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Case Report

Mixed Phenotype Acute Leukemia Resulting from a BCR-JAK2 Balanced Translocation

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ABSTRACT:

This is a case report of a Mixed Phenotype Acute Leukemia (MPAL) patient, with a BCR-JAK2 fusion gene. This is the 1st case presenting as a mixed lymphoid/myeloid neoplasm. The BCR-JAK2 fusion protein resulting from a t(9;22)(p24;q11.2) translocation, and containing domains of both BCR and JAK2, is a very active tyrosine kinase which leads to abnormal cell proliferation. These rare BCR-JAK2 fusions presenting in ''Ph-like ALL" cases suggest common pathways between JAK2 activation and the pathogenesis of both myeloid and lymphoid neoplasms. In addition to this, the aim of this paper is to point out the fact that while BCR-JAK2 positive neoplasms are very aggressive and require allogeneic stem cell transplantation for long term remission, further identification and investigation is warranted, due to the fact that JAK2 inhibitors also seem to be effective.

KEY WORDS: *BCR-JAK2, JAK2, Ph-like ALL, Ruxolitinib*

INTRODUCTION

Mixed phenotype acute leukemia (MPAL) is a heterogeneous disease characterized by the concurrent expression of both lymphoid and myeloid antigens. MPAL is usually associated with the presence of t(9;22)(q34;q11) and t(v;11q23.3) translocations. However, in more than 50% of cases the characteristic translocations are absent and other as yet unknown genetic abnormalities are pathogenetically linked to MPAL. JAK2 is located on chromosome 9 and encodes for a kinase which serves as an important cytokine signalling mediator. Although JAK2 mutations are the hallmark of Philadelhia-negative myeloproliferative neoplasms (MPN), gain-of function mutations, amplification and translocations involving JAK2 have been described in other haematological neoplasms including B-ALL cases.[1] Here we report a very rare case of a MPAL patient, with a BCR-JAK2 fusion gene resulting from a t(9;22)(p24;q11.2) translocation.

CASE REPORT

A 55 year old patient was admitted for evaluation of fatigue and dyspnea on exertion of 3 weeks duration. Clinical examination was unremarkable except for the presence of pallor. Full blood count was as follows: Hb=8gr/dl, WBC=25x10^3/μl, PLT=35X10^3/μl, while microscopy of the peripheral blood smear revealed 80% blasts. Biochemistry was normal except for an elevated LDH. Bone marrow aspiration and biopsy showed the presence of a

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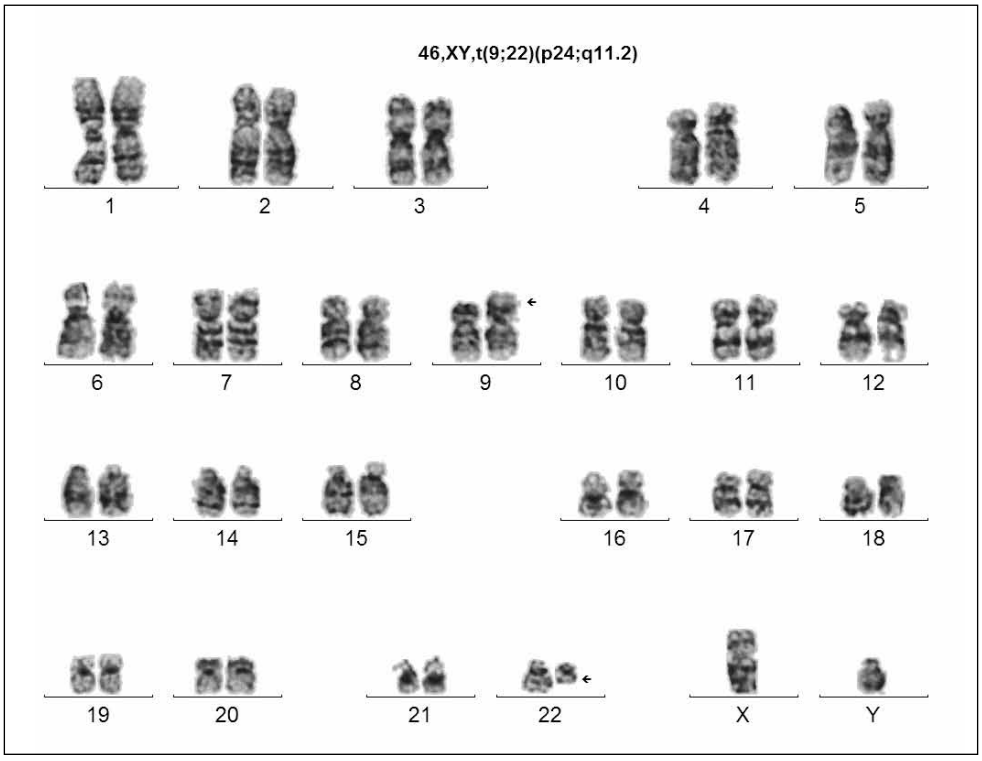

