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PHILADELPHIA CHROMOSOME AND FISH-NEGATIVE, CRYPTIC BCR/ABL1 POSITIVE ACUTE MYELOID LEUKAEMIA: A DIAGNOSTIC DILEMMA

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INTRODUCTION

Acute myeloid leukaemia (AML) with BCR/ABL1 is a provisional entity classified in the most recent WHO classification of AML with recurrent genetic abnormalities. This entity can pose diagnostic dilemmas as it can be confused with blastic phase of chronic myeloid leukamia (CML) or mixed phenotype acute leukaemia (MPAL) with BCR-ABL1. We present here a patient with Philadelphia chromosome negative AML and BCR/ABL1 fusion detected by PCR.

CASE REPORT

A 65-year-old man presented with constitutional symptoms for three weeks. Physical examination revealed a thin man with hepatomegaly and no appreciable splenomegaly. The full blood picture showed bicytopenia with leucoytosis and 58% blasts cells. The bone marrow aspirate was hypercellular, with 48% MPO-positive blasts cells and heterogenous background of granulocytic cells and abundant eosinophils. Cytogenetic analysis showed 46 XY, del (7q) (q22q23) and no BCR/ABL1 was detected using FISH probe BCR/ABL1. However, using multiplex ARMS PCR, both b3a2 and b2a2 fusion genes were detected. This patient is currently on treatment with standard chemotherapy regime and Nilotinib.

DISCUSSION

AML with BCR/ABL1 usually have equal distribution of p190 and p210 transcripts and clinically, is associated with no splenomegaly or basophilia and lower bone marrow cellularity. AML with BCR/ABL1 show aberrations that are normally seen in lymphoid pathologies such as deletions of IKZF1 and/or CDKN2A/B genes. IGH and TCR can also show cryptic deletions.[1] These events along with the findings of different rearrangement of BCR/ABL1 reflects the genetic heterogeneity of this subtype. In this patient, the presence of two PCR product both representing major transcript (p210), raises suspicion that there are two different breakpoints. The translocation of BCR exon 13 with ABL1 exon2 (leading to b2a2 transcript) and BCR exon 14 with ABL1 exon2 (leading to b3a2 transcript) would normally be seen on FISH.[2] Factors that could contribute to non detection on FISH include these novel breakpoints may not be covered by the standard BCR/ABL1 FISH probes and cryptic rearrangement involving multiple chromosomes. Masked Ph positivity in this patient may be due to insertion of ABL1 into BCR region or the translocation of 9;22 is followed by another translocation of both products leading to fairly normal chromosome morphology.[3]

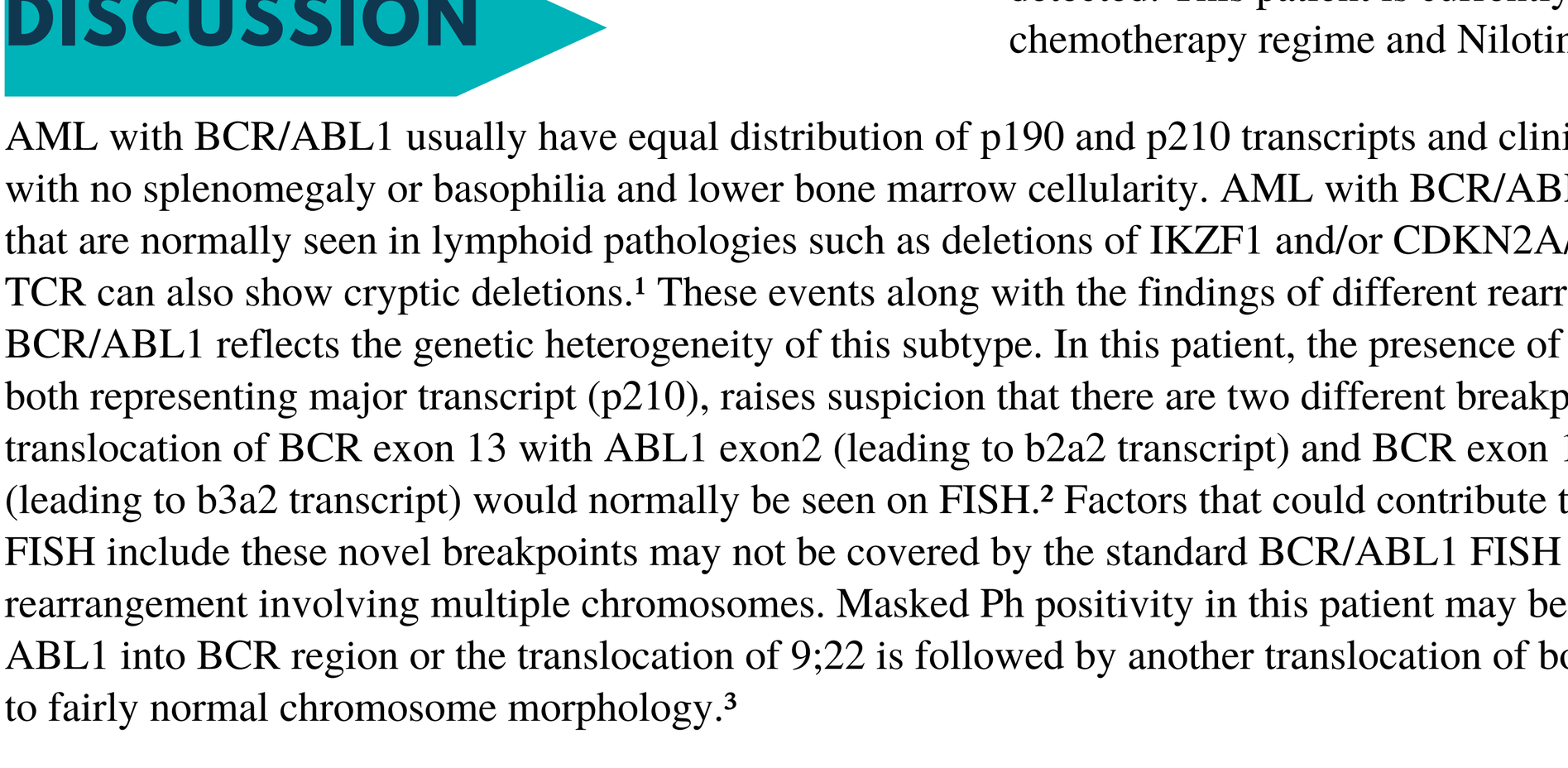

FIGURE 1: Agarose gel electrophoresis. M (DNA ladder 100bp), 1= Normal control 2= Major b3a2 control 3= minor e1a2 control 4= Positive control

CONCLUSION

Philadelphia chromosome negative BCR/ABL1 positive AML is extremely rare. Moving forward, the utilisation of FISH mapping using Bacterial Artificial Chromosomes (BAC) probes, which can cover both minor and major breakpoint, Whole Chromosomes Painting and direct sequencing can offer new insights into the formation of masked Ph chromosomes.

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