Di Guglielmo Syndrome in a t(DqDq) Heterozygote

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The centric fusion translocation involving the long arm of two D group chromosomes, t(DqDq), is the commonest structural abnormality observed in human populations (Court Brown, 1967; Lubbs and Ruddle, 1968; Sergovich et al, 1969; Walzer, Breau, and Gerald, 1969). Several of these translocations are familial and some are sporadic; the ascertainment of such translocations has often been as a result of the occurrence of trisomy 13 syndrome or by the study in families of patients with other aneuploidies and also by the surveys of normal populations (review in Palmer, Conneally, and Christian, 1969). Occasionally this structural abnormality occurred in subjects selected for chromosome examination because of mental retardation, congenital malformations (Walker and Harris, 1962; Büher and Stalder, 1963; de Grouchy et al, 1963; Jagiello, 1963; Dekaban, 1966; Bowen, Lee, and Harvey, 1968; Neu and Gardner, 1969), or increased frequency of spontaneous abortions (Court Brown, 1967; Wilson, 1969).

Even if it is well known that chromosome anomalies can predispose the cell to malignant transformation (review in Koller, 1967, and in Baserga, 1970), the occurrence of leukaemia in patients with t(DqDq) hitherto has been reported only twice (Engel et al, 1965; Krompotic, 1969).

In the present paper we describe haematological and cytogenetic findings in a case of Di Guglielmo syndrome occurring in a t(DqDq) heterozygote.

Case Report

M.C., a 62-year-old white man, was in good health until March 1969. At that time he was admitted to our Institute because of severe weakness, anaemia, and mild fever. No lymph nodes, spleen, or liver were palpable. His haemoglobin was 5.7 g/100 ml, haematocrit 22% red blood cells 1.63 million/mm³, platelets 42,000/mm³, reticulocytes 0.5%, leucocytes 1,500/mm³, with 39% neutrophils, 60% lymphocytes, and 1% monocytes. The blood contained 2% nucleated red cells and the mature red cells showed anisocytosis, poikilocytosis, and polychromasia. Score for leucocyte alkaline phosphatase was moderately decreased. Serum iron was 190 μg/100 ml; lupus erythematosis test and Coombs tests were negative. The electrophoresis of haemoglobin was normal. Gastric juice contained no free acid. The bone-marrow was intensely cellular with marked increase in the cells of the erythroid series and mild increase in the reticular series. M:E ratio was 1:1.5. The maturation appeared to be satisfactory. Forty to fifty per cent of erythroblastic cells showed megaloblastoid changes. Mitotic figures were common. Megakaryocytes were present, but most of them were young promegakaryocytes. Several erythroid cells were PAS positive. The iron content of the marrow was much increased and some ring sideroblasts were present.

The anaemia was refractory to trials of vitamin B12, folic acid, citrovorum factor, crude liver extracts, vitamin B6, B complex, ascorbic acid, ACTH, and prednisone. Repeated blood transfusions were necessary to maintain an adequate haemoglobin level.

In June 1969, the haemoglobin was 6.9 g/100 ml, red blood cells 2.04 million/mm³, platelets 35,000/mm³, reticulocytes 1.1%, leucocytes 2,400/mm³, with 37% neutrophils, 59% lymphocytes, 3% monocytes, 1% blasts. The blood contained 2% nucleated red cells. A bone-marrow biopsy revealed a further increase of undifferentiated reticular cells. A new trial of therapy was unsuccessful.

In July 1969 the patient developed diffuse skin haemorrhages and the spleen became palpable at the left costal margin.

In September 1969, the haemoglobin was 7.2 g/100 ml, red blood cells 2.20 million/mm³, platelets 25,000/mm³, reticulocytes 0.7%, leucocytes 2,000/mm³, with 30% neutrophils, 64% lymphocytes, 2% monocytes, 4% blasts. The blood contained 9% nucleated red cells. The bone-marrow was still hyperplastic with overwhelming erythroid hyperplasia (M:E ratio 1:3). The erythroid series showed megaloblastic changes; presence of multinucleated giant cells and cells with asynchronism of nuclear and cytoplasmic maturation. Many of the erythroblasts were PAS positive. Cells of the granulocytic series were decreased. Indifferentiated blast cells were clearly increased.