Figure 1. Translocation (9;22)(p24;q11.2).

monotonous infiltration of blast cells and markedly diminished normal myeloid elements. Immunophenotypic analysis of bone marrow blast cells was consistent with biphenotypic acute lymphoid/myeloid leukemia (MPO+, CD33+, CD13+, CD10+, CD19+, CD22+, Tdt+), while PCR examination for the presence of bcr/abl fusion gene was negative. Cytogenetic examination of bone marrow metaphases revealed t(9;22)(p24;q11.2) translocation, which is known to create a BCR-JAK2 fusion gene.

The patient received treatment with Hyper-CVAD alternating with high dose MTX plus HiDAC which is an ALL-chemotherapy regimen and achieved complete morphologic and immunophenotypic remission after the completion of the 1st induction cycle. Unfortunately, 3 months after the completion of chemotherapy and while on maintenance treatment, the patient relapsed. Salvage chemotherapy with Ida-FLAG regimen followed, achieving a second complete remission, and allogeneic stem cell transplantation from a matched unrelated donor was performed as consolidation of the second remission.

The patient remained in continuous complete remission but chronic GVHD developed 6 months after transplantation. He succumbed from refractory extensive chronic GVHD 18 months post-transplant, with no evidence of disease recurrence.

DISCUSSION

With most of the cytokine receptors lacking intrinsic kinase activity, Janus kinases (JAKs) act as signalling intermediates. Four human JAKs have been identified: JAK1, JAK2, JAK3 and TYK2 (tyrosine kinase-2).

Only recently it is that JAK mutations have standed out among many others, with the discovery of the V617F mutation in JAK2 in a substantial proportion of patients with MPNs. Gain of function point mutations and translocations involving JAK2 and subsequent activation of the JAK2 kinase have been described in various hematological neoplasms.[1] However, in contrast to JAK2 point mutations, JAK2 translocations are very rare.

Currently, the chromosomal translocations that have been identified and are involving JAK2, result most commonly to TEL–JAK2, PCM1–JAK2, and SSBP2–JAK2 fusion genes. In addition to these, and together with our case presented here, a total of 17 BCR-JAK2 fusion gene cases have also been described, resulting from t(9;22)(p24;q11.2) translocation (Table 1). The majority of these very rare cases, presented as a myeloid neoplasm [6 patients with atypical chronic myeloid leukemia (aCML), 1 patient with myelodysplastic syndrome (MDS), 5 patients with MPN/MDS, and 1 patient with acute myeloid leukemia (AML)], while few other cases presented as a lymphoid neoplasm [3 patients with B-

TABLE 1. List of 17 BCR-JAK2 fusion gene cases described to date and hematological malignancy

