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A Rare Variant Translocation (t(5;9;22)(q13;q34;q11.2)) In A Case With Chronic Myeloid Leukemia

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Abstract

Chronic myeloid leukemia is a severe hematologic disorder with blastic transformation following a chronic phase. The specific cytogenetic findings of the disorder is t (9; 22) or Philadelphia (Ph1) chromosome. Ph1 is detected in most cases (95%). However, when a different chromosome other than 9 and 22 chromosomes are involved in translocation, the typical appearance of Ph1 chromosome does not occur and can be missed. In this case, the anomaly which is not detected in conventional cytogenetic analysis can be determined by molecular cytogenetics (FISH) analysis. In this paper we describe a unique clonal abnormality, t(5;9;22)(q13;q34;q11.2)- as a rare variant translocation in a case with chronic myeloid leukemia.

Keywords: Chronic myeloid leukemia, Variant translocation, t(5;9;22)(q13;q11.2)

Kronik Miyeloid Lösemili Bir Olguda Nadir Bir Varyant Translokasyonu (t(5; 9; 22) (q13; q34; q11.2))

Öz

Kronik miyeloid lösemi, kronik bir seyri takiben akut blastik dönüşüm görülen ciddi bir hematolojik hastalıktır. Özgün sitogenetik bulgusu t(9;22) veya orijinal ismi ile Philadelphia (Ph1) kromozomudur. Olguların çoğunda Ph1 saptanır. Ancak 9 ve 22. kromozomlar dışında başka bir üçüncü kromozomun translokasyona katılması halinde sitogenetik olarak Ph1 kromozomunun tipik görünümü oluşmaz ve gözden kaçabilir. Bu durumda konvansiyonel sitogenetik analizde saptanmayan anomali moleküler sitogenetik (FISH) analizle saptanabilir. Yazıda, Kronik Miyeloid Lösemili olguda Ph1 kromozomunu baskılayan varyant t(5;9;22) (q13; q34; q11.2) klonal anomalisi tanımlanmıştır.

Anahtar Kelimeler: Kronik miyeloid lösemi, Varyant translokasyon, t(5;9;22)(q13;q11.2)

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Introduction

Chronic myeloid leukemia (CML) is a haematological malignancy with a relatively favorable course. It is characterized with a chronic phase followed by an accelerated phase and blastic transformation occurs eventually (1). The most frequent (90-95%) cytogenetic finding in patients with CML is translocation between chromosome 9 and chromosome 22 [t(9;22)(q34;q11.2)]. Variant or complex translocations can be observed in the remaining (1,2,3).

Herein we describe a variant translocation, t(5;9;22)(q13;q34;q11.2) in a patient with chronic phase of CML who was refractory to treatment with respect to cytogenetic responce; to our knowledge this chromosomal abnormality has not been reported before.

Case

The patient, a 56-year old male, had splenomegaly on physical examination. On routine blood count, the hemoglobin level was 11.7 g/dL, hematocrite: 34%, leukocyte: 100.000/mm^3 and platelets 432.000/mm^3. Bone marrow biopsy was hypercellular marrow with erythroid line dominance that showed megaloblastic changes. These findings were in agreement with the diagnosis of CML.

Cytogenetic analyses were performed on bone marrow by high-resolution banding technique (4,5). t(5;22)(q13;q11.2) was observed in all the metaphase figures analysed (Figure 1-2). To exclude the possibility of a constitutional chromosomal abnormality, cytogenetic analysis with PHA-M on peripheral lymphocytes was carried out and the karyotype was found to be 46, XY.

