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CASE REPORT

Myelodysplastic syndrome with t(9;22)(p24;q11.2), a BCR-JAK2 fusion: case report and review of the literature

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Abstract The human JAK2 gene is mainly targeted by two types of genetic lesions that play roles in the pathogenesis of hematologic malignancies: intragenic mutations and chromosomal translocations. Chromosomal translocations of JAK2 are typically associated with myeloid or lymphoid malignancies with an aggressive course and poor outcome. Here we report a t(9;22)(p24;q11.2) translocation, in a MDS patient and review results associated with BCR-JAK2 fusion reported in the literature.

Keywords t(9;22) · Myelodysplastic syndrome · BCR-JAK2 · Fusion gene · JAK2 rearrangement

Introduction

The translocation t(9;22)(p24;q11.2) is a rare event that results in the fusion of Janus activated kinase 2 (JAK2) to BCR and thus leads to the activation of the JAK2. The consequences of JAK2 activation are neoplastic transformation and abnormal cell proliferation in various malignancies [1–4].

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The human JAK2 gene is mainly targeted by two types of genetic lesions playing a role in the pathogenesis of hematologic malignancies. The first one is intragenic mutations such as point mutations or insertions/deletions (e.g. exon 12–14 mutations) and the second one is chromosomal translocations. The somatic V617F gain-of-function mutation in exon 14 of JAK2 gene, and less common exon 12 mutation of JAK2 have been found in ≥95 % of patients with polycythemia vera and about in 50 % of patients with essential thrombocythemia and myelofibrosis. The chromosomal translocations of JAK2 appear to lead to gene fusions such as PCMI-JAK2, ETV6–JAK2, or BCR–JAK2 and are usually associated with myeloid or lymphoid malignancies with an aggressive course and poor outcome. In most cases, long-term remissions have only been achieved after allogeneic stem cell transplantation (ASCT) [1–4].

The product of t(9;22)(p24;q11.2) translocation which leads to formation of BCR-JAK2 fusion is a very rare event in the literature. Here we report a t(9;22)(p24;q11.2) translocation in a MDS patient indicating that the addition of this translocation maybe a precursor lesion causing disease progression, and can be related with poor prognosis.

Written informed consent was obtained from the patient's family for publication of this manuscript and accompanying images.

Case report

A 64 year old female patient presented to emergency department of Marmara University Hospital in November 2008 with history of fatigue for 1 month and new onset high grade fever with chills. Her complete blood count was consistent with pancytopenia in which her white blood cell (WBC) count was 800/mcl, Hb 9.1 g/dl and platelet count

