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LETTER TO THE EDITOR

Myeloid/Lymphoid Neoplasms With Eosinophilia And Specific Gene Rearrangements: A Genetic Approach

Eozinofilisi ve Spesifik Gen Yeniden Düzenlenmeleri Olan Miyeloid/ Lenfoid Neoplazmalara Genetik Yaklaşım

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ABSTRACT

Eosinophils are granular leukocytes derived from a pluripotent stem cell in the bone marrow. An increase in the number of eosinophils in the blood and/or tissues requires a multifaceted clinical approach. It is important to determine the cause of the increase in order to make a correct diagnosis. Myeloid/lymphoid neoplasms with eosinophilia and specific gene fusions involve abnormal tyrosine kinase or cytokine receptor activity. Due to the similarity and heterogeneity of clinical findings, there may be diagnostic confusion in this group of diseases. Confirmation of the diagnosis is possible with genetic testing. This article briefly summarises the genetic approach to myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.

Keywords: Eosinophilia, hematological neoplasm, myeloid/lymphoid neoplasm with eosinophilia

ÖZ

Eozinofiller kemik iliğinde pluripotent bir kök hücreden köken alan granüler lökositlerdir. Eozinofillerin sayısında, kan ve/veya dokuda artış gözlemlenmesi, klinik açıdan çok yönlü bir yaklaşım gerektirir. Doğru tanı için bu artışın sebeplerini belirlemek önemlidir. Eozinofilisi olan ve spesifik gen füzyonlarının eşlik ettiği miyeloid/lenfoid neoplazmalar da, anormal tirozin kinaz veya sitokin reseptörü aktivitesi söz konusudur. Klinik bulguların benzerliğinden ve heterojenitesinden dolayı , bu grup hastalıklarda tanı karmaşası söz konusu olabilmektedir. Tanıyı doğrulamak genetik testler ile mümkündür. Bu yazıda, eozinofilisi ve tirozin kinaz gen füzyonları olan miyeloid/lenfoid neoplazmalar, hakkında genetik yaklaşım kısaca özetlenmiştir.

Anahtar Kelimeler: Eozinofili, hematolojik neoplazma, eozinofilisi olan miyeloid/lenfoid neoplazmalar

Eosinophils originate from a pluripotent stem cell in the bone marrow. An increased number of eosinophils requires a multifaceted approach in the clinic. The causes of such an increase must be established to make an accurate diagnosis. Depending on the cause, eosinophilia can be classified as familial, secondary, primary, or of unknown significance. Primary eosinophilia is characterized by the presence of a malignant clone of eosinophils in myeloid/stem cell neoplasms (1). According to the World Health Organization (WHO) classification (2), eosinophilia is classified in four groups [Platelet-derived growth factor receptor alpha (PDGFRA); Platelet-Derived Growth Factor Receptor-β (PDGFRB); Rearrangements of the fibroblast growth factor receptor-1 (FGFR1); Pericentriolar material-1::The Janus kinase-2 (PCM1::JAK2)]; according to the International Consensus Classification (ICC) (3), myeloid/lymphoid neoplasms (MPN) with eosinophilia and tyrosine kinase gene fusions are classified in six groups [PDGFRA; PDGFRB; FGFR1; The Janus kinase-2 (JAK2); Fms-related receptor tyrosine kinase-3 (FLT3); ets variant 6:: v-abl Abelson murine leukemia viral oncogene homolog-1 (ETV6::ABL1)].

Myeloid/lymphoid neoplasm with PDGFRA rearrangement: The PDGFRA gene is located at 4q12 and encodes a receptor protein involved in cell division. The most common fusion is the FIP1L1-PDGFRA, caused by the deletion of Cysteine Rich Hydrophobic Domain 2 (CHIC2) due to an 800-kb deletion at 4q12

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(4). Patients with this fusion respond to imatinib, but the T674I mutation causes resistance. T674I and D842V mutations were reported to cause resistance to imatinib, sorafenib, and dasatinib (5).

Myeloid/lymphoid neoplasm with PDGFRB rearrangement: The PDGFRB gene is located at 5q32 and encodes a tyrosine kinase receptor protein that plays a role in cell growth and differentiation. Among the numerous part genes, the most common is the PDGFRB-ETV6 fusion, which results from t(5;12) (q32;p13.2). Response to imatinib treatment is favorable (1, 6).

Myeloid/lymphoid neoplasm with FGFR1 rearrangement: The FGFR1 gene on 8p11 has been observed with different partners (4). The FGFR1 rearrangement is linked to an aggressive clinical course in patients. Transformation can lead to acute leukemia or lymphoma. In the absence of a targeted inhibitor, allogeneic transplantation may be an option. The most common fusion partners in patients with FGFR1 rearrangement are ZMYM2(13q12), BCR(22q11), CNTRL(9q33), and FGFR1OP(6q27) (1). Patients with BCR fusion may be misdiagnosed due to similarities to those with chronic myeloid leukemia (CML). A cytogenetic analysis is crucial (7).

Myeloid/lymphoid neoplasm with JAK2 rearrangement: The JAK2 gene on chromosome 9p24 synthesizes a tyrosine kinase involved in cell proliferation. Translocations are uncommon and involve different fusion partners. The most common PCM1-JAK2 fusion is the result of a t(8;9) translocation. The other partners are ETV6-JAK2 and BCR-JAK2, exhibiting a similar clinical picture (8).