Figure 1: A sample metaphase figure showing t(5;22)

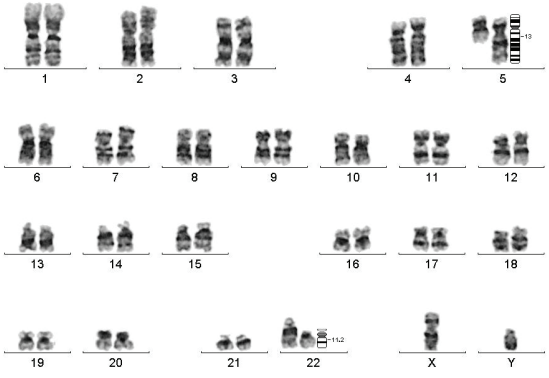

Figure 2: Karyogram showing t(5;22)(q13;q11)

The identification of the breakpoints of the translocated chromosomes was achieved by FISH analysis. Cytocell DiGeorge/VCFS N25 (D22S75) region dual color and wcp5 probes were used and all procedures were applied according to the manufacturer's protocols. The wcp 5 probed chromosomes 5 and 22 (Figure 3). D22S75 probe revealed that the 22q11.2 signal was located on the derivative chromosome 22 while the control region of chromosome 22 moved to chromosome 5 (Figure 4).

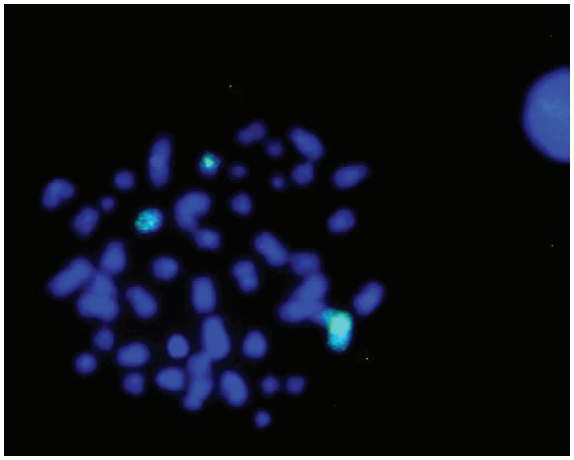

Figure 3: Three chromosomes were stained green with wcp 5.

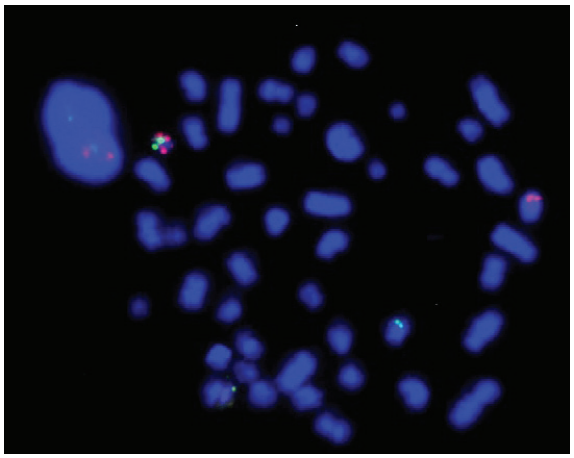

Figure 4: Chromosome 22 control region moved to derivative chromosome 5.

Interphase FISH analysis with dual color dual fusion bcr/abl Cytocel probe showed a t(9;22) translocation (Figure 5). Fusion gene transcript analysis of t(9;22)-bcr-abl cDNA was accomplished by reverse –transcriptase PCR technique which gave a positive result with a rate of 5.3x10 fussion –gene.

