Clinical and Experimental Health Sciences

Search, Look, and See; Late Recognised Hypereosinophilic Syndrome with Deletion (4) (q12)

Nurhilal Büyükkurt[1], Funda Pepedil Tanrıkulu[2]

[1] Başkent University, Faculty of Medicine, Department of Hematology, Ankara, Türkiye.
[2] Adana City Hospital, Department of Hematology, Adana, Türkiye.

Correspondence Author: Nurhilal Büyükkurt
E-mail: nurhilalsk@gmail.com
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ABSTRACT

The hypereosinophilic syndrome (HES) is a group of rare disorders characterized by persistently high peripheral blood eosinophiles (≥ 1.5x109/L), and related signs or symptoms of organ involvement without secondary causes. Eosinophilia with recurrent genetic abnormalities (PDGFRA/B, FGFR1) comprises a minority of these patients. In this report, we aimed to point out a case with 4q12 deletion whose diagnosis and treatment were delayed for quite a while. The patient was followed for bronchial asthma for a long time and the recognition of hypereosinophilia yielded a suspicion for HES / Chronic eosinophilic leukemia (CEL). During the initial part of his diagnostic evaluation, there was an unawareness of the cryptic deletion which was a target for tyrosine kinases. The symptoms resolved and complete cytogenetic response was achieved with 100 mg imatinib continuing for 57 months.

Keywords: Hypereosinophilic syndrome, del (4) (q12), tyrosine kinase inhibitors

1. INTRODUCTION

The hypereosinophilic syndromes (HES) are a group of rare disorders characterized by a persistently high peripheral blood eosinophilia (≥ 1.5x109/L), signs or symptoms of organ involvement and no secondary causes such as allergies, atopic diseases and asthma, infections (mainly helminthic), autoimmune disorders, exposure to toxins, solid or hematopoietic neoplasias (1).

The incidence of eosinophilias with recurrent genetic abnormalities (PDGFRA/B, FGFR1) comprises a minority of these patients. Larger studies conducted in developing countries indicate that the FIP1L1-PDGFRA fusion occurs in approximately 10–20% of patients with idiopathic HES (2-4).

The severity of eosinophilia has been divided into mild (AEC from the upper limit of normal to 1,500/ mm^3), moderate (AEC 1,500–5,000/mm^3), and severe (AEC > 5,000/mm^3) (5-7).

The most common symptoms of patients have been showed weakness and fatigue, cough, dyspnea, myalgias or angioedema, rash or fever, and rhinitis in two retrospective studies (8). In the laboratory, peripheral eosinophilia in the range of 30–70% and leukocytosis up to 30000/mm3 or higher are common results (9-11). The other hematologic findings; as neutrophilia (in peripheral or bone marrow), basophilia, myeloid immaturity, and both mature and immature eosinophils with varying degrees of dysplasia can also be seen (12,13). All organ systems can be affected with sustained eosinophilia and can be seen insufficiencies of these systems (14).

The screening of the peripheral blood for the FIP1L1-PDGFRA gene fusion is the first step of evaluation of primary eosinophilia. FISH probes that hybridize to the region between the FIP1L1 and PDGFRA genes should be used to detect the presence of the cytogenetically occult 800-kb deletion on 4q12 that results in FIP1L1-PDGFRA. Absence of the FIP1L1-PDGFRA fusion should prompt evaluation for other primary eosinophilia associated with recurrent molecular abnormalities (8). We aimed with our case to point out examining the results of genetic assessment for primary HES. While incomplete or incorrect result evaluations may delay the appropriate treatment approach.

2. CASE PRESENTATION

A 47-year-old male patient admitted to our center for evaluation of leukocytosis with hyper – eosinophilia. He has been treated with inhaled steroids because of chronic cough

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lasting four years. The patient was consulted with hematology for eosinophilia which was noticed during the follow-up. The hypereosinophilia was confirmed by another center with controlling whole blood count and 90% eosinophiles were detected in the peripheral blood smear without blastic cells. The bone marrow smear and flow cytometric analyses revealed 23% eosinophiles without blastic transformation. The secondary causes and organ involvement were excluded by using molecular test of BCR-ABL and JAK2 V617F mutation, karyotype analysis of bone marrow cells, ultrasonographic evaluation of the abdomen, endoscopic review and endoscopic biopsy of the gastrointestinal system, high-resolution chest tomography, and echocardiography.

The fusion of FIP1L1 and PDGFRA was found negative by interphase-FISH and 1 mg/kg metilprednisolon po was initiated. However, there was not any regression in the eosinophilic leukocytosis or clinical symptoms. After the patient's admission to our center, we reviewed all the previous examinations and noticed that a FIP1L1and PDGFRA fusion had been found negative in the interphase FISH analysis with one-month interval, but as a remarkable result, 4q12 deletion had been found 24% and 74% respectively. The screening of the peripheral blood or the bone marrow for the FIP1L1-PDGFRA gene fusion is the first step of the evaluation of primary clonal eosinophilia. FISH probes that hybridize to the region between the FIP1L1 and PDGFRA genes should be used to detect the presence of the cytogenetically occult 800-kb deletion on 4q12 that results in FIP1L1-PDGFRA. This cryptic deletion of 4q12 producing the FIP1L1/PDGFRA fusion gene has been indicated as a distinct CEL subgroup. The results of interphase-FISH had been misinterpreted by the previous center. We have got approval for off-label use of imatinib mesylate from the Ministry of Health and started it immediately. The symptoms resolved and complete cytogenetic response was achieved with 100 mg imatinib continuing for 57 months.