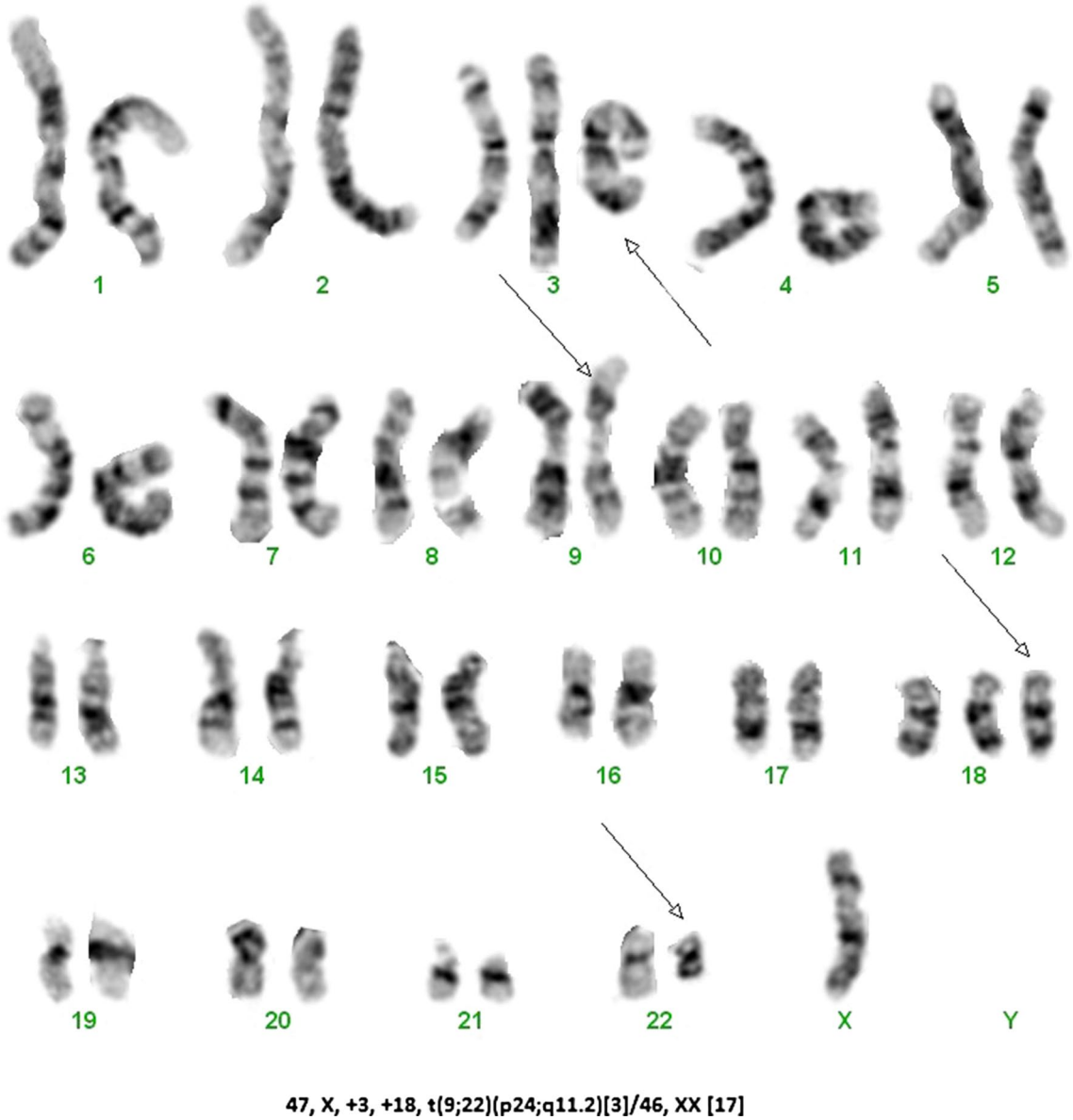

Fig. 1 Conventional cytogenetics showing; 47, X; +3, t(9;22)(p24;q11.2), +18[3]/46, XX [17]

was 1,04,000/mcl. In her physical examination she did not have spleen enlargement and peripheral lymphadenopathy. The patient was hospitalized for neutropenic fever and she was started on broad spectrum antibiotics.

A bone marrow aspiration and biopsy were performed, which revealed hypercellularity with myeloid erythroid ratio of 2–3:1, blasts were 2–3 %. In myeloid lineage, maturation was continuous with hypogranulation and Pseudo-pelger Huet cells. In erythroid lineage, there were nucleocytoplasmic dyssynchrony and cytoplasmic budding. Megakaryocytes were increased and hypolobulated. There was grade 2–3 reticulin fibrosis. Flow cytometric analysis of bone marrow was insignificant, showing no evidence of B cell lymphoproliferative disease. Bone marrow cytogenetics demonstrated a pathological clone in 3 of 20 metaphases; 47, X; +3, t(9;22)(p24;q11.2), +18[3]/46, XX [17], which showed a translocation between chromosome 9 and 22. FISH or RT-PCR analysis for BCR-JAK2 was not available in our institution at that time. Interphase FISH for t(9;22)(q34;q11.2) and RT-PCR for BCR-ABL1 were negative. The patient was diagnosed as having a myelodysplastic syndrome-refractory cytopenia with multilineage dysplasia (MDS-RCMD) (Fig. 1).