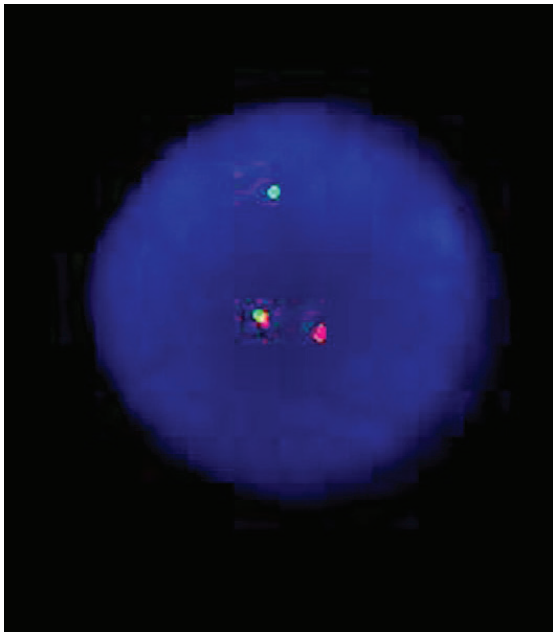

Figure 5: Fusion gene signal detected in the interphase by FISH

Discussion

It has been reported that in patients with a variant translocation, complete major cytogenetic response can be achieved in 74% of the cases in the chronic phase, which is not different from patients having the t(9;22) translocation (6,7,8). In the present case, a 3-month treatment with Imatinib mesylate 400 mg/d resulted in haematological remission (as assessed by bone marrow examination) where as the t(5;22) translocation persisted in all the metaphase figures analysed. After 600 mg/day Imatinib mesylate treatment for 16 months, the haematological responce was complete while the cytogenetic response was partial (8). The clonal abnormality persisted with a ratio of 50% in bone marrow cells.

This finding implies that the t(5;22)(q13;q11.2) translocation may be conferring resistance to Imatinib mesylate treatment. However, it may be more appropriate to interpret the persistance of cells carrying the variant chromosome and haematological response separately with respect to patient's outcome after treatment.

In Ph (-) cases in where there is high clinical suspicion of CML and presence of additional translocations, FISH and / or molecular analysis should be performed to detect the existence of bcr/abl fusion gene (2,3,7,9). Because conventional cytogenetic analysis may not be able to detect Ph1 chromosome in the presence of variant translocations involving chromosome 22 (8,10,11).

REFERENCES

1. http:/www.merck.com/mmpe/inhtmlde.

2. Naumann S, Decker HJ. Genesis of variant Philadelphia chromosome translocations in chronic myelocytic leukemia. Cancer Genet Cytogenet 2003;147(1):18-22.

3. Costa D, Carrió A, Madrigal I et al. Studies of complex Ph translocations in cases with chronic myelogenous leukemia and one with acute lymphoblastic leukemia. Cancer Genet Cytogenet 2006;166(1):89-93.

4. Swansbury J. Cancer Cytogenetics Methods and protocols. Humana Pres, New Jersey, 2003.

5. Barch MJ. 1991. Cytogenetics Laboratory Manual, second edition, New York: Raven Pres. p. 27-128.

6. Balatzenko G, Grudeva-Popova J, Krustev T et al. Philadelphia variant, t(5;9;22)(q13;q34;q11), in a case with chronic myeloid leukemia. J BUON 2003;8(1):65-67.

7. Alimena G, Hagemeijer A, Bakhuis J et al. Cytogenetic and molecular characterization of a masked Philadelphia chromosome in chronic myelocytic leukemia. Cancer Genet Cytogenet 1987;27(1):21-26.

8. Kanakasetty GB, Kuntejowdahalli L, Thanky AH et al. Predictive and Prognostic Implications of Variant Philadelphia Translocations in CML: Experience From a Tertiary Oncology Center in Southern India. Clin Lymphoma Myeloma Leuk 2017;17(1):52-59.

9. Gorusu M, Benn P, Li Z, Fang M. On the genesis and prognosis of variant translocations in chronic myeloid leukemia. Cancer Genet Cytogenet 2007;173(2):97-106.

10. Eyüpoğlu D, Bozkurt S, Haznedaroğlu İ et al. The impact of variant philadelphia chromosome translocations on the clinical course of chronic myeloid leukemia. Turk J Haematol 2016;33(1):60-65.

11. Bakshi SR, Patel BP, Brahmbhatt MM et al. Complex karyotype with a masked Philadelphia translocation and variant BCR-ABL fusion in CML. 2009;189(2):142-143.