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Myelodysplastic syndrome with del (5q) and JAK2V617F mutation transformed to acute myeloid leukaemia with complex karyotype

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Myelodysplastic syndrome with isolated del (5q) and $JAK2_{V617F}$ mutation is a distinct entity within the World Health Organization (WHO) category myelodysplastic syndromes (MDS) [1]

$JAK2_{V617F}$ is a gain of function mutation, typically associated with myeloproliferative neoplasms (MPN) [2]. However, approximately 5% of patients with isolated del (5q) also harbours the $JAK2_{V617F}$ mutation [3,4].

No correlation was found between isolated del (5q) $JAK2_{V617F}$ mutated cases and clinical presentation, morphological features, disease transformation or patient outcome [4,5], although a few cases presented with higher platelet and WBC count [3]. Lenalidomide was reported to be an effective treatment for the disease [6].

We have recently studied a patient with del (5q) and $JAK2_{V617F}$ mutation transformed to acute myeloid leukaemia (AML) with complex karyotype and increased $JAK2_{V617F}$ mutation load.

A 66 year old female presented with moderate anaemia and high platelet count (haemoglobin 100g/l, WBC 7.2 x 10^9/l, platelets 800 x 10^9/l). Neutrophils were 4.95 x 10^9/l, eosinophils 0.21 x 10^9/l, monocytes 0.14 x 10^9/l and lymphocytes 1.9 x 10^9/l. No blast cell was present in the peripheral blood. There was no spleno- or hepatomegaly. On marrow aspirate, only 8 metaphases showing a normal karyotype (46XX) could be analysed, due to the lack of growth of an adequate number of metaphases and the poor cellularity of the sample. FISH analysis was limited to the study of 5q and demonstrated 5q31 deletion in 12% of the nuclei. Thus, additional aberrations could not be identified. BCR/ABL rearrangements (p210, p190) were absent, while $JAK2_{V617F}$ mutation displayed an allele burden of 4.28%.

BM biopsy showed a 70% cellularity, slight dyserythropoiesis, moderate myeloid hyperplasia and marked proliferation of the megakaryocytic lineage with some dysplasia. A few megakaryocytes were large with hyperlobulated nuclei; others were medium-sized, with round and/or hypolobulated nuclei. There were 3% CD34 positive blasts and moderate reticulin fibrosis (WHO MF-2). (Fig.1 a,b,c,e). A strong nuclear p53

immunostaining was detected in 2% hematopoietic cells (Fig.1 d). We proposed a diagnosis of MDS with del (5q) and JAK2$_{V617F}$ mutation.

The patient did not receive any therapy. No organomegaly nor leukoerythroblastosis was reported during the course of the disease. Twenty-seven months later, she was admitted to the hospital because of persistent fever, severe anaemia and neutropenia (Hb level 7.5 g/l, WBC 2.3x10^9/l, neutrophils 0.75x10^9/l, platelets 137x10^9/l). There were 5% blast cells in the peripheral blood.

Chromosome banding analysis showed: 46,XX [1] / 45,XX, -7, del(5)(q13q33), del(13)(q14q34) [7] / 45, idem, del(2)(p12) [2]. FISH analysis demonstrated -7, del(5)(q31), del(13)(q14) (80%) without BCR/ABL, AML1/ETO, PML/RARA, inv(16), MLL(11q23) translocation and +8. Molecular analysis didn't identify FLT3 (ITD, D835), NPM1 (exon 12) or MLL-PTD mutations. RQ-PCR (real-time quantitative polymerase chain reaction) detected 4,164 WT1 copies/10^4 ABL copies and 55.6% JAK2$_{V617F}$ mutation load. p53 sequencing analysis of exons 2-11 showed a c.742C>T, p.R248W mutation in exon 7, that is considered a missense deleterious mutation.

BM demonstrated marked dyserythro-, dysgranulo- and dysmegakaryopoiesis, diffuse reticulin fibrosis and excess (25%) of CD34, CD117, CD33 and MPO positive blasts. (Fig.1 f,g,h,i,l). Strong nuclear p53 immunostaining was found in more than 20% of hematopoietic cells, including some blasts (Fig.1 m).

A diagnosis of AML with myelodysplasia-related changes was established. Induction therapy with fludarabine, cytarabine and idarubicin failed; reinduction therapy with clofarabine and cytarabine was then performed. However, the disease still persisted in a control BM biopsy performed three months later.

Contrary to previous reports [4,5], our case of del (5q) with JAK2V617F mutation transformed to AML. MDS with isolated del(5q) has a very long median survival (145 months) and a low rate of transformation (<10%) to AML [1]. On the contrary, our case transformed to AML in 27 months only: it is possible that the simultaneous presence of del (5q), JAK2V617F mutation and expression of p53 accelerated leukemic transformation. Indeed, a strong p53 immunostaining in >1% of bone marrow progenitor cells is known to be significantly associated with higher acute myeloid leukemia risk [7]. The percentage of strongly p53 positive BM cells was 2% at the time of the initial biopsy but more than 20% at the time of the leukemic transformation and included some blasts. Sequencing confirmed a p53 mutation. Therefore, it is possible that p53 mutation contributed to the unfavourable course of this case.

Moreover, the increase of JAK2$_{V617F}$ mutation load (10x of the initial value) can also explain the high number of large megakaryocytes with hyperlobulated or cloudy nuclei, typical of a MPN disease, that were appreciated in the BM biopsy performed at the time of the leukemic transformation.

WHO recommends to classify patients with isolated del (5q) and JAK2$_{V617F}$ mutation in the MDS category rather than in the MDS/MPN category [1].

However, the present case at diagnosis showed morphological features either of MDS and MPN. Furthermore, in the following transformation into AML, some morphological features of MPN were retained (large megakaryocytes with hyperlobulated or cloudy nuclei), together with myelodysplasia related changes (marked dyserythro-, dysgranulo- and dysmegakaryopoiesis).

Therefore, on the basis of the clinical and pathological features of the present case, we suggest that it would be more appropriate to classify MDS with del (5q) and JAK2V617F mutation in the WHO MDS/MPN category rather than in the MDS category.

All procedures followed were in accordance with the ethical standards of the local institutional responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from the patient for being included in the study.

The authors declare that they have no conflict of interest.

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Legends

Fig.1 Bone marrow biopsies of myelodysplastic syndrome with isolated del (5q) and JAK2V617F mutation (A,B,C,D,E) and acute myeloid leukaemia with myelodysplasia-related changes (F,G,H,I,L).

a Slight dyserythropoiesis, moderate myeloid hyperplasia and marked proliferation of the megakaryocytic lineage with some dysplasia (H&E). b Large megakaryocytes with hyperlobulated nuclei and medium-sized megakaryocytes with round and/or hypolobulated nuclei (Dominici). c Moderate reticulin fibrosis (WHO MF-2) (Gomori). d Strong nuclear p53 immunostaining in a few hematopoietic cells. e Dyserythropoiesis is well shown by CD71 immunostaining.

f Hypercellular marrow with marked dyserythro-, dysgranulo- and dysmegakaryopoiesis and numerous blasts (H&E). g A few micromegakaryocytes and one large megakaryocyte with hyperlobulated nucleus (Dominici). h Diffuse reticulin fibrosis (Gomori). i CD34 immunopositive blasts. l CD117 immunopositive blasts. m Strong nuclear p53 immunostaining in numerous hematopoietic cells, including some blasts.

Figure