After the infection was resolved, she started to receive G-CSF and red cell transfusions for supportive care, and was discharged. In the follow up, her leukocyte count

Table 1 Features of myeloid and lymphoid neoplasms associated with t(9;22)(p24;q11.2) and BCRJAK2 fusion

References	Age	Gender	WBC	Splenomegaly	BM blasts	Cytogenetics	Fusion gene	Type of disease	Treatment	Clinicial course
Griesinger et al. [5]	63	F	42,000	Left upper quadrant pain	<5 %	t(9;22)(p24;q11.2)	BCR-JAK2	Atypical CML- > myeloid blast crisis	Hydroxyurea-IFN- high dose ARAC/mitox-antrone induction	Died after 24 months after diagnosis
Cirmena et al. [6]	67	F	NA	NA	25 %	t(9;22)(p24;q11)	BCR-JAK2	AML-M1	High dose chemotherapy allogeneic HSCT salvage protocol	Died after 8 months after diagnosis
Lane et al. [7]	44	M	11,900	NA	1 %	t(9;22)(p24;q11.2)	BCR-JAK2	Atypical CML leuke-mia Cutis	NA	Presented with extramedullary site involvement
Impera et al. [8]	49	F	18,400	NA	NA	t(9;18;22)(p23;p11.3; q11.2)	BCR-JAK2	MDS/MPN	Imatınıb refractory dasatinib refractory	In hematological remission after 1 year treatment with IFN
Angelova et al. [9]	53	M	18,000	NA	1%	t(9;22)(p24;q11)	BCR-JAK2	MDS/MPN	Refused treatment blast crisis	Died after 2 months after diagnosis
Elnaggar et al. [10]	84	M	98,000	Present	Normal	t(9;22)(p24;q11.2)	BCR-JAK2	Atypicial CML	Hydroxyurea imatinib	Lost the follow up but survived >7 years
Xu et al. [11]	28	M	50,000	Present	NA	ins(22;9)(q11;p13p24)	BCR-JAK2	Atypical CML	Low dose IFN alpha and hydroxyurea	In remission more than 3 years
Bellesso et al. [12]	54	M	93,380	Present	NA	t(9;22)(p24;q11.2)	BCR-JAK2	Atypical CML	Hydroxyurea allogeneic HSCT	Died postransplant day 53 due to aGVHD
Schwaab et al. [13]	NA	NA	46,300	NA	NA	t(9;18)(p24;q12)	BCR-JAK2	Atypical CML	Ruxolitinib allogeneic HSCT	Relapse occured 18th month of ruxolitinib. Allogeneic HSCT performed
Tirado et al. [14]	14	M	25,3000	NA	80 % in PB	t(9;22)(p24;q11.2)	?-JAK2	B-ALL	Induction chemo 2nd line induction chemo allogenec HSCT	In remission in 6 months of follow up
Cuesta-Domínguez et al. [15]	58	M	10,800	Present	58%	49, XY, +X, +2, +4,29, 211, +19, add(19)(q13), +20,222, +mar	BCR-JAK2	B-ALL	Induction chemotherapy consolidation	In remission more than 6 years of follow up
Roberts et al. [16]	27	M	95,8000	NA	NA	47,XY,+2, del(2)(p23), t(3;22;9)(p12;q11.2; p24)[10]/46, XY[2]	BCR-JAK2	B-ALL	NA	Treated as Ph-like high risk ALL
The presented case	64	F	800	Not present	5 %	t(9;22)(p24;q11.2)	NA	MDS	Supportive care	Died after 3 months after diagnosis

WBC white blood cell, *NA* not aplicable, *CML* chronic myeloid leukemia, *AML* acute myeloid Leukemia, *ALL* acute lymphoblastic leukemia, *IFN* interpheron, *HSCT* hematopoetic stem cell transplantation, *MDS* myelodysplastic syndrome, *GVHD* graft versus host disease

normalized. She needed periodic red blood cell transfusions for the developing anemia. She did not need any platelet transfusion. She was doing so well until February 2009 that she refused any kind of chemotherapy.

In February 2009 her leukocyte and Hb levels started to decrease and she had another febrile neutropenic episode which needed hospitalization. During hospitalization with the suspicion of disease progression she had another bone marrow examination. The morphology was the same with 5 % of blasts, hypercellularity and reticulin fibrosis in marrow but bone marrow cytogenetics showed a larger population of pathological clone in which there was 47, X; +3, t(9;22)(p24;q11.2), +18[13]/46, XX [2] in 13 of 15 metaphases. After obtaining this data she was offered to take low intensity chemotherapy. She was scheduled to start a hypomethylating agent but she died of hospital acquired pneumonia with sepsis in March 2009.

