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Acute myeloid leukemia in a patient with constitutional 47,XXY karyotype

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1. Introduction

Klinefelter syndrome (KS), a 47,XXY chromosomal abnormality, has been shown to be associated with a number of malignancies, but has not been linked to acute leukemias to date. We present a case of a 54-year-old male diagnosed with acute myeloid leukemia (AML) with monocytic differentiation, whose cytogenetic and subsequent FISH analyses revealed a constitutional 47,XXY karyotype. We also review and discuss relevant prior literature.

2. Case

A 54-year-old male with a medical history of non-insulin dependent diabetes mellitus, hypertension, and gastroesophageal reflux, initially presented to his dentist with left-sided gum pain. Due to persistence of the pain, he was then evaluated by his primary care physician, who noted a marked leukocytosis. He was subsequently referred to the emergency room, where he was found to have a white blood cell count (WBC) of 33,500/mm³, of which 2% were blasts, a hematocrit of 22.2%, and a platelet count of 1.74 mg/dL, and there was concern for tumor lysis syndrome, associated with the sex chromosome abnormality 47,XXY [1].

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approximately 10 days. His clinical status improved gradually, with resolution of renal failure and pneumonia, and a mid-treatment marrow biopsy at day 14 revealed an ablated marrow without morphologic evidence of leukemia (less than 5% cellularity with no increase in monoblasts). The remainder of his hospitalization was complicated by Clostridium difficile colitis, which was treated with antibiotics. He experienced normal peripheral blood count recovery and was discharged from the hospital in good condition.

A bone marrow biopsy subsequently confirmed complete remission 32 days after the start of induction therapy. Given the relatively favorable prognostic risk associated with an isolated NPM1 mutation, the patient has gone on to receive cycles of consolidation chemotherapy with high dose cytarabine. He remains in remission, now five months after his initial diagnosis.

3. Discussion

Cases of AML have been reported in patients with Klinefelter syndrome since the 1960s [4], and there has been an interest in investigating a potential association between a 47,XXY chromosomal abnormality and myeloid malignancies. Certain constitutional chromosomal abnormalities are known to be associated with malignancy. For example, children with trisomy 21 (Down syndrome) have a 10–20 fold higher risk of developing acute leukemia than other children [5]. Additional hematological malignancies have been reported in patients with other constitutional chromosomal abnormalities (Table 1).

A 2002 review by Keung and colleagues summarized cases of hematologic malignancy in patients with KS reported between 1961 and 2002 [3]. They described 12 cases of AML in KS in the literature during that time period. Based on the review of the current literature, we found approximately 10 additional cases of AML in patients with constitutional 47,XXY. Overall, this is a rather small number of reported cases over a period of greater than 5 decades, and studies to date have not definitively established an epidemiological link [3,6].

Intriguingly, almost half the cases of AML with KS occurred in the pediatric population (< 18 years old at diagnosis) [3,7,8]. No cases were diagnosed over the age of 64 [4,9,10]. This is noteworthy given that the median age of AML at diagnosis is above 65, and that the majority of AML cases are diagnosed in older patients. These observations raise the question of whether KS, like certain other constitutional abnormalities, may predispose to an earlier onset of AML.

Additionally, in all but two cases in the reported literature, the diagnosis of KS was made at the time of AML diagnosis. This would suggest that an epidemiological association between the two conditions may be overstated, as KS may be under-diagnosed in the general population due to its range of phenotypic manifestation. Larger and more comprehensive studies would be needed to study the possibility of an epidemiological link between AML and Klinefelter syndrome, an association that may shed light on disease genetics and mechanisms, and possibly further guide monitoring and treatment in this population.

Authors’ contributions

MMJ and ATF conceptualized the case, carried out the review and analysis, and wrote the manuscript.
ARS, PD, and RPH interpreted the pathology and created Figures. JAM and AMB contributed to patient care, reviewed the manuscript and provided edits.

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