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Case report

Klinefelter Syndrome and Acute Basophilic Leukaemia – Case Report

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A B S T R A C T

Patients with 47, XXY karyotype (Klinefelter syndrome) appear to have increased risk of developing cancer, especially male breast cancer, germ cell tumours and non Hodgkin lymphomas, but rarely acute myeloid leukaemia. We report a patient with acute basophilic leukaemia with 47, XXY karyotype in both the tumour and constitutional cells. Acute basophilic leukaemia is very rare disease comprising less than 1% of all acute myieloid leukaemias. Morphological characteristic of leukaemic blast cells is moderately basophilic cytoplasm containing a variable number of coarse basophilic granules. The most characteristic cytochemical reaction is metachromatic positivity with toluidine blue. Blast are myeloperoxidase negative. Also leukemic blasts express myeloid and monocyte markers. There is no consistent chromosomal abnormality identified in this leukaemia. This is the first reported case of acute basophilic leukaemia in patient with Klinefelter syndrome. In this article the medical history of the patient is given and the possible connection between Klinefeter syndrome and acute myeloid leukaemia is discussed.

Key words: *Klinefelter syndrome, acute myeloid leukaemia, acute basophilic leukaemia*

Introduction

Acute basophilic leukaemia is an acute myeloid leukaemia (AML) in which the primary differentiation is to basophils. As in other acute leukaemia, patients present features related to bone marrow failure. Cutaneous involvement, organomegaly, lytic lesions and symptoms related to hyperhistaminemia may be present[1]. Morphological characteristic of leukaemic blast cells is moderately basophilic cytoplasm containing a variable number of coarse basophilic granules. The most characteristic cytochemical reaction is metachromatic positivity with toluidine blue. Blast are negative for myeloperoxidase by cytochemistry. Leukaemic blast cells express myeloid markers CD13 and CD33 and are usually positive for CD123, CD203c and CD11b. In contrast to normal basophils may be positive for HLA-DR, but are negative for CD117[2]. It has been generally associated with poor prognosis.

Klinefelter syndrome is the most common cause for male hypogonadism[3]. It is characterised with underdeveloped testis, gynaecomastia, eunuchoidism, aspermia and an increased level of serum gonadotropin[4]. The essential characteristic is an abnormal karyotype with one or more extra X. There have been several reports of patients with Klinefelter syndrome who developed various types of tumours, especially breast cancer, germ cell tumours and lymphomas. Thus the relationship between this constitutional chromosome alteration and incidence

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of leukaemia seems questionable and also its relationship to tumorogenesis. Herein, we review a case of Klinefelter syndrome along with acute myeloid leukaemia (AML).

Case Report

The 63-year old male with history of Klinefelter syndrome was admitted to our hospital with high fever and cough. In the patient medical history he had never had previous haematological disease. Physical examination demonstrated reduced sounds on the right chest and few ecchymoses. Laboratory investigation revealed leucopoenia (white blood cell count of $2.16x10^9$ /L), anaemia (red blood cells count of $2.12x10^{12}$/L and hemoglobin 76 g/L) and thrombocytopenia (platelet count of $8x10^9$/L). Blood chemistry showed elevated level of aspartat transferase (42 U/L) and lactate dehydrogenase (883 U/L). C-reative protein was also elevated (45 g/L). Ultrasound of the abdomen showed hepatomegaly. In peripheral blood smear were found 10% myeloblasts, 4% bands, 51% neutrophilic granulocytes, 2% eosinophils, 2% basophils and 37% lymphocytes. Bone marrow aspirate demonstrated hypocellular smear with reduced erythrocytopoiesis, reduced, morphologically regular thrombocytopoiesis and 33% leukemic blast cells proving morphologically acute myeloid leukaemia (Figure 1). Blast cells were of medium size with a high nuclear-cytoplasmic ratio, a nucleus with dispersed chromatin and one or three prominent nucleoli. The cytoplasm was moderately basophilic and contained a variable number of coarse basophilic granules. Also we found 14% basophilic cells. Toluidin blue cythocemical staining showed positivity of 17% of cells (Figure 2) and leukemic blast cells were myeloperoxydase (Figure 3) and Sudan black negative, so the diagnosis of acute basophilic leukaemia was set. Histological examination of the bone marrow confirmed AML. Flow cytometric analysis of blast cells showed CD45, CD13, CD33 and HLA D/DR positive expression. Chromosome analysis of bone marrow cells revealed the same karyotype, 47 XXY (Figure 4), like in peripheral karyotype blood. FISH analyses for probes 6q21, 8q24, 7q22 and 7q35 showed no clonal aberration and FISH analysis for BCR/ABL fusion gene was not done. Patient was treated with cytarabin and daunorubicin (7+3) with partial response. Three months following the diagnosis, the patient died due to sepsis with multiorganic failure.