Discussion

Here we report a case of myelodysplastic syndrome carrying t(9;22)(p24;q11.2) which suggests the formation of the BCR-JAK2 fusion gene. The translocation t(9;22)(p24;q11.2) has been rarely reported as a recurrent abnormality in some leukemia types. To date, a total of 12 cases, comprising with BCR-JAK2 fusion have been published. Among them only 7 cases were carrying the translocation t(9;22)(p24;q11.2). The age range was 2, 7–84 years. Among these patients, the BCR-JAK2 fusion mostly presented clinically as a myeloid neoplasm ($n = 9/12$) at the time of diagnosis. (Atypical CML $n = 6$; AML $n = 1$; MDS/MPN $n = 2$) There were 3 other cases primarily diagnosed with a lymphoid malignancy that have been reported ($n = 3/12$): all three cases were B-ALL. In two cases, transformation into blast crisis during the course of the disease was reported: both patients developed a myeloid blast crisis presenting as AML, one developed after an atypical CML and the other developed after a MDS/MPN. In these presented cases, the clinical course was generally aggressive; most of the patients were resistant to conventional therapeutics. While in myeloid type of cases four of nine patients died within approximately 2, 5 years after diagnosis. One atypical CML case presented with leukemia cutis which is a sign of poor prognosis in a myeloid malignancy. Two atypical CML case had to receive allogeneic HSCT during the course of their disease. Only 3 myeloid type of case survive in long term without high dose therapies. However, two of three patients that were diagnosed with B-ALL have been reported that they had survived with remission. This is perhaps because they were known to have a high-risk disease, and received appropriate effective treatment option. Another explanation of this situation is the outcome maybe dependent on the phenotype of the disease. Eventually the precise treatment option for BCR-JAK2 fusion remains uncertain. (Table 1).

Recently, the in vitro efficacy of the janus kinase inhibitor ruxolitinib against JAK2 fusions was described[17]. After that the first two PCM1-JAK2-positive patients who achieved remissions on ruxolitinib were reported [18, 19]. Following that, another PCMI-JAK2 and a BCR-JAK2-positive patient, who were both treated with ruxolitinib were reported; initial responses were very good but relapse occurred eventually and allogeneic HSCT had to be performed [13]. And authors mentioned ruxolitinib as the most useful treatment option before ASCT in eligible patients.

As a result t(9;22)(p24;q11.2) is a very rare genetic event and is the identical counterpart of BCR-JAK2 fusion cytogenetically. It may cause both myeloid and lymphoid neoplasms. Especially, the prognosis is worse than expected, when it occured in myeloid type of malignancy. Although more data is needed to make a decision, early results of JAK2 inhibition with ruxolitinib is promising, but the duration of response is limited. Even newer generation JAK2 inhibitors may have a potential role in this regard, today allogeneic HSCT is the only curative treatment option in eligible patients.

Although further studies are needed to understand the importance and the role of t(9;22)(p24;q11.2) in disease production, we strongly encourage colleagues considering a possible BCR-JAK2 fusion. We want to emphasize the activity of JAK2 inhibition and highlight the curative potential of allogeneic HSCT for consideration. To our knowledge it is the first reported case of t(9;22)(p24;q11.2) in a patient with myelodysplastic syndrome.

Conflict of interest The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

References

1. Smith CA, Fan G. The saga of JAK2 mutations and translocations in hematologic disorders: pathogenesis, diagnostic and therapeutic prospects, and revised World Health Organization diagnostic criteria for myeloproliferative neoplasms. Hum Pathol. 2008;39(6):795–810.
2. Tefferi A. JAK and MPL mutations in myeloid malignancies. Leuk Lymphoma. 2008;49(3):388–97.
3. Walz C, Cross NC, Van Etten RA, Reiter A. Comparison of mutated ABL1 and JAK2 as oncogenes and drug targets in myeloproliferative disorders. Leukemia. 2008;22(7):1320–34.
4. Bain BJ, Ahmad S. Should myeloid and lymphoid neoplasms with PCM1-JAK2 and other rearrangements of JAK2 be recognized as specific entities? Br J Haematol. 2014;166:809–17.
5. Griesinger F, Hennig H, Hillmer F, Podleschny M, Steffens R, Pies A, et al. A BCR-JAK2 fusion gene as the result of a t(9;22)(p24;q11.2) translocation in a patient with a clinically