In October 1969, a high percentage of erythroblastic cells, ranging between 24 and 47% of the figured cells, appeared in the peripheral blood. Most of them were PAS positive and showed nuclear and cytoplasmic abnormalities.

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At the beginning of November 1969, white blood cells progressively raised up to 28,000/mm³, with 63% blasts and 4% myeloblasts. Bone-marrow showed an acute leukaemia-like picture with an absolute preponderance of indifferenated blast cells. Vinblastine and prednisone therapy was unsuccessful and the patient died in November. The necropsy was not authorized by the patient’s family.

**Chromosome studies.** During the 8 months of the duration of the illness, chromosome analyses were done on several occasions. For examination of bone-marrow the direct technique described by Kiossoglou, Mitus, and Dameshek (1964) was followed. Chromosomes from peripheral blood cultures were prepared according to the technique described by Moorhead et al (1960); on one occasion a direct chromosome preparation from peripheral blood was made according to the technique previously described by us (Malacarne and Dallapiccola, 1969).

Data obtained from cytogenetic examinations are shown in the Table.

Metaphase plates obtained from leucocytes cultured with phytohaemagglutinin (PHA) had a modal count of 45 chromosomes. Two D group chromosomes were missing and there was an additional large metacentric chromosome, similar in morphology to a No. 3. The latter was interpreted as a t(DqDq), resulting from centric fusion of the long arm of two D chromosomes.

Cells from the bone-marrow showed the same chromosome abnormality (Fig. 1), ie, proved to have a t(DqDq). In addition, in the first preparation, before any treatment, an abnormal superfragmentation (Fig. 2) and stickiness (Fig. 3) of chromosomes was observed in several metaphase plates. These morphological findings were less distinct in the subsequent preparations. In the third and following preparations, as well as in the direct preparation from the peripheral blood, performed 6 days before the death of the patient, inconsistent numerical and morphological abnormalities were found (Fig. 4 and 5). A few cells contained 46 chromosomes; karyotype analysis of these cells showed several different aberrations (Table). In the last bone-marrow preparation one cell had 47 chromosomes (Table).

Chromosome analyses were carried out on all members of the patient’s family available for the study. Three of them were found to be t(DqDq) heterozygotes. A pedigree is shown in Figure 6.

**Discussion**

Di Guglielmo syndrome has been defined as a self-perpetuating, myeloproliferative disorder of undetermined origin, characterized by progressive anaemia, striking erythroblastic hyperplasia of bone marrow and of megaloblastic, megaloblastoid, or normoblastic types; and the gradual development of increasing numbers of myeloblasts’ (Dameshek, 1969). In the reported patient the diagnosis was

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**TABLE**

**CHROMOSOME COUNTS IN MARROW CELLS, PHA-CULTURED LEUCOCYTES, AND DIRECT PREPARATION FROM PERIPHERAL BLOOD**

<table>
<thead>
<tr>
<th>Date</th>
<th>Tissue</th>
<th>No. of Chromosomes</th>
<th>Total Cells</th>
<th>Chromosome Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt;42*</td>
<td>42*</td>
<td>43*</td>
</tr>
<tr>
<td>14 March, 1969</td>
<td>Marrow</td>
<td>1</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>18 March, 1969</td>
<td>Leucocytes</td>
<td>—</td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>8 April, 1969</td>
<td>Marrow</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>12 June 1969</td>
<td>Marrow</td>
<td>—</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>11 September, 1969</td>
<td>Marrow</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6 November, 1969</td>
<td>Marrow</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>18 November, 1969</td>
<td>Peripheral blood</td>
<td>—</td>
<td>—</td>
<td>2</td>
</tr>
</tbody>
</table>

* Random chromosome losses.
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The chromosomal anomaly in the patient's family is similar to that observed by other authors (review in Palmer et al, 1969), and is to be interpreted as deriving from fusion of two chromosomes of group D, accompanied by the loss of a small centric fragment. The analysis of the pedigree indicates that the anomaly segregates at least through three generations. The study of all the available members of the family has not allowed us to elucidate if the translocation has originated de novo in the propositus, or has been transmitted to him through the parents.

