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Case Report

FIP1L1-PDGFRA Mutation in a Patient with Hypereosinophilia after Treatment for Lymphoblastic T non-Hodgkin Lymphoma

Mesut Ayer[1]*, Nükhet Tüzüner[2], Ayşegül Yılmaz Karaca[3], Fatma Aylin Ayer[4], Makbule Ulusoy[4], Yeşim Gürkan[4], and Hilal Günaydın[1]

[1]*Department of Hematology, Haseki Training and Research Hospital, Turkey*
[2]*Department of Pathology, İstanbul University, Turkey*
[3]*Department of Family Medicine, Haseki Training and Research Hospital, Turkey*
[4]*Department of Internal Medicine, Haseki Training and Research Hospital, Turkey*

***Corresponding author**
Mesut Ayer, Department of Hematology, Haseki Training and Research Hospital, Hematology Polyclinic Akasaray, Fatih/Istanbul, Turkey, Tel: 90-2125-294-400; Email: mesutayerdr@hotmail.com

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Abstract

FIP1L1-PDGFRA fusion gene, which has been reported in patients with hypereosinophilic syndrome or hypereosinophilia associated malignancies, is an important marker that led us perform molecular targeting treatment. FIP1L1-PDGFRA fusion gene, could occur primarily or secondary to a chemotherapy procedure or radiation.

Here we report a case with FIP1L1-PDGFRA positive hypereosinophilic syndrome that was taken given chemotherapy for lymphoblastic T non-Hodgkin lymphoma. Hematological and cytogenetic remission of hypereosinophilic syndrome after treatment with low doses of imatinib was achieved. Response to low doses of tyrosine kinase inhibitors is excellent whether the translocation is primary or secondary.

More than one hundred reported cases confirm the positive outcome with low-doses of imatinib, but it is still controversial how long the therapy should be performed and when should be stopped.

The case is reported because it can be added to the few reported in the literature where FIP1L1-PDGFRA fusion gene is secondary to chemotherapy.

INTRODUCTION

Factor interacting with Poly(A) polymerase alpha-Platelet-derived growth factor receptor-α(FIP1L1-PDGFRA) fusion is a clonal marker which was described in patients with hypereosinophilic syndromeas well as Myeloproliferative Neoplasms (MPNs)associated with hypereosinophilia. FIP1L1-PDGFRA was reported in patients with acute myeloid leukemia (AML) and lymphoblastic T-cell non-Hodgkin-lymphoma (T-NHL) [1], and Polycythemia Vera [2].

Fusion genes, such as BCR-ABL in chronic myeloid leukemia (CML), are encoding novel chimeric kinase proteins leading absence of natural ligands resulting in disregulation of hemopoiesis [1]. Molecular studies suggested that FIP1L1-PDGFRA may increase the proliferation of multipotent myeloid progenitors, but does not block cell differentiation. FIP1L1-PDGFRA fusion gene could replace hematopoietic growth factors and promote differentiation into the granulocyte/macrophage lineage [3]. As a result, fusion genes could provide clonal proliferation of any hematological cell lineage besides eosinophils.

Hypereosinophilia associated MPNs are very rare, so the certain prevalence of FIP1L1-PDGFRA fusion gene is unknown. More than a hundred cases of FIP1L1-PDGFRA-positive MPNs are reported to date, only two of them are secondary to chemotherapy for a primary cancer [4,5] and one of them was after occupational and therapeutic exposure to radiation [6]. The three aforementioned cases were diagnosed as chronic eosinophilic leukemia (CEL).

Here we report a patient with FIP1L1-PDGFRA positive hypereosinophilic syndrome after one year from Hyper CVAD therapy for his primary T-NHL.

CASE PRESENTATION

Fifty-two-year-old man admitted internal medicine polyclinic 4 years ago due to the appearance of lymphadenopathy in the laterocervical, axillary and inguinal regions. He was diagnosed as

lymphoblastic T non-Hodgkin lymphoma (T-NHL) after the biopsy from inguinal region. He took 8 cures of Hyper-CVAD therapy and accepted in remission and referred to our hematology polyclinic for his further follow up.