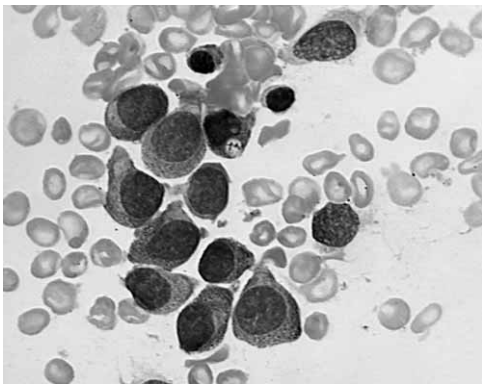

Fig. 1. Smear of bone marrow aspiration of acute basophilic leukemia, Pappenheim x1000.

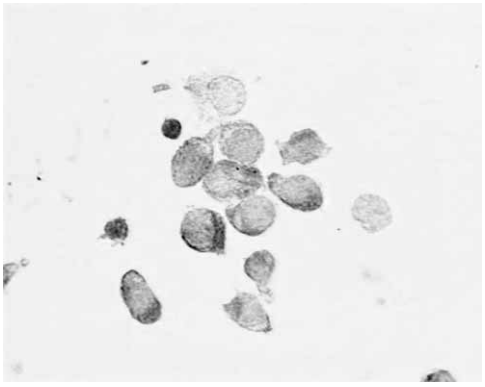

Fig. 2. Toluidin blue positive staining of leukemic blast cells in bone marrow aspirate (x1000).

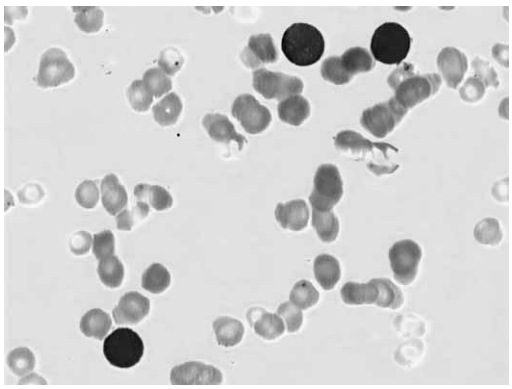

Fig. 3. Myeloperoxydase negative staining of leukemic blast cells in bone marrow aspirate (x1000).

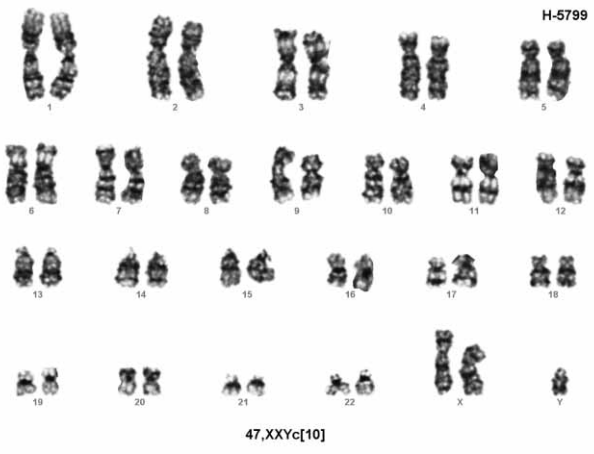

Fig. 4. Chromosome analysis of bone marrow cells shows 47, XXY karyotype

Discussion

Klinefelter syndrome is the most common sex chromosome disorder and affects 1 in 500 men. It was first reported in 1942, describing a syndrome characterised by gynaecomastia, aspermiogenesis without a Leydigism and increase excretion of follicle stimulation hormone[4]. In 1959 it was discovered that these abnormalities are derived from the chromosome alteration, 47 XXY[5]. Patients may lack some clinical features, but small testicles and azoospermia are constant. Serum testosterone and dihydrotestosterone levels are low and serum gonadotropins are uniformly increased.