3. DISCUSSION

The identification of FIB1L1/PDGFRA fusion gene in patients with HES/CEL, imatinib mesylate treatment has significantly changed the course of this disease (15). Regarding the reported literature, in one case series, some differences have shown in the clinical features between patients with HES and 4q-/CEL (17). The incidence of hepatomegaly and splenomegaly in the 4q-/CEL group has been found higher than the HES group. In our case, we did not found organomegaly. While this case series has the largest patient number according our knowledge, the authors detected 3 patients whose results did not completely fulfill the WHO criteria for either HES or CEL since they did not show end-organ involvement but del (4) (q12)-FIB1L1/PDGFRA lesion had been found. While except one issue which we did not detect increased blast in our patient's bone marrow examination with flow cytometric analysis, this description was also quite suitable for our patient as we mentioned above and we started imatinib mesylate immediately. We took very impressive results with imatinib treatment in our patient in term of symptoms and hematological parameters even which consist of complete cytogenetic response.

4. CONCLUSION

As targeted therapy with tyrosine kinas' inhibitors could dramatically change the prognosis of FIP1L1-PDGFRA (+) CEL/HES, we should be aware of misinterpreted test results which may retard the accurate diagnosis and treatment.

REFERENCES

[1] Klion AD. How I treat hypereosinophilic syndromes. Blood. 2015 Aug 27;126(9):1069-1077.

[2] Jovanovic JV, Score J, Waghorn K, Cilloni D, Gottardi E, Metzgeroth G, Erben P, Popp H, Walz C, Hochhaus A, Roche-Lestienne C, Preudhomme C, Apperley J, Rondoni M, Ottaviani E, Martinelli G, Finella Brito-Babapulle, Saglio G, Hehlmann R, C P Cross N, Reiter A, Grimwade D. Low-dose imatinib mesylate leads to rapid inductionof major molecular responses and achievement of complete molecular remission in FIP1L1-PDGFRA-positive chronic eosinophilic leukemia. Blood. 2007;109:4635–4640.

[3] Pardanani A, Brockman SR, Paternoster SF, Flynn HC, Ketterling, Lasho TL, Ho C-L, Li C-Y, Dewald GW, Tefferi A. FIP1L1-PDGFRA fusion: Prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. Blood. 2004;104:3038–3045.

[4] Pardanani A, Ketterling RP, Li CY, Patnaik M M, Wolanskyj AP, Elliott MA, Camoriano JK, Butterfield JH, Dewald GW, Tefferi A. FIP1L1-PDGFRA in eosinophilic disorders:Prevalence in routine clinical practice, long-term experience with imatinib therapy, and a critical review of the literature. Leuk Res. 2006;30:965–970.

[5] Brigden M, Graydon C. Eosinophilia detected by automated blood cell counting in ambulatory North American outpatients. Incidence and clin-ical significance. Arch Pathol Lab Med. 1997;121:963-967.

[6] Rothenberg ME. Eosinophilia. N Engl J Med. 1998;338:1592–1600.

[7] Pardanani A, Patnaik MM, Tefferi A. Eosino-philia: Secondary, clonal and idiopathic. Br JHaematol. 2006;133:468-492.

[8] Gotlib J. World Health Organization-defined eosinophilic disorders: 2014 update on diagnosis, risk stratification, and management**.** Am J Hematol. 2012;87(9):903-914.

[9] Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. Ann Intern Med. 1982;97:78-92.

[10] Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, Nutman TB, Pfab F, Ring J, Rothenberg ME, Roufosse F, Sajous MH, Sheikh J, Simon D, Simon HU, Stein ML, Wardlaw A, Weller PF, Klion AD. Hypereosinophilic syndromes: A multicenter, retrospective analysis of clinical characteristics and response to therapy. J Allergy Clin Immunol. 2009;124:1319-1325.

[11] Lefebvre C, Bletry O, Degoulet P, Guillevin L, Bentata-Pessayre M, Huong D u Le Thi, P Godeau P. Prognostic factors of

hypereosinophilic syndrome. Study of 40 cases. Ann Med Interne. 1989;140:253-257.

[12] Flaum MA, Schooley RT, Fauci AS, Gralnick H R. A clinicopathologic correlation of the idiopathic hypereosinophilic syndrome. Blood. 1981;58:1012-1020.

[13] Gotlib J, Cools J, Malone JM, Schrier S L, Gilliland D G, Coutré S E. The FIP1L1-PDGFRa fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: Implications for diagnosis, classification, and management. Blood. 2004;103:2879-2891.

[14] Cool J, DeAngelo DJ, Gotlib J, Stower EH, Legare RD, Stover E H, Legare R D, Cortes J, Kutok J, Clark J, Galinsky I, Griffin J D, Cross N C P, Tefferi A, Malone J, Alam R, Schrier S L, Schmid J, Rose M, Vandenberghe P, Verhoef G, Boogaerts M, Wlodarska I, Kantarjian H, Marynen P, Coutre S E, Stone R, Gilliland D G. A tyrosine kinase created by fusion of the PDGFRA and FIB1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. N. Engl J Med. 2003;348:1201-1214.

[15] La Starza L, Specchia G, Cuneo A, Beacci D, Nozzoli C, Luciano L, Aventin A, Sambani C, Testoni N, Foppoli M, Invernizzi R, Marynen P, Martelli M F, Mecucci C. The hypereosinophilic syndrome: Fluorescence in situ hybridization detects the del (4) (q12) – FIB1L1/PDGFRA but not genomic rearrangements of other tyrosine kinases. Haematologica. 2005;90(5):596-601.

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