Supernumerary derivative (22) syndrome resulting from a maternal balanced translocation

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ABSTRACT

Supernumerary derivative (22) syndrome is one of the rare genomic syndromes. It is characterised by severe mental retardation, microcephaly, failure to thrive, ear anomalies, preauricular tags or sinus, cleft palate or high arch palate, microganathia, renal anomalies, congenital cardiac defects and genital abnormalities in males. In 99 percent of the cases, one of the parents is a balanced carrier of a translocation between chromosome 11 and chromosome 22. We report the first known case, a female neonate, of supernumerary derivative (22) syndrome from Malaysia.

Keywords: Emanuel syndrome, supernumerary derivative (22) syndrome, t(11;22), trisomy 11, trisomy 22

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Fig. 1 Photograph shows the facial features with microtia, supra-auricular skin tag and skin pit, and microganathia.

INTRODUCTION

The constitutional translocation between chromosomes 11 and 22 is the most common non-Robertsonian translocation in humans. Clustered breakpoints involving q23 of chromosome 11 and q11 of chromosome 22 have been reported in numerous unrelated families.[1] Balanced translocation carriers are clinically normal, and are often identified after the birth of an offspring with supernumerary der(22)t(11;22)syndrome. This genomic syndrome was named as Emanuel syndrome in 2004 (OMIM # 609029). Patients with Emanuel syndrome has a distinctive phenotype, which consists of severe mental retardation, microcephaly, prominent forehead, epicanthal folds, down-slanting palpebral fissures, broad and flat nasal bridge, long and pronounced philtrum, micrognathia, cleft palate, abnormal auricles ranging from microtia to large ears often associated with a preauricular ear pit and/or skin tags, and genital anomalies in boys.[2] This unbalanced translocation syndrome usually arises through a 3:1 meiosis I malsegregation during gametogenesis in a balanced translocation carrier.[1]

CASE REPORT

Our patient was the second child of young, healthy consanguineous parents. She was delivered at term after an uncomplicated pregnancy. At birth, she was noted small for gestational age. Birth weight was 2.3 kg (< third percentile), length was 48.5 cm (between third and tenth percentile) and head circumference was 32 cm (< third percentile). She also had a remarkable facial appearance which included bilateral microtia with supra-auricular skin tag and skin pit, cleft palate and microganathia (Fig. 1). Her cardiovascular assessment revealed a moderately large ventricular septal defect and a small patent ductus arteriosus. Renal ultrasonography, ophthalmological assessment and the hearing assessment did not reveal any abnormality. During the follow-up examination, she was found to have significant central hypotonia, developmental delay, and all growth parameters remained well below the third percentile.

Karyotyping using G-banding analysis at 550 band levels showed an extra supernumerary marker chromosome (SMC) (Fig. 2a). To ascertain the origin of this SMC, karyotyping for her parents was performed. The mother was found to be a balanced carrier; 46,XX,t(11;22)(q23.3;q11.2), which means there is an even exchange of genetic material between

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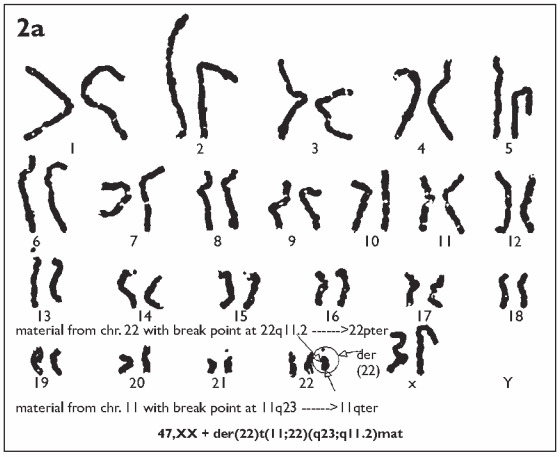

