Case Report

Chronic myeloid leukemia in case of Klinefelter syndrome

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Klinefelter syndrome (KS) is a sex chromosome disorder and has been reported to be associated with increased risk for malignancies. We report a 22-year-old male patient who was diagnosed to have chronic myeloid leukemia in chronic phase. Bone marrow cytogenetic examination revealed karyotype 47, XXY, t (9; 22)(q34, q11) suggestive of KS with presence of Philadelphia chromosome. The patient was treated with oral imatinib mesylate (400 mg/day). Complete hematological response was achieved after 2 months of therapy. The *bcr-abl*/*abl* transcript percentage measured from peripheral blood at baseline, 1 and 2 years after imatinib were 97%, 1.99%, 0.007%, respectively. He remains in complete hematological and major molecular remission after 2 years of continued imatinib therapy.

Key words: Chronic myeloid leukemia, imatinib, Klinefelter's syndrome

Introduction

Klinefelter syndrome (KS) is the most common sex chromosomal disorder affecting approximately 1 in 500 males. It manifests clinically as infertility, delayed secondary sexual characters, gynecomastia and learning disabilities.[1] These patients are detected incidentally during cytogenetic evaluation of neoplasia.[2] Patients of KS have been reported to have a higher risk of breast cancer, extra-gonadal germ cell tumor and a lower risk of developing prostate cancer.[3]

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We describe a 22-year-old male patient with chronic myeloid leukemia (CML) who was detected to have sex chromosomal abnormality (47, XXY) during cytogenetic evaluation for Philadelphia (Ph) chromosome. He was successfully treated with imatinib.

Case Report

This is a case report of a 22-year-old male patient who presented with abdominal distension and heaviness on the left side of the abdomen of 1 month duration. There was no history of fever, weight loss, bleeding episodes and recurrent infections. Patient had history of delayed development of secondary sexual characters. He was average in studies and IQ was 92 (by Wechsler adult intelligence scale-III). General physical examination revealed height of 172 cm (normal), arm span was 173 cm and weight 55.5 kg (body mass index by Quetlet formula: 18.76). No pallor, icterus or enlarged peripheral lymph nodes were present. The spleen was enlarged (16 cm below the sub costal margin) and the liver was palpable 5 cm below the costal margin. The testes were firm and atrophic (right testis volume: 6 ml, left testis volume: 5 ml), the pubic, axillary, body and facial hair were sparse, suggestive of hypogonadism. Stretched penile length was 10 cm (normal).

Hematological investigations revealed hemoglobin of 9.6 g/dl, total leukocyte count (TLC) of 130 × 10^9/l, platelet count of 162 × 10^9/l. The differential leukocyte count on peripheral blood smear was – neutrophils 32%, lymphocytes 1%, eosinophils 1%, monocytes 1%, basophils 6%, promyelocytes 2%, myelocytes 46%, metamyelocytes 10%, normoblasts 2% and blasts 1% respectively. Bone marrow aspiration and biopsy showed

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myeloid hyperplasia with predominance of myelocytes, metamyelocytes and neutrophils. Erythroid cells and lymphocytes appeared reduced. Megakaryocytes were increased in number. Blasts were less than 5% and basophils were mildly increased (approximately 8%). Chromosomal analysis was performed after unstimulated 72 h culture of bone marrow cells, followed by conventional Giemsa staining of metaphase spreads. Examination of 30 metaphases revealed a karyotype of 47, XXY, t (9;22)(q34;q11) [Figure 1]. The *bcr-abl*/*abl* transcript level in the peripheral blood were measured by quantitative polymerase chain reaction (PCR) (minor groove binder with reverse transcriptase PCR methodology) and were normalized to *bcr* transcript concentration and expressed as a percentage. The *bcr-abl*/*abl* ratio was 97% in the peripheral blood before the start of imatinib therapy. Baseline endocrinological investigations revealed serum follicular-stimulating hormone level 40.2 IU/l (normal 1.8-13.6 IU/l) and serum testosterone level 6.4 nmol/l (normal 2.3-14 nmol/l). Semen analysis revealed azoospermia. A diagnosis of KS with CML was made.

The patient was started on hydroxyurea to reduce the TLC along with on oral imatinib mesylate (400 mg/day). Monotherapy with oral imatinib (400 mg/day) was continued. He achieved complete hematological remission after 2 months of therapy. The *bcr-abl*/*abl* ratios in the peripheral blood were 1.99% and 0.007% (3-log reduction over baseline) at 1 and 2 years after treatment respectively.

