CASE REPORT

A case of acute myelogenous leukaemia characterised by the BCR-FGFR1 translocation

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SUMMARY

The 8p11 myeloproliferative syndrome is a rare atypical disorder defined by the presence of rearrangements between the fibroblast growth factor receptor 1 (FGFR1) and 1 of 13 partner genes described to date, including the BCR gene on chromosome 22. The disease characterised by the BCR-FGFR1 fusion gene has distinct biological and clinical features, with significant diversity among the published cases. We report a case of BCR-FGFR1 disease which was presented as acute myeloid leukaemia with an aggressive clinical course and we review all the adult cases published in the literature.

BACKGROUND

The 8p11 myeloproliferative syndrome (EMS) is a rare atypical disorder defined by the presence of rearrangements between the fibroblast growth factor receptor 1 (FGFR1) and 1 of 13 partner genes described to date, with the most common being ZMYM2 (ZNF198) on chromosome 13q12, and is characterised by myeloid hyperplasia, eosinophilia and lymphadenopathy.¹ Patients carrying the t(8;22)(p11;q11) translocation and the subsequent BCR-FGFR1 fusion gene follow an aggressive course. Since it was first described in 2001 until now,² only 11 cases of this rare entity have been reported.³⁻⁴ It usually presents as chronic myelogenous leukaemia-like (CML-like) disease which rapidly progresses to blast crisis, but two cases of B-acute lymphoblastic leukaemia (B-ALL) have also been reported.³⁻⁵ Here, we present a case of t(8;22)/BCR-FGFR1 rearrangement, which was presented as acute myelogenous leukaemia (AML) and we review all the adult cases published in the literature.

CASE PRESENTATION

A 74-year-old woman was referred to our department for further evaluation of leucocytosis. The patient was at her usual state of health until 1 month before admission (September 2011), when she suffered a left femoral head fracture. Laboratory testing undertaken at the hospital where she was operated was reportedly normal. Two weeks after the operation, a follow-up complete blood count revealed leucocytosis with monocytosis and anaemia and the patient was referred to the Hematology, Lymphoma and Bone Marrow Transplant Department, 'Evangelismos' Athens General Hospital. The rest of her medical history and the physical examination were unremarkable.

INVESTIGATIONS

Complete blood count confirmed the previous findings (white blood cell count (WBC) 59,840/μl 30% neutrophils, 7% lymphocytes, 42% monocytes/Ht 33.3%, haemoglobin 10.8 gr/dl/PLT 200 000/μl). Examination of peripheral blood and bone marrow smears revealed the presence of blasts >80% with no Auer rods. Immunophenotypic characteristics were CD13(+), CD33(+) 24%, CD34(+)weak, CD38(+)weak, CD117(-), HLA-DR(+), MPO(-), further classifying it as FAB M0 AML. Chromosome analysis by GTG banding and FISH performed at a third-party laboratory were diagnostic of the BCR-FGFR1 translocation: 46,XX,del(5)q33q35,t(8;22)(p11;q11) (figure 1). Detection of the bcr-abl fusion gene by PCR was negative. Further characterisation of the translocation by DNA sequencing was not possible due to unavailability of the technique.

TREATMENT

The patient was treated with two cycles of 2 days idarubicin and 5 days cytarabine, without achieving a complete response (minimal residual disease 0.56% as detected by flow cytometry). Owing to the rapid increase of WBC (120 000/μl day 38 of the second cycle) the patient was offered again cytarabine with no response and then a cycle of 2 days mitoxandron and 5 days etoposide, achieving morphological remission but with excess toxicity. The remission was of very short duration and subsequent trials of interferon α, hydroxyurea and fludarabine failed to control WBC.

OUTCOME AND FOLLOW-UP

Taking into account the patient's age and ineligibility for stem cell transplant, the aggressive clinical course and the failure of multiple chemotherapeutic regimens, comfort measures were offered and the patient died 9 months after the diagnosis.

DISCUSSION

To our knowledge, this is the 12th published case of t(8;22)/BCR-FGFR1 rearrangement. All the other cases are presented in table 1. Our case confirms the diversity of the clinical and pathological hallmarks of this rare entity. Constitutive activation of FGFR1, thought to activate the AKT and MAPK signalling pathways, is considered to be the primary oncogenic event.⁶ However, consistent with the other BCR-FGFR1 cases, our patient did not share the common EMS features such as lymphadenopathy and eosinophilia. This implies that BCR and subsequently all the partner genes may have a role

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Figure 1 Karyotype of the patient: 46,XX,del(5)(q33q35),t(8;22)(p11;q11) (abnormalities marked by asterisks).