Patient	Reference	Year	Age/Sex	Translocation	Disease	Follow up
1	Griesinger et al.	2005	63/F	t(9;22) (p24;q11.2)	aCML	Death at 24-month FU from blast crisis
2	Cirmena et al.	2008	67/F	t(9;22) (p24;q11)	AML	Death at 22-month FU from disease relapse
3	Lane et al.	2008	44/M	t(9;22) (p24;q11.2)	aCML	Presented with extramedullary site involvement
4	Tirado et al.	2010	14/M	t(9;22) (p24;q11.2)	B-ALL	CHR at 6-month FU
5	Angelova et al.	2011	53/M	as part of complex karyotype	MPN/MDS	Death at 2-month FU from blast crisis
6	Impera et al.	2011	49/F	t(9;18;22)(p23;p11.3;q11.2)	MPN/MDS	CHR at 21-month FU
7	Roberts et al.	2012	2.7/M	as part of complex karyotype	B-ALL	ND
8	Cuesta-Domınguez et al.	2012	58/M	as part of complex karyotype	B-ALL	CR at 72-month FU
9	Elnaggar et al.	2012	84/M	t(9;22) (p24;q11.2)	aCML	Survival at 84-month FU
10	Bellesso et al.	2013	54/M	t(9;22) (p24;q11.2)	aCML	Death at 32-month FU from aGVHD
11	Xu et al.	2013	28/M	ins(22;9) (q11;p13p24)	aCML	CHR at 27-month FU
12	Schwaab et al.	2014	ND/M	t(9;18) (p24;q12)	aCML	Relapse at 18-month FU on Ruxolitinib
13	A.N. Chamseddine et al.	2015	49/M	t(9;22) (p24;q11)	MPN-U	CMR at 39-month FU
14	Kantarcioglu et al.	2015	64/F	as part of complex karyotype	MDS	Death at 4-month FU
15	He R et al.	2016	36/F	as part of complex karyotype	MPN-U	CHR at 18-month FU
16	Duployez N et al.	2016	58/M	t(9;22;15)(p24;q11;q21)	MPN-U	Progress at 10-month FU
17	Pessach et al.	2017	55/M	t(9;22) (p24;q11)	MPAL	Death from cGVHD

acute lymphoblastic leukemia (B-ALL)].

Our case is the first case of a patient diagnosed with MPAL while harboring a BCR-JAK2 fusion gene; indicating further that t(9;22)(p24;q11.2) translocation can occur in a more primitive progenitor capable for differentiation to both myeloid and lymphoid lineage.

Recently, a subgroup of B-ALL with a gene expression profile similar to Philadelphia-positive B-ALL, but lacking the BCR-ABL1 fusion gene, has been described in both children and adults. This subtype of B-ALL has given the name Phi-like B-ALL and is associated with high risk of relapse and shortened overall survival.[2] The percentage of adults with Phi-like B-ALL has been estimated as 30% among the Philadelphia-negative B-ALL cases. Interestingly, a significant number of Phi-like ALL cases harbor JAK2 mutations, highlighting the importance of JAK-STAT signaling in the pathogenesis of this B-ALL subtype.[3]

The importance behind the identification of JAK2 mutations and rearrangements is the potential therapeutic efficacy of JAK2-inhibitors. Regarding treatment, JAK2 inhibitors, either alone or in combination with standard chemotherapy may be promising for patients with JAK2-rearranged hematologic malignancies.[4] In support of this, there are reports of PCM1-JAK2-positive patients who achieved long term remissions on ruxolitinib. However, though long term the responses, later reports on PCMI-JAK2 and BCR-JAK2 patients showed relapse eventually.[5] As a result, ruxolitinib and other JAK2 inhibitors can be an effective treatment both for fit patients who are eligible for stem cell transplantation – the only curative treatment till today, as well as for unfit patients.

To conclude, the BCR-JAK2 fusion protein contains both the dimerization domain of BCR and the protein tyrosine kinase domain of JAK2, and is a very active tyrosine kinase with transforming and tumorigenic prop-

erties leading to abnormal cell proliferation. These rare BCR-JAK2 fusions, suggest common pathways between JAK2 activation and the pathogenesis of myelo/lymphoproliferative hematologic malignancies. Regarding prognosis, BCR-JAK2 positive neoplasms are aggressive and premise allogeneic stem cell transplantation (ASCT) for long-term remission – even in the era of JAK2 inhibitor ruxolitinib. Thus, patients with atypical CML and acute types of leukemia associated with t(9;22)(p24;q11.2)/BCR-JAK2 should be documented in order to elucidate the incidence of BCR-JAK2 fusion in the development of leukemia in the general population. Also, further investigation and identification of all these conditions is important because of the possibility of response to existing JAK2 inhibitors or ASCT. To our knowledge, this is the first case with MPAL and a JAK2-rearrangement reported so far.

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Conflict of Interest: None.

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