Discussion

KS is the most common sex chromosomal disorder and manifest with male hypogonadism and infertility. The chromosome complement 47, XXY is seen in 80% of cases and occasionally karyotypes may be 48XXXY or 49XXXXY or mosaic 47XXY/46XY. The chromosomal abnormality results due to non-disjunction of X or Y chromosome during gametogenesis. The extra X chromosome is of maternal origin in 54% of cases and the extra X or Y is of paternal origin in remaining 46% cases. There is often a delay in diagnosis due to mild hypogonadism and normal physical features like in our case.[1]

KS is associated with malignancies such as male breast cancer and germ cell tumors. In their study Swerdlow *et al*., showed KS cases have increased mortality risk (relative risk [RR] = 1.63; confidence interval [CI] =1.40-1.91) and increased mortality from lung cancer (RR = 2.45, CI = 1.55-3.67) and breast cancer (RR = 61.7; CI = 7.47-227.7).[3] Men with KS have 50 times higher risk of breast cancer compared with normal karyotype. Similarly, the risk for mediastinal germinal cell tumor is 67 times higher in males with KS. The mechanisms that increase cancer risk in cases with constitutional chromosome aneuploidies such as Down syndrome and KS are unknown. The postulated mechanisms include mitotic instability, hormonal imbalance, immunologic surveillance abnormality and over expression of genes from the extra chromosome.[2-4] Mukerjee *et al*. reported that the XXY cells from a patient with XY/XXY mosaic were frequently transformed when exposed to simian papovavirus.[5]

An association with malignant hematological disorders has also been described in several case reports. Welborn *et al*. reviewed literature to find 66 cases KS with hematological malignancies.[6] Acute myeloid leukemia (23%), non-Hodgkin lymphoma (23%), acute lymphocytic leukemia (18%) and myelodysplastic syndrome (17%) were the most frequently reported cases in literature.[6] Hasle *et al*. followed a cohort of 696 KS cases and did not find any increased risk of lymphoma or leukemia.[7] Similarly, Horsman *et al*. in a review of 1200 patients with hematological malignancies who

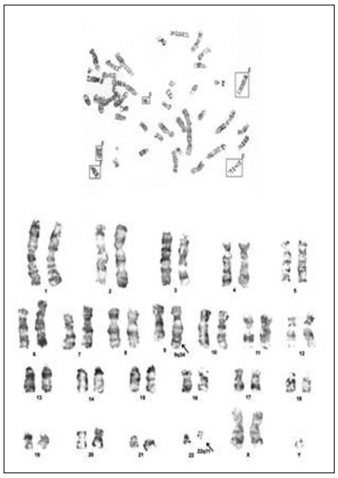

Figure 1: Cytogenetic study shows 47, XXY karyotype with Philadelphia chromosome abnormality

had cytogenetic evaluation carried out detected only one case of KS with acute leukemia.[8] However, this relationship may be apparent as cases with hematological malignancies are likely to undergo cytogenetic evaluation leading to detection of KS.

Multiple case reports of CML in patients with KS have been described in literature.[4,9-11] In all these cases the KS was incidentally detected during the routine cytogenetic evaluation for CML. Oguma *et al.*[10] in their study have reported a 2-year old CML patient who had KS. The cytogenetic analysis showed that the Ph chromosome occurred monoclonally in the XXY cells but not in XY cells. This observation gives credence to the hypothesis that the chromosomal aberrations predispose stem cells to further genetic instability leading to clonal evolution of hematological disorders.

Imatinib mesylate, a selective inhibitor of this abnormal *bcr-abl* protein tyrosine kinase has dramatically changed the treatment of Ph positive CM. The treatment of patients with Ph positive CML with imatinib has resulted in complete cytogenetic responses of 65% to 85%, major molecular response rates of 40-70% and complete molecular response rates of 10-40% respectively.[12] However, there is a lack of data on response to imatinib in cases of KS with Ph positive CML.

Toubai *et al*. described a case of KS with CML with acute lymphoblastic leukemia.[13] This case was a more severe form of CML which later, despite imatinib therapy and allogenic bone marrow transplantation from an unrelated donor, did not survive. Contrary to this case our patient remains in complete hematological and major molecular remission after 2 years from start of therapy. Successful disease remission in our case despite the presence of these mechanisms and increased mortality risk could represent just a one-off case or could be a harbinger of future successes of targeted cancer drug therapy in cases of KS with neoplasia.

Conclusion

As the number of KS patients are limited and there are only few long-term follow-up studies, the exact risk of carcinogenesis in these patients still needs to be defined. Our experience suggests that response to imatinib in cases of KS with CML may not differ from cases of CML in individuals without constitutional chromosomal abnormalities.

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