typical chronic myeloid leukemia. Genes Chromosomes Cancer. 2005;44(3):329–33.
6. Cirmena G, Aliano S, Fugazza G, Bruzzone R, Garuti A, Bocciardi R, et al. A BCR-JAK2 fusion gene as the result of a t(9;22)(p24;q11) in a patient with acute myeloid leukemia. Cancer Genet Cytogenet. 2008;183(2):105–8.
7. Lane SW, Fairbairn DJ, McCarthy C, Nandini A, Perry-Keene J, Kennedy GA. Leukaemia cutis in atypical chronic myeloid leukaemia with a t(9;22)(p24;q11.2) leading to BCR-JAK2 fusion. Br J Haematol. 2008;142(4):503.
8. Impera L, Lonoce A, Fanfulla DA, Moreilhon C, Legros L, Raynaud S. Two alternatively spliced 5′BCR/3′JAK2 fusion transcripts in a myeloproliferative neoplasm with a three-way t(9;18;22) (p23;p11.3;q11.2) translocation. Cancer Genet. 2011;204:512–5.
9. Angelova S, Spassova S, Toshkov S, Shivarov V. Chromosomal translocation t(9;22) (p24;q11) appears to be recurrently associated with myeloid malignancy with aggressive course. Leuk Lymphoma. 2011;52(9):1809–10.
10. Elnaggar MM, Agersborg S, Sahoo T, Girgin A, Ma W, Rakkhit R, et al. BCR-JAK2 fusion as a result of a translocation (9;22)(p24;q11.2) in a patient with CML-like myeloproliferative disease. Mol Cytogenet. 2012;5(1):23.
11. Xu Y, Yin J, Pan J, Wu C, Wang Q, Yao H, et al. A BCR-JAK2 fusion gene from ins(22;9) (q11;p13p24) in a patient with atypical chronic myeloid leukemia. Leuk Lymphoma. 2013;54(10):2322–4.
12. Bellesso M, Santucci R, Dias DF, Centrone R, Elias RC. Atypical chronic myeloid leukemia with t(9;22) (p24,11.2), a BCR-JAK2 fusion gene. Rev Bras Hematol Hemoter. 2013;35:218–9.
13. Schwaab J, Knut M, Haferlach C, Metzgeroth G, Horny HP, Chase A. Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes. Ann Hematol. 2015;94:233–8.
14. Tirado CA, Chen W, Huang LJ, Laborde C, Hiemenz MC, Valdez F, et al. Novel JAK2 rearrangement resulting from a t(9;22)(p24;q11.2) in B-acute lymphoblastic leukemia. Leuk Res. 2010;34(12):1674–6.
15. Cuesta-Domínguez Á, Ortega M, Ormazábal C, Santos-Roncero M, Galán-Díez M, Steegmann JL, et al. Transforming and tumorigenic activity of JAK2 by fusion to BCR: molecular mechanisms of action of a novel BCR-JAK2 tyrosine-kinase. PLoS One. 2012;7(2):e32451.
16. Roberts KG, Morin RD, Zhang J, Hirst M, Zhao Y, Su X, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012;22(2):153–66.
17. Chase A, Bryant C, Score J, Haferlach C, Grossmann V, Schwaab J, et al. Ruxolitinib as potential targeted therapy for patients with JAK2 rearrangements. Haematologica. 2013;98(3):404–8.
18. Lierman E, Selleslag D, Smits S, Billiet J, Vandenberghe P. Ruxolitinib inhibits transforming JAK2 fusion proteins in vitro and induces complete cytogenetic remission in t(8;9) (p22;p24)/PCM1-JAK2-positive chronic eosinophilic leukemia. Blood. 2012;120(7):1529–31.
19. Rumi E, Milosevic JD, Casetti I, Dambruoso I, Pietra D, Boveri E, et al. Efficacy of ruxolitinib in chronic eosinophilic leukemia associated with a PCM1-JAK2 fusion gene. J Clin Oncol. 2013;31(17):e269–71.