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Primary myelodysplastic syndrome with complex chromosomal rearrangements in a patient with Klinefelter's syndrome

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SUMMARY A patient with Klinefelter's syndrome and diabetes mellitus was diagnosed as having myelodysplasia. Cytogenetic analysis of the peripheral blood and the bone marrow cells confirmed the presence of a constitutional 47,XXY chromosome complement. In addition, complex karyotypic abnormalities were present.

Several studies have suggested an increased incidence of extragonadal germ cell tumours,¹ carcinoma of the breast,² and acute myeloid leukaemia³⁻⁵ in patients with Klinefelter's syndrome. In this report we describe a patient with Klinefelter's syndrome who developed a preleukaemic state (myelodysplastic syndrome). Cytogenetic analysis of the bone marrow and peripheral blood of this patient showed a constitutional 47,XXY chromosome complement. In addition, complex karyotypic abnormalities were present. The significance of these findings is discussed.

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Case report

A male Caucasian, aged 68, presented with a four month history of increasing breathlessness. Eight years previously he had been admitted to another hospital in a hyperosmolar, non-ketotic diabetic coma and at that time he was noted to be tall (185 cm) and to have hypogonadism and prognathism. He had been investigated for acromegaly and was found to have raised levels of FSH and LH and normal levels of TSH, free T4, growth hormone, and prolactin. Skull x-ray showed a normal pituitary fossa. His diabetes had been controlled with oral hypoglycaemic agents and the only other drug therapy he had received was testosterone at six monthly intervals. He was unmarried and had no children. He had no history of exposure to chemicals.

On presentation at this hospital he was noted to be pale and lacking facial and body hair. He had gynaecomastia and small testes. Full blood count showed Hb 7.5 g/dl, WBC $3.5 \times 10^9/l$ (neutrophils 46%, lymphocytes 45%, monocytes 3%, eosinophils 6%), and platelets $309 \times 10^9/l$. Blood film showed dimorphic red cells, hypogranular neutrophils, and platelet anisocytosis. Bone marrow aspirate showed

TABLE Karyotype of peripheral blood and bone marrow.

Karyotypes	No of cells
Bone marrow	
45.XXY,-5,-7,-12,-21,+m ¹ ,+m ² ,del(3p)	3
46.XXY,-5,-7,-12,-21,+m ¹ ,+m ² ,+fra.del(3p)	2
46.XXY,-5,-7,-21,+t(7p;21q),+m ¹ ,t(3;12)(p21;13)	2
47.XXY	4
Total	11
Peripheral blood	
With PHA	
47.XXY	10
Without PHA	
46.XXY,-5,-7,-12,-21,+m ¹ ,+m ² ,+fra.del(3p)	1

diserythropoietic erythroid hyperplasia and dysplastic features in both granulopoiesis and thrombopoiesis. The myelogram showed 82% erythroblasts and 2% myeloblasts. Iron stain revealed that 68% of the erythroblasts were ring sideroblasts.

Cytogenetic analysis of bone marrow and peripheral blood cells showed a 47,XXY constitutional chromosome complement. In addition, cell lines with complex rearrangements were detected in 64% of cells from 24 hour cultures of bone marrow (table). All the abnormal cells showed monosomy 5. In one cell, rearrangements between 7p and 21q were identified (resulting in monosomy 7q) and in another cell a t(3;12)(p21;p13) was present. A small unidentifiable marker was also seen.

A diagnosis was made of Klinefelter's syndrome and of refractory anaemia with ring sideroblasts. The patient is being treated by blood transfusion at six weekly intervals and maintains an otherwise stable condition.

Discussion

In 1961 the first case of acute myeloid leukaemia in a patient with Klinefelter's syndrome was reported.⁵ Since then at least 12 more such associations have been documented. Muts-Homsma *et al*⁴ performed cytogenetic analysis on 51 adult males with acute myeloid leukaemia and found five patients to have a chromosome complement of 47,XXY. On the basis of these figures it was estimated that Klinefelter's syndrome patients have a 100-fold increased risk of developing acute myeloid leukaemia compared to the normal population.

The myelodysplastic syndrome constitutes a group of disorders in which the bone marrow is progressively replaced by an abnormal clone of haemopoietic cells. The patients usually present with anaemia associated with neutropenia or thrombocytopenia or both. The FAB Cooperative Group have identified five sub-groups of myelodysplastic

syndrome.⁶ These comprise refractory anaemia, refractory anaemia with ring sideroblasts, refractory anaemia with excess of blasts, refractory anaemia with excess of blasts in transformation, and chronic myelomonocytic leukaemia.

It is estimated that 17 to 25% of all patients with myelodysplastic syndrome transform to acute myeloid leukaemia.^{7,8} Non-random chromosome anomalies, such as monosomy 5, monosomy 7, and trisomy 8, are commonly found in patients with these conditions. These facts together suggest a close link between the two disorders. Patients with myelodysplastic syndrome who show complex karyotypic abnormalities at presentation have an especially high risk of developing acute leukaemia.⁸

In our previously reported series of 141 cases of myelodysplastic syndrome,⁸ 26 patients had refractory anaemia with ring sideroblasts and had normal chromosomes or single stable abnormalities at presentation. The Klinefelter's syndrome patient reported here was not included in this series. He is unusual in that, at the time of diagnosis of refractory anaemia with ring sideroblasts, cytogenetic analysis showed cell lines with complex chromosome rearrangements. Although this is considered to be the most benign form of myelodysplastic syndrome, with very few patients in this category developing acute myeloid leukaemia, our experience of patients with myelodysplastic syndrome who have complex karyotypic abnormalities suggest that this patient is at grave risk of developing acute leukaemia.

Mukerjee *et al*⁹ have shown that XXY cell lines manifest a three-fold increase in their susceptibility to SV 40 transformation compared to normal cells. However, the events at the genetic level which may predispose Klinefelter patients' cells to become malignant have yet to be elucidated.

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Partial trisomy 6p and partial trisomy 22 resulting from 3:1 meiotic disjunction of maternal (6p;22q) translocation

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SUMMARY A male infant, partially trisomic for a small segment of chromosomes 6 and 22 resulting from a maternal translocation, is described. Comparison of the phenotypic features of the proband with those noted in partial 6p and partial 22 trisomies revealed some common features found in both chromosome anomalies but especially reinforced those features thought to be characteristic of 6p trisomy syndrome.

Case report

A 13 day old white male (fig 1) was the 2780 g product of a 38 to 39 week gestation for a 22 year old gravida 2 (FO, PO, Abl, LO) mother. Admission to

hospital and hormone injections were required to maintain the pregnancy complicated by first trimester bleeding. Maternal drug or alcohol abuse, radiation or chemical exposure, and smoking were denied. Family history was remarkable for several maternal relatives with multiple miscarriages and several unexplained early infant deaths.

Caesarean section was performed because of maternal toxemia. Polyhydramnios was noted at delivery. The neonatal course was complicated by hyperbilirubinaemia and hypoglycaemia.

Physical examination showed a vigorous infant with microcephaly, facial asymmetry, overriding sagittal suture, small anterior fontanelle, right sided microphthalmia, blepharophimosis, blepharoptosis, downward slanting palpebral fissures, mild hypertelorism, slightly flattened nasal bridge, flammeus naevus over the nasal bridge and nape of the neck, bilateral preauricular pits, holosystolic murmur, partial soft tissue syndactyly of the second to fourth

FIG 1 The proband at 15 months.

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