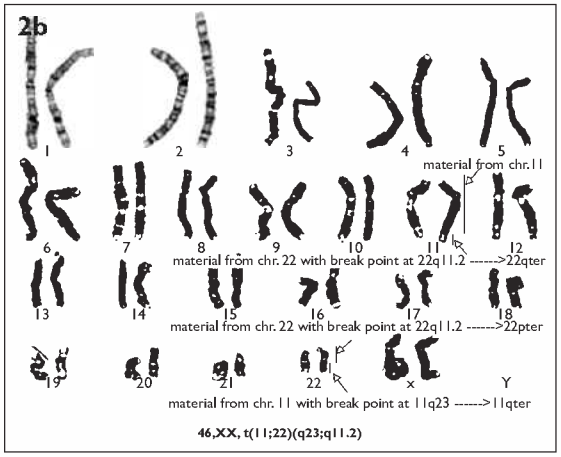

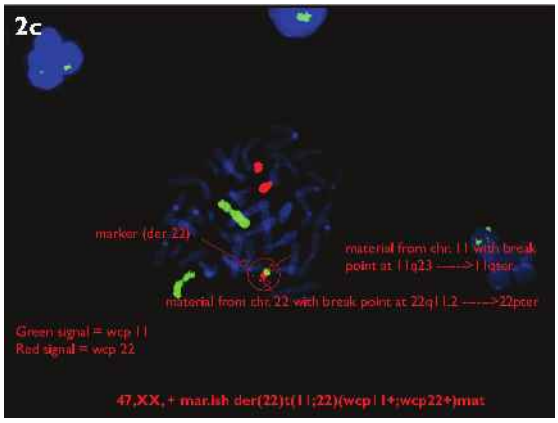

Fig. 2 (a) The patient's karyotype shows an extra supernumerary chromosome. (b) Her mother's karyotype shows a balanced non-Robertsonian translocation between chromosome 11 and chromosome 22. (c) Fluorescent *in situ* hybridisation with whole-chromosome paint probes for chromosome 11 (green) and chromosome 22 (red) show that the supernumerary derivative 22 chromosome has chromosomal material originated from chromosome 11 and chromosome 22.

the long arm of chromosome 11 (from band 11q23.3 to 11qter) and the long arm of chromosome 22 (from band 22q11.2 to 22qter) (Fig 2b). The mother had passed the structurally-rearranged chromosome 11 (or derivative chromosome 11), which is the result of a translocation between the long arm of chromosome 11 at band q23.3 and long arm of chromosome 22 at band q11.2 onto this patient, and resulted in an abnormal karyotype delineated as 2n = 47,XX,+der(22)t(11;22)(q23;q11.2) mat. Using dual-colour fluorescent *in situ* hybridisation with whole-chromosome paint probes, chromosomes 11 and 22 were selectively painted with two different colours and confirmed that the SMC in this patient has chromosome material originated from chromosome 11 and chromosome 22 (Fig. 2c).

DISCUSSION

SMC are frequent findings at pre- and postnatal cytogenetic studies. Approximately 9% of SMC are derived from chromosome 22.[3] Though chromosome 22 represents only about 1.9% of the total haploid autosome length, numerous rearrangements of this chromosome have been associated with numerous genetic disorders and developmental anomalies.[4] The clinical phenotype of Emanuel syndrome arises from duplication of 22q10–22q11 and duplication of 11q23–11qter on the supernumerary derivative 22. In more than 99% of cases, one of the parents of a proband with Emanuel syndrome is a balance carrier of t(11;22) and is phenotypically normal. This syndrome almost always results from a 3:1 meiotic I malsegregation of t(11;22) in an unaffected parent.[1] However, there is a single case of Emanuel syndrome reported arising from *de novo* (11;22) translocation in the paternal germline with probable unbalanced adjacent 1 segregation and maternal non-dysjunction of chromosome 22 in meiosis I.[5]

Our patient had the classical features of Emanuel syndrome described in the literature. She showed a significant developmental delay at six months of age, and to the best of our knowledge, is the first reported case of Emanuel syndrome from Malaysia. Care of such patients requires a multidisciplinary approach. The long-term prognosis is directly related to the associated congenital malformations. Highest mortality is in the first few months of life. Affected children should have regular developmental assessments to guide therapeutic interventions and educational modalities.

In terms of genetic counselling of this family, three issues needed to be addressed. Firstly, the female carrier

of a balanced t(11;22) are reported to be at an increased risk of premenopausal breast cancer,[6] thus breast cancer surveillance has been recommended for the mother in our case. Secondly, when one of the parents of Emanuel syndrome is a carrier of t(11;22), future pregnancies are at an increased risk for either Emanuel syndrome, balanced t(11;22) or another meiotic malsegregation. This reproductive implication has been fully explained to this couple and prenatal cytogenetics testing could be offered in future pregnancy. Thirdly, carrier testing for the unaffected siblings are normally offered when they have reached adulthood and are able to understand the reproductive implications of being a carrier. The possibility of the four-year-old female sibling of the proband as being a balanced carrier of t(11;22) has been discussed with her parents, and they have opted for testing her carrier status later when she is a legal adult.

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