Leukemia in Patients with Klinefelter Syndrome: A Report of Two Cases.

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SHORT COMMUNICATION

Leukemia in Patients with Klinefelter Syndrome: A Report of Two Cases

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Abstract Klinefelter syndrome (KS) is a chromosome abnormality characterized by a 47, XXY karyotype associated with hypogonadism and infertility. We present two cases of leukemia in patients with KS. The first patient presented with acute promyelocytic leukemia. He relapsed after the end of treatment. The second patient was diagnosed with chronic myeloid leukemia. Treatment with imatinib failed and the patient presented with myeloid blast crisis.

Keywords Klinefelter syndrome · Acute promyelocytic leukemia · Chronic myelogenous leukemia · Karyotype

Introduction

Klinefelter syndrome (KS) is a sex chromosome disorder usually associated with 47 chromosomes, including two X and one Y (47, XXY). Men with KS have small testes, gynecomastia, sparse body hair and infertility with increased gonadotropin levels. The expression of these symptoms is variable, sometimes leading to a delayed diagnosis.

We report two adult male patients diagnosed with previously unsuspected KS as a result of cytogenetic testing for suspected hematologic malignancies.

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Patient 1

A 20-year-old man was diagnosed with acute promyelocytic leukemia (APL). The patient was tall with long arms and sparse body hair. The blood count showed a white blood cell count (WBC) of 3×10^9/L, hemoglobin (Hb) of 138 g/L and platelet count (PLT) of 18×10^9/L.

The PML/RARA fusion gene was found by RT-PCR testing. Cytogenetic analysis found the t (15; 17) (q22; q12) in addition to a 47, XXY karyotype. The 47, XXY karyotype was also demonstrated in peripheral blood lymphocytes, corresponding to KS.

The patient was treated according to LPA-99 protocol, within the intermediate-risk arm, which resulted in complete remission (CR). At 33 months of CR, the patient had a morphologic relapse. Cytogenetic analysis found a trisomy 8 in addition to the previously described abnormalities (Fig. 1). Second molecular CR2 was achieved after salvage therapy. Then, the patient underwent autologous stem cell transplantation. Five months later, he sustained a second relapse and died promptly.

Patient 2

A 32-year-old man was diagnosed with chronic myeloid leukemia (CML) in the accelerated phase. Hematological investigations showed: WBC: 157×10^9/L, Hb: 78 g/L and PLT: 196×10^9/L. A high Sokal score of 1.57 was found. The bcr-abl fusion transcript was found by RT-PCR testing.

Cytogenetic study showed a 47, XXY karyotype with Philadelphia chromosome abnormality. The 47, XXY karyotype was also demonstrated in peripheral blood lymphocytes, corresponding to KS (Fig. 2).

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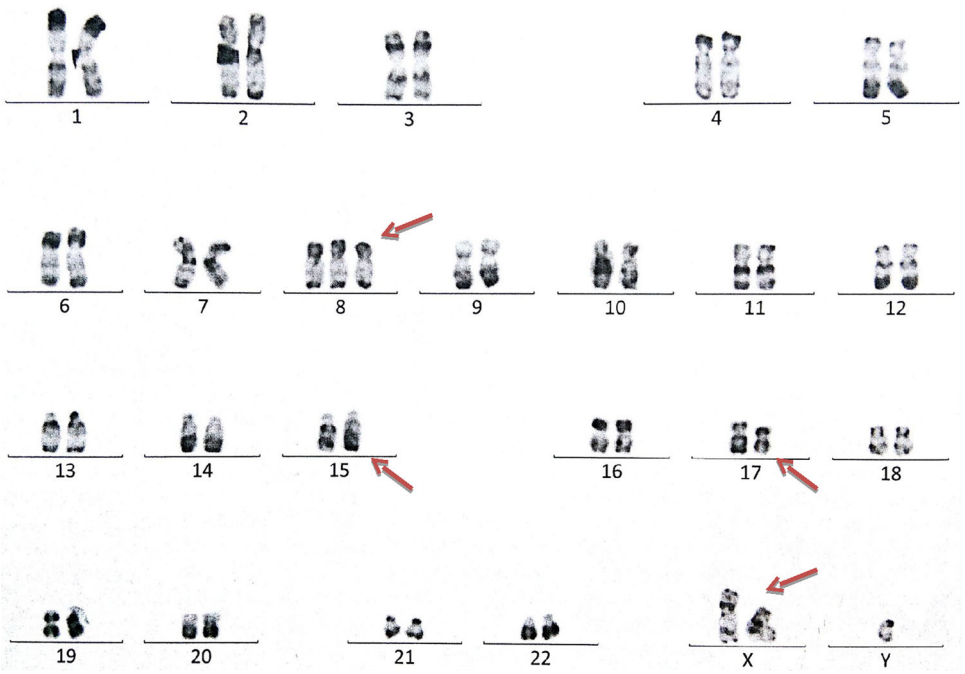