Many case reports have suggested an association between Klinefelter syndrome and various cancers. Therefore much attention has been paid to the relation between chromosomal alteration and oncogenesis. The increased risk in several types of cancers suggests that the extra X chromosome may be involved in tumorogenesis associated with this syndrome. The date demonstrated that loss-of-inactive X in the female derived cancer cells is mainly achieved by loss of an inactive X chromosome, followed by multiplication of an identical active X chromosome[6].

Also it was published that XXY cell line from patients with lung cancer manifested a 3-fold increase in susceptibility to SV 40 transformation compared to the normal cell line of the same patient and in individuals with normal karyotype and no history of cancer. Such an abnormal susceptibility to SV 40 infection in vitro has been suggested as an indicator of individuals with predisposition to cancer[7]. Simian virus (SV40) is DNA tumor virus. Different domains of large T protein encoded by SV 40 bind to p53 and Rb inhibiting their function which induce cell transformation in cell cultures. Cell cultures from patients with diseases that is associated with incidence of chromosomal aberrations and the greatly increased risk of neoplasia showed a much greater susceptibility to transformation in culture by SV 40 when compared from normal individuals and from the individuals with disease not associated with an increased tumor incidence.

Increased incidence of malignant disorders of patients with Klinefelter syndrome is still investigated. Besides some case reports being published, there are only few cohort studies investigating this problem. Danish cohort study in 1992[8], British cohort study in 2001[9] and in 2005 study of UK Clinical Cytologic Group[10]. They all agree that although findings in these studies were not mutually consistent there is evidence that men with Klinefelter syndrome have increased risk of breast cancer, midline teratoma and there seems a supported suggestion of increased risk of several other malignancies compared with men in general population. In 1961 Mammunes was the first who describe a case of acute myeloid leukaemia in patient with Klinefelter syndrome[11]. Although several case reports were published, cohort studies showed that AML in Klinefelter syndrome was a by-chance association.

Concerning acute basophilic leukaemia this is the first described case in patient with Klinefelter syndrome. Acute basophilic leukaemia is very rare disease comprising less than 1% of all acute myeloid leukaemias. There is no consistent chromosomal abnormality identified in these cases[1]. Although some authors described increase in prevalence of AML, they assume that these findings are intriguing, because it is at least partly due to the increased frequency of cytogenetic studies in the patients with haematological malignancies[12]. So we assume that larger studies are required to either confirm or disapprove the association of Klinefelter syndrome and acute myeloid leukaemia.

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PRIKAZ SLUČAJA KLINEFELTEROVA SINDROMA I AKTUNE BAZOFILNE LEUKEMIJE

S A Ž E T A K

Bolesnici s 47, XXY kariotipom (Klinefelterovim sindromom) pokazuju veći rizik razvoja karcinoma dojke, karcinoma zametnih stanica i non- Hodgkin limfoma, ali rijetko dolazi do razvoja akutne mijeloične leukemije. Prikazali smo bolesnika s akutnom bazofilnom leukemijom, s ranije dijagnosticiranim Klinefelterovim sindromom, kod kojeg se i u tumorskim stanicama nalazi 47, XXY kariotip. Akutna bazofilna leukemija je veoma rijetka bolest, koja sačinjava manje od 1% svih akutnih mijeloičnih leukemija. Kod nje se u koštanoj srži nalaze nezrele bazofilne stanice, gdje se u citoplazmi nalaze bazofilne granule. Blasti su izrazito pozitivni na toluidin dok su mijeloperoksidaza negativni. PAS reakcija i klor-acetat-esteraza u bazofilnim blastima su često pozitivni. Imunološki blasti nose mijeloidne i monocitne biljege. Kod ovog oblika leukemije nije dokazana povezanost sa specifičnim kromosomskim poremećajima. Ovo je prvi prikazani slučaj akutne bazofilne leukemije kod bolesnika s Klinefelterovim sindromom. U ovom radu smo iznijeli medicinsku povijest bolesti bolesnika, a također smo razmotrili moguću vezu Klinefelterovog sindroma i akutne mijeloične leukemije.