After hyper-CVAD therapy, physical examination revealed no lymphadenopathy or hepatosplenomegaly, as well as thorax and abdominal CT. Pathological FDG enhancement was not detected in PET CT. Prophylactic cranial irradiation was also performed. After one year under the maintained therapy, hypereosinophilia and neutrophilic leukocytosis were detected. Bone marrow biopsy was repeated in order to determine CML or any MPNs. Cytogenetic analysis for BCR/ABL t(9;22), t(4;11) and trisomy 8 was negative, where FIP1L1-PDGFRA fusion gene, employing the polymerase chain reaction (PCR) assay, was positive in bone marrow material. (FIP1L1-PDGFRA fusion gene analysis did not perform before start chemotherapy at the T-NHL diagnosis). After therapy with imatinib mesylate, the patient got into complete hematologic and molecular remission; this led us to stop therapy. The patient did not have relapse for two years.

The patient is now being follow up without chemotherapy.

DISCUSSION

Detecting fusion genes such FIP1L1-PDGFRA in hypereosinophilia, or BCR-ABL in CML, gave us specific treatment options in the area of molecular targeting treatment. FIP1L1-PDGFRA positive hypereosinophilia associated malignancies are very good candidates for treatment with tyrosine kinase inhibitors and their response to therapy is excellent even they have aggressive clinical manifestation [1].

FIP1L1-PDGFRA fusion gene can occur spontaneously or secondary to chemotherapy or radiotherapy. To date, more than a hundred of FIP1L1-PDGFRA positive malignancies reported, only two of them were secondary to chemotherapy and one of them was secondary to radiotherapy and occupational exposure to radiation [4-9].

In our case, primary diagnose was T-NHL and the patient took 8 cures of Hyper-CVAD therapy and prophylactic cranial irradiation was performed. After one year of the chemotherapy, when the patient was in complete hematological remission for T-NHL, hypereosinophilia and neutrophilia occurred and FIP1L1-PDGFRA fusion gene was positive. At the time of T-NHL was diagnosed, there was no evidence of hypereosinophilia, ~~and~~ therefore FIP1L1-PDGFRA fusion gene analysis was not performed.

Recent studies showed that, FIP1L1-PDGFRA positive patients with eosinophilia associated hypereosinophilic malignancies are excellent candidates for treatment with tyrosine kinase inhibitors, even if they present with an aggressive phenotype such as AML. Thus, all patients with hypereosinophilia associated malignancies should be screened for the presence of FIP1L1-PDGFRA [1].

Hypereosinophilia associated malignancies, whether primary or secondary, are well treated with low doses of imatinib if they are positive for FIP1L1-PDGFRA fusion gene. A 27 patient's follow up study presenting long term results of FIP1L1-PDGFRA positive CEL after imatinib, showed that treatment with low doses of imatinib may maintain molecular remission despite low imatinib plasma levels [10]. A study of 19 patients, which 8 of them were positive for FIP1L1-PDGFRAfusion gene, showed that treatment with low dose imatinib may maintain molecular remission [11].

In our case, after one year of treatment for primary T-NHL hypereosinophilia occurred and FIP1L1-PDGFRA was positive. Successful results achieved with low doses of imatinib and maintain therapy for two years was given. Re-analysis of FIP1L1-PDGFRA was negative and the patient was in complete hematological and cytogenetically remission. We stopped imatinib treatment and the patient is being followed up without relapse.

CONCLUSION

In conclusion, since in case of hypereosinophilia associated malignancies FIP1L1-PDGFRA fusion gene is reported, and since our patient at the time of first diagnosis did not show hypereosinophilia, we marked the FIP1L1-PDGFRA fusion gene as secondary to chemotherapy.

The case is reported because it can be added to the few reported in the literature where FIP1L1-PDGFRA fusion gene is secondary to chemotherapy. Moreover, in hypereosinophilic syndrome or hypereosinophilia associated malignancies FIP1L1-PDGFRA screening is always recommended; in these cases most patients achieving remission with low doses of tyrosine kinase inhibitors. It is still controversial when to stop treatment and longer follow up needed to clarify duration of treatment.

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