Myeloid/lymphoid neoplasm with FLT3 rearrangement: The FLT3 gene plays a key role in regulating cell differentiation, proliferation, and survival. It is a tyrosine kinase receptor localized to 13q12. While mutations are common in hematological neoplasms, translocations involving this gene are rare. The most prevalent is the FLT3::ETV6 translocation (1, 9).

Myeloid/lymphoid neoplasm with ETV6::ABL1: The ABL1 gene at 9q34.12 encodes a tyrosine kinase

Table. Clinical findings, genetic characteristics, and treatment options in myeloid/lymphoid neoplasms with eosinophilia and specific gene rearrangements

Gene	Fusion Partners	Genetic Method	Clinical Findings	Diagnostic Confusion	Therapy	Resistance Mutations
PDGFRA (4q12)	**FIP1L1(4q12)*** STRN (2p24), FOXP1 (3p14), CDK5RAP2 (9q33), KIF5B (10p11), TNKS2 (10q23), ETV6 (12p13), BCR (22q11)	Chromosome Analysis, FISH, PDGFRA-FIP1L1 fusion RT-PCR	Eosinophilia	Blastic phase MPN / AML associated with eosinophilia / T-cell lymphoblastic lymphoma	Imatinib (Allo-SCT in the presence of resistance mutation	T674I D842V
PDGFRB (5q31- 33)	**ETV6 (12p13)*** TPM3 (1q21), PDE4DIP (1q22), SPTBN1 (2p16), SPDR (2q32), WDR48 (3p22), GOLGA4 (3p22), GOLGB1 (3q12), PRKG2 (4q21), DIAPH1 (5q31), TNIP1 (5q33), CEP85L (6q22), HIP1 (7q11), KANK1 (9p24), CCDC6 (10q21), GPIAP1 (11p13), ERC1 (12p13), BIN2 (12q13), CPSF6 (12q15), SART3 (12q23), GIT2 (12q24), NIN (14q24), CCDC88C (14q32), TRIP11 (14q32), TP53BP1 (15q22), NDE1 (16p13), SPECC1 (17p11), MPRIP (17p11), RABEP1 (17p13), NDEL1 (17p13), MYO18A (17q11), DTD1 (20p11)	Chromosome Analysis, FISH, maybe NGS	Eosinophilia, sometimes monocytosis or neutrophilia	MPN/eosinophilia MDS/MPN, AML/ALL	Imatinib	
FGFR1 (8p11)	**ZMYM2 (13q12)* BCR (22q11)* CNTRL (9q33)* FGFR1OP (6q27)*** TPR1 (1q25), RANBP2 (2q13), LRRFIP1 (2q37), TFG (3q12), SQSTM1 (5q35), CUX1 (7q22), TRIM24 (7q34), PCM1 (8p21), FGFR1OP2 (12p11), CPSF6 (12q15), MYO18A (17q11), HERV-K (19q13)	Chromosome Analysis, FISH	Eosinophilia, sometimes monocytosis or neutrophilia	MPN, lymphoblastic lymphoma, acute leukemia, myeloid, lymphoid, or mixed-lineage disease	Pemigatinib, Futibatinib Midostaurin, Ponatinib (Allo SCT)	
JAK2 (9p24)	**PCM1(8p21)*** ETV6 (12p13) BCR (22q11)	Chromosome Analysis, FISH	Eosinophilia	MPN, MDS/MPN, ALL, de-novo AML, T-cell lymphoma	Ruxolitinib, Fedratinib Pacritinib, Momelotinib (Allo SCT)	
FLT3 (13q12)	**ETV6 (12p13)*** BCR (22q11), SPTBN1 (2p16), GOLGB1 (3q12), LYN (8q12), MYO18A(17q12), SYK (9q22), TRIP11 (14q32), NTRK3 (15q25), ZMYM2(13q12)	Chromosome Analysis, FISH, ETV-FLT3 fusion nested RT-PCR	Eosinophilia	MPN, B/T-ALL, AML.	Gilteritinib, Midostaurin Sorafenib, Sunitinib	
ABL1 (9q34)	ETV6 (12p13)*	Chromosome Analysis, FISH	Eosinophilia Basophilia	CML, AML, Ph-like B-ALL.	Dasatinib, Nilotinib Imatinib, Bosutinib Ponatinib, Asciminib	

*The most common gene partner FISH=Fluorescence *in situ* hybridization, RT-PCR: Reverse transcription-polymerase chain reaction, NGS: Next Generation Sequencing, AML: Acute Myeloid Leukemia, MDS: Myelodysplastic Syndrome, ALL: Acute Lymphoblastic Leukemia, Allo-SCT: Allogeneic Stem Cell Transplantation

protein regulating cell proliferation and apoptosis. The fusion of ABL1 and ETV6 results in the activation of the tyrosine kinase, as observed in BCR-ABL1. Clinical manifestations are similar to those in chronic phase CML, but often with eosinophilia and basophilia (1, 5).

Myeloid/lymphoid neoplasms with eosinophilia and specific gene rearrangements are difficult to classify. The following table summarises the fusion partners of each specific gene rearrangement, the genetic methods that can be used to identify them, the clinical findings, and the treatment options (4, 10). The genetic tests selected based on the preliminary diagnosis help clinicians confirm the diagnosis and identify and implement treatment options accurately and quickly.

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