The association between t(DqDq) and haemopathies is rare. As far as we know this is the first report of Di Guglielmo syndrome in a t(DqDq) heterozygote.

Published information concerning cytogenetic findings in Di Guglielmo syndrome has demonstrated the presence of inconsistent chromosome anomalies. Several observations consist only of individual case reports (Baserga and Ricci, 1964; di Grado, Mendes, and Schroeder, 1964; Strosselli and Bernardelli, 1964; Ceppellini et al, 1965; Heath and Moloney, 1965; McClure, Thaler, and Conen, 1965; Stahl et al, 1965; Weatherall and Walker, 1965; Introzzi and Buscarini, 1966; Becak, Becak, and Saraiva, 1967; Smalley and Bouroncle, 1967; Krompotic et al, 1968; Crossen et al, 1969). Patterns emerging from cytogenetic studies of larger series of patients with Di Guglielmo syndrome (Kiossoglou, Mitus, and Dameshek, 1965; Castoldi et al, 1968; Heath et al, 1969) suggest similarities with cytogenetic findings in acute leukaemia. In fact, some cases show no discernible chromosome

made on the basis of cytological findings in the bone-marrow and blood, and the clinical course. Further criteria of the condition included hyperferraemia, both in the blood and in the marrow, low blood granulocyte alkaline phosphatase, a variable degree of PAS-positive reactions in nucleated red cells, the presence of erythroblasts with iron granules (sideroblasts) and the presence of 'ringed' sideroblasts.

Fig. 2. Chromosome superfragmentation in a cell from a direct marrow preparation.

Fig. 3. Stickiness of chromosomes in a metaphase from direct marrow preparation.
changes, others show abnormal chromosome patterns unique to individual patients. Aneuploidy, increased polyploidy, chromosome breakages, presence of markers, or of modes either hypodiploid or hyperdiploid are the commonest findings. Even if the occurrence of these abnormalities seems to be due to random and accidental involvement, Castoldi et al (1968) suggests that in Di Guglielmo syndrome, as in other myeloproliferative disorders, the chromosomes of the G group are more labile and undergo deletion, translocation, or loss more frequently than the other chromosomes.

The cytogenetic findings in our case support the evidence of inconsistent anomalies in Di Guglielmo syndrome. In fact, the rare abnormalities observed during the blast phase of the disease were unique to individual metaphases and did not demonstrate the existence of a clonal evolution.

The abnormal chromosome superfragmentation observed in several metaphase plates obtained from bone-marrow cells in our patient, before any treatment, is similar to one demonstrated in some pathological situations, as radiation injury (Bender, 1960), treatment with cytostatic drugs (Castoldi and Malacarne, 1964), viral infections (Nichols, 1963), pernicious anaemia (Baserga, Ballerini, and Castoldi, 1968), Fanconi’s anaemia (Bloom et al, 1966), Louis Barr’s syndrome (Hecht et al, 1966), Bloom’s syn-
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Fig. 6. Pedigree of the family.

drome (German and Crippa, 1966), and congenital porphyria (Burchardt, Wichmann, and Zernahlez, 1968). The significance of the structural abnormality observed in our case is not clear. It can be indicative of an abnormal DNA metabolism; this view is supported by coexistent megaloblastosis (Crossen et al., 1969).

Since the centric fusion translocation involving the long arm of two D group chromosomes is the commonest structural abnormality in human populations (incidence 1/1000), and the occurrence of this anomaly in leukemic patients is rare, the reported case of an association between the congenital t(DqDq) and Di Guglielmo syndrome could be fortuitous.

Summary

Repeated chromosome analyses were carried out during 8 months of illness of a t(DqDq) heterozygote with Di Guglielmo syndrome. Cytogenetic findings included superfragmentation, stickiness of chromosomes, and inconsistent numerical and morphological abnormalities.

Three members of the patient's family were found to be normal t(DqDq) heterozygotes.

References


Dallapiccola and Malacarne


