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Case Report

Genetics Section

A Unique Constitutional Robertsonian Translocation t(13;14) Associated with Severe Aplastic Anaemia

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ABSTRACT

Aplastic anaemia is characterised by cytopenias and hypocellular bone marrow without any evidence of marrow fibrosis or marrow infiltration. There is no specific cytogenetic abnormality associated with aplastic anaemia. Most common abnormalities are trisomies of chromosome 6, 8 and loss of 7. A 17-year-old female, presented with generalised weakness, exertional breathlessness and menorrhagia for last six months. She also gave a history of 12 units Packed Red Blood Cells (PRBC) transfusion, at the rate of 2-3 units per month in the last five months. Routine haematology showed severe pancytopenia with reticulocytopenia. Bone marrow evaluation revealed hypoplastic marrow with 15% bone marrow cellularity suggesting aplastic anaemia. Karyotyping using Giemsa (GTG) banding of unstimulated culture showed a very unique constitutional Robertsonian Translocation (RT) karyotype 45+XX, der(13;14)(q10;q10). Patient responded partially to treatment with cyclosporine and anabolic steroids. The final diagnosis was severe aplastic anaemia associated with constitutional RT t(13;14) karyotype. Although cytogenetic abnormalities are neither common nor specific in aplastic anaemia, some of them can have diagnostic and therapeutic implications.

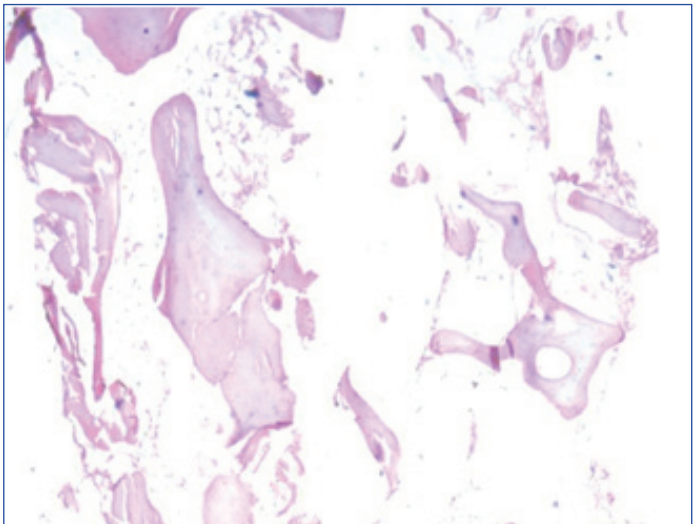
Keywords: Bone marrow failure, Cyclosporine, Cytogenetic abnormalities, Karyotyping

CASE REPORT

A 17-year-old female presented to the Outpatient Department of Clinical Haematology with generalised weakness, exertional breathlessness and menorrhagia from past six months. She also gave a history of 12 units of Packed Red Blood Cells (PRBC) transfusions at local hospitals in the last 5 months (2-3 PRBC units per month) for severe symptomatic anaemia. There was no history of any other bleeding, fever, weight loss, bone pains or recurrent infections. The patient had no history of any co-morbid condition like diabetes, hypertension, tuberculosis or any other chronic illness, and had not taken any medication for a long duration. She had two siblings, a brother and a sister and both were absolutely fine. The patient was a non vegetarian. In last six months, she regularly received multivitamins and iron supplements along with on and off oral tranexamic acid at a primary care centre. She remained grossly unresponsive to the treatment and hence was referred to our centre.

On examination, the patient had severe pallor, no icterus, lymphadenopathy, oedema or palpable organomegaly. Patient was carefully examined for physical anomalies like abnormal skin or oral mucosa pigmentation, syndromic facies, abnormal skin or nails, thrombocytopenia with absent radius, brown hair patch, abnormal dentition and any other abnormalities, but no abnormalities could be detected. The patient had normal mentation, her stature was absolutely normal and she had menarche at the age of 13 years with normal menstrual cycles.

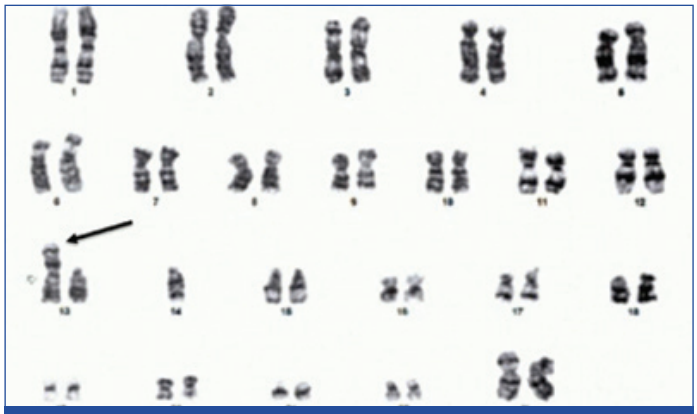
Baseline laboratory investigation showed haemoglobin of 69 gm/L, Total Leukocytes Count (TLC) was 2.9×10^9/L with lymphocytic predominance (80%), platelet count of 15×10^9/L and absolute reticulocyte count was 0.2%. Liver function test and kidney function test were normal and Hepatitis B surface Antigen (HbsAg), Hepatitis C Virus (HCV) antibody and Human Immunodeficiency Virus (HIV) antibodies were non reactive by Enzyme-Linked Immunosorbant Assay (ELISA). To exclude nutritional deficiencies, serum vitamin B12 and folate level performed and showed normal levels. Anti IgM antibodies and Deoxyribonucleic Acid-Polymerase Chain Reaction (DNA-PCR) for Cytomegalovirus (CMV), Epstein-Barr Virus (EBV) and parvovirus were negative. Bone marrow aspiration/biopsy was performed and the result showed hypoplastic marrow with cellularity 15% without any dysplastic cells, blast or fibrosis [Table/Fig-1]. To rule out other causes of hypoplastic marrow, Paroxysmal Nocturnal Haemoglobinuria (PNH) by Fluorescein-Labeled proaerolysin (FLAER) was performed but no abnormal clone detected. Stress cytogenetics performed for Fanconi anaemia using Mitomycin-C did not show any significant chromosomal breakage. Provisionally, she was diagnosed as a case of acquired aplastic anaemia.