Fig. 1 RHG banding karyotype of bone marrow revealed: 48, XXY, +8, t(15; 17) (q24;q21)

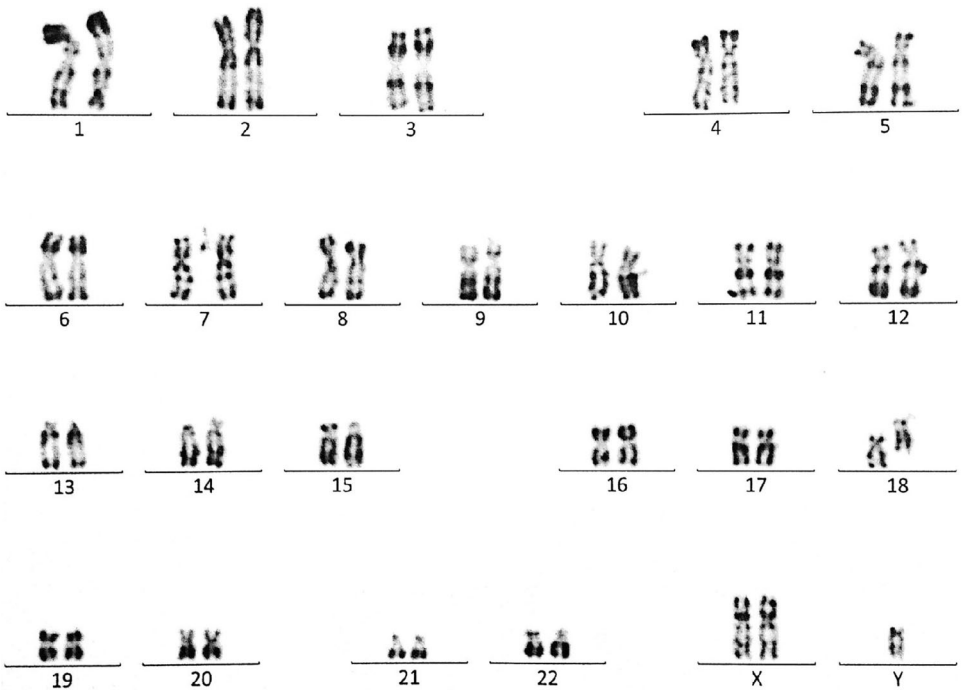

Fig. 2 RHG banding karyotype of peripheral blood cells revealed an extra X chromosome (47, XXY)

The patient was treated with imatinib 600 mg daily. But the treatment was discontinued several times because of severe thrombocytopenia, in spite of dose reduction. Therefore, a complete hematologic response couldn't be achieved. Then the patient presented with myeloid blast crisis. The patient was treated with dasatinib: 140 mg daily in combination with AML induction therapy. But he died of severe sepsis during the induction course.

Discussion

Several case reports have suggested an increased risk for cancer in men with KS. Some cohort studies found an increased incidence of male breast cancer and mediastinal germ cell tumor [1, 2].

There are many reports about the occurrence of leukemia in KS [3–5]. However, epidemiological studies haven't

found an increased leukemia risk [1, 2, 6]. This can result from the use of routine cytogenetic investigation in patients with leukemia, which increases the probability of coincidental diagnosis of KS. That was the case of our two patients.

In spite of the usually known good prognosis of CML and APL, our two patients had an adverse outcome. It is unclear whether the presence of KS has any prognostic significance.

Garcia and al reported an APL associated with KS; the patient was in complete remission during maintenance therapy [5].

In one case reported by Toubai and al, the patient presented with CML in blast crisis [7]. He underwent allogenic bone marrow transplantation, but he relapsed after and died due to disease progression.

In other cases of CML, one patient presented in the chronic phase and had a persistent suboptimal molecular response despite therapy with second generation Tyrosine kinase inhibitor [8]. One second patient, reported by Chennuri et al., was treated with oral imatinib mesylate and remained in complete hematological and major molecular remission after 2 years of continued imatinib therapy [9].

The most important cohort study of KS found an increased risk of mortality from breast cancer, lung cancer and non Hodgkin lymphoma, but no association with leukemia was found [2].

Klinefelter syndrome can be diagnosed incidentally during cytogenetic analysis for leukemia. Long-term follow up studies are needed to define the prognosis of leukemia in patients.

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Compliance with Ethical Standards

Conflicts of interest No conflict-of-interest.

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