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Case Report

The Clinical Relevance of Detection of BCR-ABL in an Asymptomatic Patient: A Case Report and Review of the Literature

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Abstract

Chronic myelogenous leukemia is associated with the hallmark BCR-ABL translocation. With the increase in sensitivity in methods detecting the BCR/ABL copy number, a small percentage of healthy subjects have been found to harbor low levels of the Philadelphia chromosome without evidence of chronic myelogenous leukemia. We present a case of a 71 year old male who was incidentally found to have a BCR/ABL chromosomal translocation on bone marrow biopsy being completed for a marginal zone lymphoma. The patient had no hematologic abnormalities on complete blood count when the BCR/ABL translocation was detected. The patient was treated with imatinib and developed a major molecular response. Currently no data exists on what percentage of healthy subjects that harbor low levels of the Philadelphia chromosome will go on to develop CML. These patients pose a clinical dilemma with regards to if they should be treated and when treatment should be initiated.

INTRODUCTION

Chronic myelogenous leukemia (CML) is a myeloproliferative disorder associated with a characteristic chromosomal translocation, the Philadelphia chromosome t (9;22), a hallmark of the disease. Approximately 85% of patients are diagnosed in the chronic phase of CML, and often are completely asymptomatic. However, studies have shown a group of healthy asymptomatic individuals with evidence of the BCR-ABL fusion gene [1,2]. These healthy, asymptomatic individuals with the BCR-ABL fusion gene pose a particular problem for physicians with regards to management. No guidelines have been established to evaluate and predict which individuals may progress to CML. In this case report, we present a patient with a diagnosis of marginal zone lymphoma of the right medial canthus. He was found to have the BCR-ABL fusion gene on bone marrow biopsy performed for staging purposes.

CASE PRESENTATION

A 71 year old male presented with a lesion under his right eye in July 2013. Subsequent pathology from a biopsy of the right medial canthus was consistent with extranodal marginal zone lymphoma. The patient was referred to oncology and staging was completed. The patient's white blood cell count was 6.6 $x10^9$/L with a slight increase in the absolute number of basophils at 0.3 $x10^9$/L (normal 0-0.2 $x10^9$ /L), hemoglobin was 15.4 g/dL, and platelets were 196 $x10^9$/L. The bone marrow showed a moderate increase in myeloid precursors with a left shift in maturation with no evidence of lymphoma. Cytogenetics showed 46XY, t (9;22) (q34;q11.2)[15]/46,XY [5]3. Flourescent in-situ hybridization (FISH) confirmed the findings with 62.5% of cells positive for the BCR-ABL fusion gene. FISH on peripheral blood confirmed the presence of the BCR-ABL rearrangement in 73.5% of cells. Given the rarity of these findings and the lack of data on how to manage this patient, the decision to begin treatment with Imatinib was made based on the high level of BCR-ABL noted. The patient was started on Imatinib in December of 2013. Interestingly, laboratory assessment just prior to starting therapy showed that the patient's white blood cell count did increase to 16.8 $x10^9$/L with a differential showing 5% metamyelocytes and 4% myelocytes. The differential included an absolute neutrophil count of 12.4 $x10^9$/L, eosinophil count of 1.2 $x10^9$/L and basophil count of 0.3 $x10^9$/L.

Quantitative BCR-ABL by PCR was reassessed after six months of Imatinib therapy. The patient had a significant decline

in his copy percentage of BCR-ABL on PCR to 1.6% IS. The patient has now been on treatment for 1 year and has a peripheral blood copy percentage of 0.0063% IS, constituting a major molecular response. The patient also had a complete hematologic response, with a white blood cell count of 3.8 $x10^9$ /L, with a completely normal differential, hemoglobin of 13.2g/dL, and platelets of 204 $x10^9$ /L. The patient has tolerated the treatment well with minimal side effects, including mild fatigue and acid reflux.

DISCUSSION

Prior to 1995, the Philadelphia chromosome had never been identified in normal subjects. With the increase in sensitivity in methods detecting the BCR/ABL copy number, a small percentage of healthy subjects were found to harbor low levels of the Philadelphia chromosome without evidence of CML [1-4]. In a study conducted by Biernaux and colleagues, 117 healthy subjects were tested and 23 were positive for the BCR-ABL mRNA ranging from 5 to 20 copies/5 x 10^7 to 10^8 white blood cells [1]. When evaluated by age, patients who were 20 to 80 years old were more likely to express the BCR-ABL transcript. Cord blood samples from newborns were also examined and no positive results were detected. It is likely that with age, there is a greater chance of accumulating somatic genetic changes [1].

The incidence of the BCR-ABL fusion gene noted in healthy individuals indicates that merely the presence of the Philadelphia chromosome is not sufficient to cause CML [3,5]. To develop leukemia, the fusion gene structure must allow for the production of a functional protein with direct or indirect oncogenic properties and the chromosomal translocation must occur in a relatively early precursor cell with self -renewal capacity [2]. Additional mutations may also need to occur before an actual disease state can arise [2]. In healthy individuals with the BCR-ABL fusion gene, it is likely that the original progenitor cell in which the t (9;22) occurred was more differentiated and prone to undergo apoptosis [1]. The assays used for these studies are also more sensitive for the BCR-ABL transcript than the assays used in commercially available labs [1].

There have been no studies with long term follow up evaluating what percentage of individuals with the presence of the BCR-ABL fusion gene will progress to CML, particularly in older individuals. Without data to suggest which individuals will develop CML, it is unclear how to manage patients with the presence of the BCR-ABL gene and no evidence of hematologic disease. In our review of the literature, we found one other case reported by Bayraktar and colleagues. They describe a case of a 39 year old male with a white blood cell count of 15 $x10^9$/Lfound on routine complete blood count ordered by the primary care physician. Bone marrow studies revealed t (9;22) in 4 of 20 metaphases on cytogenetics and positivity on FISH in 52% of bone marrow cells. He had been observed for 1 year at the time that the case was reported, with monitoring of the peripheral blood for the BCR-ABL fusion protein every three months, with no evidence of disease [3]. The IRIS study established Imatinib as the new standard of care when compared to interferon. Long term follow up confirms that patients who achieve at least a partial cytogenetic response by 12 months are less likely to progress to accelerated phase or blast crisis [6]. A quicker and deeper molecular response is associated with an improved 3 year progression free survival as well as overall survival based on Kaplan Meier analysis as evidenced in the DASISION trial [7]. For this reason, our plan was to start treatment prior to the emergence of overt hematologic disease. Future research should include long term follow up of the asymptomatic patients with the presence of the BCR-ABL fusion gene to try to determine which individuals are more likely to progress to CML and thus warrant early treatment.

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