in the pathogenesis of the disease, each resulting in a distinct malignant phenotype.⁷ Furthermore, the biphenotypic nature of the disease supports the hypothesis that the cell of origin in EMS is a pluripotent stem cell.⁸ Contrary to previous cases, our patient presented with AML without a documented CML-like phase and she did not harbour chromosomal abnormalities that disrupt RUNX1, as was the case with two cases that progressed to AML. Chromosome 5 deletions, such as the one our patient had, are common in acute myelogenous leukaemia but are

usually associated with previous treatment with alkylating agents.⁹

The rapid course and fatal outcome are clear indicators that better treatment strategies are needed. Although allogeneic stem cell transplantation has been reported to result in complete remission, it is not always feasible.⁴⁻⁸ The response to conventional chemotherapy is brief and bcr-abl inhibitors have no activity.¹⁰ A trial of interferon α was given based on data that show modest response among patients with FGFR1 EMS, with

Table 1 Summary of the clinical and genetic characteristics of the 11 published cases of BCR-fibroblast growth factor receptor 1 syndrome in adult patients

Patient	Author, date	Age, Sex	Clinical presentation	Chromosomal abnormalities	Treatment	Outcome
1	Fioretos, 2001 ²	75, male	AML	46,XY,t(8;22)(p11;q11), t(9;21)(q34;q22)	Not reported	Not reported
2	Demiroglou, 2001 ¹⁰	65, female	Chronic CML	Not reported	Hydroxyurea, IFN α	Alive on publication
3	Demiroglou, 2001 ¹⁰	51, female	Chronic CML	Not reported	Hydroxyurea, IFN α	Alive on publication
4	Pini, 2002 ¹⁵	74, female	Chronic CML	Not reported	Not reported	Not reported
5	Murati, 2005 ¹⁶	Not available	Chronic CML and B cell proliferation	Not available	Not available	Not available
6	Agerstam, 2007 ¹⁷	58, female	AML	46,XX,t(8;22)(p11;q11)	Not reported	Not reported
7	Richebourg, 2008 ¹⁸	56, female	CML, evolved to blast crisis	47,XX,t(3;21)(q26;q22), t(8;22)(p11;q11),+der(22) t(8;22)	Hydroxyurea+IFN α , arsenic trioxide, cytarabine, daunorubicin+cytarabine	Death 24 months after presentation
8	Baldazzi, 2010 ⁵	70, female	pre-B ALL	45,XX,del(3)(p11p21), del(7)(p12p15), t(8;22)(p11;q11), add(8)(p23),-9	Induction combination chemotherapy	Death 11 months after presentation
9	Wakim, 2011 ³	43, male	B-ALL	45,XY,t(6;11)(q11;p13),-7, t(8;22)(p11.2;q11.2), del(9)(p13p22)	Hyper-CVAD	Death
10	Haslam, 2012 ⁴	21, male	B-ALL	46,XY,t(8;22)(p12;q11)/45,idem,der(3;9)(q10;q10),dic(7;11)(p11;q13),+r[cp3]	UKALL 2003, FLAG-Ida and allogeneic HSCT	Alive on publication
11	Morishige, 2012 ⁸	50, male	Trilineage acute leukaemia lymphoma	Not available	Cord blood transplantation	Alive on publication

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CML, chronic myeloid leukaemia; FLAG-Ida, Fludarabine, Idarubicin, Cytarabine; HSCT, haematopoietic stem cell transplantation; Hyper-CVAD, Cyclophosphamide, Vincristine, Doxorubicin alternating with Methotrexate, Cytarabine; IFN α , interferon α ; UKALL 2003, Vincristine, Prednisolone/dexamethasone, L-asparaginase, Daunorubicin.

no response.¹¹ Targeted anti-FGFR treatment with sorafenib, a multikinase inhibitor, has been used for the treatment of a patient with BCR-FGFR1 B-ALL inducing a brief hematological response.³ The introduction of more potent FGFR inhibitors in clinical therapeutics like SU5402 offers a new alternative. Ponatinib is an oral multikinase inhibitor that exhibits encouraging activity against the fusion protein BCR-ABL, including the product of the resistant T315I mutation.¹² It also exhibits pan-FGFR inhibitory activity, making it a candidate for future applications in the treatment of BCR-FGFR1 syndrome.¹³

Recently, a murine model was described which mimics this disease with the BCR-FGFR1 chimeric kinase leading to bilineage myeloid and B cell leukaemia/lymphoma, a development that may lead to a better understanding of the pathophysiology of the disease and to the optimisation of therapeutic interventions.¹⁴

Learning points

- ▶ BCR-fibroblast growth factor receptor 1 (BCR-FGFR1) is 1 of 13 possible fusion genes described that result in the 8p11 myeloproliferative syndrome.
- ▶ The BCR-FGFR1 syndrome can present as chronic myelogenous leukaemia, acute myelogenous leukaemia, acute lymphoblastic leukaemia or with bilineage features.
- ▶ Its clinical course is aggressive and the disease is chemoresistant; successful treatment with stem cell transplant has been reported.
- ▶ Future treatment prospects include targeting the protein product of the driver mutation.

Competing interests None.

Patient consent Obtained.

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