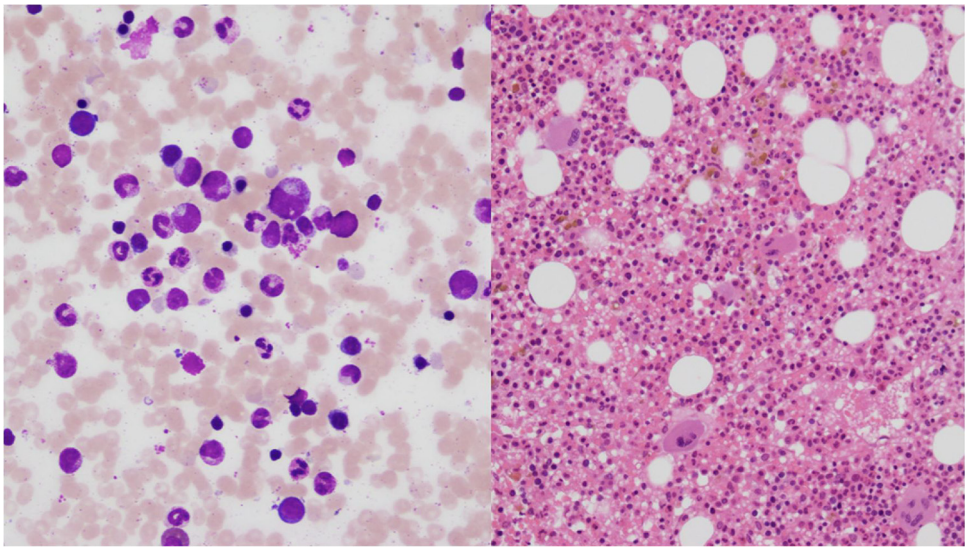

Fig. 1. Bone marrow aspirate (right) demonstrating dysplastic late erythroblasts with poor haemoglobinisation and irregular nuclear margins; and bone marrow trephine (left) demonstrating dysplastic megakaryocytes within a hypercellular marrow.

Bone marrow biopsy two months following completion of chemotherapy displayed mild morphologic dysplasia, predominantly in the megakaryocytic lineage; further supported by immunophenotyping which revealed granulocytic aberrancies including reduced expression of CD13, CD15, CD16, CD10 and aberrant CD56 expression together with loss of CD16 expression on monocytes. Repeat cytogenetic analysis confirmed a normal karyotype. There were no peripheral cytopenias.

Routine bloods in March 2007 revealed mild thrombocytopenia (Plt 125×10^9/L) and a borderline macrocytosis (MCV 100 fl) with normal haemoglobin and leukocyte count. Bone marrow biopsy confirmed ongoing remission from AML but demonstrated trilineage dysplasia, most prominent in the megakaryocytic lineage (Fig. 1). Conventional cytogenetic analysis performed on G-banded metaphases of 25 cells showed six cells had unidentified material translocated onto 6p with the G-banded karyotype 46,XX,add(6)(p22). Multicoloured fluorescence *in situ* hybridization (M-FISH) and multicoloured banding of chromosome 13 (mBAND) confirmed part of chromosome 13 was present in three copies with one copy translocated onto chromosome 6 (Fig. 2). Thus, the der(6) represented an unbalanced 6:13 translocation resulting in monosomy of the distal part of 6p and trisomy of part of 13q. The revised karyotype informed by additional FISH testing was: 46,XX,der(6)t(6;13)(p22;q14). The trilineage dysplasia, together with the clonal cytogenetic abnormality and mild thrombocytopenia were highly suggestive of myelodysplasia and a diagnosis of a therapy-related myeloid neoplasm (t-MN) was made, despite the platelet count being $> 100 \times 10^9$/L.

The patient was monitored with monthly full blood counts and three-monthly bone marrow biopsies. The der(6) was identified in approximately 50% of cells analysed at the next bone marrow biopsy in June 2007, and 57% of cells in September 2007. It remained detectable in February 2008, however the majority of cells demonstrated a normal female karyotype, and in December 2008, was no longer detectable. This was evidence of a spontaneous cytogenetic remission. The finding of a new cytogenetic abnormality in a patient with a previously normal karyotype, and the indolent clinical course, supported the t-MN as being a secondary process rather than clonal evolution of her original AML.

Over a subsequent three-year period, the patient's leukocyte count and haemoglobin remained stable, and her platelet count gradually improved into the normal range where it remains ten years later. Six subsequent bone marrow biopsies over six years demonstrated no increase in blasts morphologically and gradual improvement in the degree of megakaryocytic dysplasia. On the patient's most recent bone marrow biopsy in 2015, there was no morphological evidence of AML or MDS. Unfortunately, cytogenetic analysis was unsuccessful as few cells and no mitoses were obtained from the specimen, and more sensitive testing, including Fluorescence *in situ* Hybridisation, was not performed to exclude low level persistence of the clone.

Retrospectively, targeted amplicon next generation sequencing was performed for 26 frequently mutated genes in myeloid malignancy including *TET2*, *ASXL1*, *U2AF1*, *DNMT3A*, *SF3B1*, *SRSF2* and *RUNX1* on two bone marrow samples, (September 2007, 57% add 6q and May 2009, diploid karyotype). No mutations were detected in these two samples.

2. Discussion

This patient underwent treatment for normal karyotype AML, achieved remission and after 15 months developed an aberrant clonal haematopoietic population, as evidenced by the der(6)t(6;13), which expanded over time and subsequently regressed to become undetectable. There was morphologic trilineage dysplasia but only unilineage mild thrombocytopenia. Although none of the common MDS-associated gene mutations were detected by molecular analysis on a bespoke 26-gene myeloid panel, the presence of other less frequent mutations cannot be excluded. Clinically this patient had an indolent, regressive course; two years after the t-MN diagnosis there was resolution of the morphologic dysplasia, thrombocytopenia, and the cytogenetic abnormality. The patient remains well ten years following her t-MN diagnosis without any disease-directed therapy.

This case illustrates an exceptional manifestation of failed clonal haematopoiesis. The proposed diagnostic criteria for CHIP requires that patients have detectable somatic clonal mutations in genes recurrently mutated in hematologic malignancies but lack a known hematologic malignancy or other clonal disorder [1]. CHIP is distinguished from MDS due to lack of significant cytopenias, longer survival, and low rate of progression to AML [1]. Although never truly fulfilling criteria for CHIP (due to lack of an identifiable molecular mutation and the pre-existing haematological diagnosis of AML), this case displays a similar biology and appears to be a condition on the continuum from CHIP to MDS. The indolent course and morphological improvement seems inconsistent with our current held concept of t-MN's, where there is a typically progressive course and prognosis is poor with an overall 5-year survival of less than 10% [4].