[Table/Fig-1]: Bone marrow biopsy (H&E staining) showing markedly hypocellular intertrabecular spaces, haematopoietic precursors replaced by fat cells (H&E, 10X).

As the patient was an adolescent with severe aplastic anaemia, it was decided to perform targeted gene sequencing covering 96 clinically relevant gene mutations to rule out the possibility of inherited bone marrow failure syndrome. No pathogenic or likely pathogenic variants were detected. Karyotyping using G-Banding

revealed an abnormal constitutional karyotype 45+XX, der(13;14)(q10;q10) which is a RT [Table/Fig-2].



[Table/Fig-2]: Unstimulated G banding for karyotype showed 43 autosomes and 2 sex chromosomes with presence of Robertsonian translocation between 13q10 and 14q10 region. The chromosomes count was thus reduced to 45.

Patient was started on cyclosporine 5 mg/kg body weight, along with stanozolol 2 mg, two tablets three times a day (total 12 mg/day) and folic acid 5 mg per day with tab progesterone 10 mg three times a day to suppress menses. Monthly, follow-up with monitoring of complete blood count, kidney profile and liver profile was done. Patient showed partial improvement with 50% reduction in packed red cell requirements, platelet was stable at 30×10^9/L and TLC remained around ~2×10^9/L. Kidney and liver profile was normal throughout. In view of partial improvement and existing transfusion dependence, patient's family was counselled for allogeneic stem cell transplant. Procurement of Anti Thymocyte Globulin (ATG) was under process as the family couldn't afford the cost of transplant procedure.

DISCUSSION

Robertsonian Translocations (RTs) are one of the most common constitutional balanced translocations, in which two acrocentric chromosomes fused at their centric end [1]. Most commonly encountered RT is translocation (13;14) which constitute 75% of total RTs [2]. Patients with 45+XX/XY (13;14) (q10;q10) were reported to have various endocrine disorders including hypogonadotropic hypogonadism, precocious puberty, early puberty, growth hormone deficiency and idiopathic short stature [3].

Aplastic anaemia is a rare life-threatening haematological disorder characterised by pancytopenia with hypocellular marrow. This occurs due to chronic primary haematopoietic failure from immunological injury, toxic injury or inherited predisposition leading to diminished or absent haematopoietic stem cells [4]. Incidence of aplastic anaemia varies from 1.5-7% case per million per year according to geography, however some studies suggested that the incidence rate of aplastic anaemia is higher in Asian population than European and American population [5,6].

Cytogenetic abnormality is an infrequent finding in aplastic anaemia although some articles reported these abnormalities ranging from 4.0% to 11.9% [7]. Among these abnormal cytogenetics patterns, structural and numerical abnormalities of chromosome 7, trisomy of chromosome 6 and 8 are the common abnormalities [8].

RT are the most common chromosomal structural abnormality involving acrosomal chromosomes with incidence rate of ~1/1000 live birth in the general population [1,9]. Different studies quote that the most of the patient with RTs are associated with infertility due to oligospermia in male and miscarriage in female [10,11]. This specific chromosomal abnormality also increased the risk of Down syndrome (Trisomy 21) and Patau syndrome (Trisomy of 13) in the offsprings [1]. The specific RTs 45XX, der(13;14)(q10;q10) show various phenotypes and endocrinopathies like growth hormone deficiency, precocious puberty, early puberty, hypogonadotropic hypogonadism and idiopathic short stature [4]. Aplastic anaemia with abnormal constitutional chromosomal anomalies are fairly infrequent. According to a study done in the USA most commonly reported abnormalities were trisomy of chromosome 6 and 8 and loss of chromosome 7 [8]. One study from northern India also showed the similar results and detected abnormalities like the trisomy of 12 and 8, loss of chromosomes 7 and translocation (5;12) [7]. Another study from the same region found a unique chromosomal abnormality i.e., RTs 45XY, der(14;21)(p10;q10) associated with aplastic anaemia [12].

Nowell P et al., described the same RTs i.e., constitutional t(13;14) associated with bone marrow failure in two adult siblings [13]. Both siblings were initially presented with persistent thrombocytopenia, amongst them female siblings further progressed into aplastic anaemia while male siblings remained as a case of persistent thrombocytopenia.

Cytogenetic abnormalities are very rare in aplastic anaemia. Prognostic significance of these abnormalities for diagnosis is largely unknown. Clonal karyotypic evolution with evolution of chromosome 7 abnormalities was associated with poor outcome while trisomy 8 has shown good results with Immunosuppressive Therapy (IST) in one study [14]. RTs are so uncommon that the prognostic significance is still not known.

CONCLUSION(S)

Cytogenetic abnormalities are rare in acquired aplastic anaemia. This report is about a rare case of aplastic anaemia with RT t(13:14). The association between t(13;14) and primary bone marrow failure and the exact mechanism of development of bone marrow failure in these cases is not clear. More case reports and further research is needed to through light on these aspects.

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