CONCISE REPORT

A New Translocation, t(1;3) (p36;q21), in Myelodysplastic Disorders

By D.J. Moir, P.A.E. Jones, J. Pearson, J.R. Duncan, P. Cook, and V.J. Buckle

Three patients with myelodysplastic syndromes are reported. In each case, cytogenetic studies showed the presence of a new translocation, t(1;3) (p36;q21).

SEVERAL SPECIFIC chromosomal translocations are now known to be associated with hematologic malignant or premalignant conditions. These include the 9;22 translocation, producing the Philadelphia chromosome, in chronic myeloid leukemia, the 8;21 translocation in acute myeloblastic leukemia, and the 15;17 translocation in acute promyelocytic leukemia. We report three patients with myelodysplastic disorders characterized by a specific chromosomal translocation, t(1;3) (p36;q21), which has not previously been described.

CASE REPORTS

Patient 1

A 37-year old man presented in February 1980 with general malaise and progressive dyspnea following a “flu-like” illness 4 weeks previously. On examination he was extremely pale, but no other abnormalities were found. A full blood count showed a hemoglobin of 4.8 g/dL, a mean cell volume of 112 fL, a white cell count of 5.0 x 10^9/L (neutrophils 38%, lymphocytes 32%, monocytes 30%) and a platelet count of 567 x 10^9/L. Serum lysozyme was 2.6 μg/mL (normal range: 2.5–7.5 μg/mL) and urinary lysozyme was nil. Bone marrow aspiration yielded a sample of slightly increased cellularity. Erythroid precursors were virtually absent. Myelopoiesis was depressed, but megakaryocytes were well represented. Abnormal mononuclear cells were present (60%), which showed positive staining for nonspecific esterase. There was no response to trials of prednisolone and methandienone therapy; no cytotoxic chemotherapy was given. The patient has been transfusion-dependent and has suffered from mild mucocutaneous infective episodes but is otherwise well. Follow-up marrow aspirates have shown some increase in the number of monocytoid blast cells. By April 1983, he had received a total of 142 units of blood and, in view of his stable clinical course, iron chelation therapy with subcutaneous desferrioxamine was started. In August 1983, however, he developed a progressive increase in peripheral blood blast cells and an acute transformation was diagnosed.

Patient 2

A 40-year old Brazilian woman was referred for investigation of anemia in February 1983. In Brazil in 1977 she had a macrocytic anemia that had failed to respond to vitamin B₁₂ and folic acid therapy. She had been given occasional blood transfusions (the last transfusion being in December 1982). Apart from vitamin B₁₂ and folic acid, she was on no drug therapy, and there was no history of excessive alcohol intake. Her only complaint was of dyspnea on exertion, and there were no abnormalities on clinical examination. A full blood count showed a hemoglobin of 7.6 g/dL, a mean cell volume of 110 fL, a white cell count of 4.2 x 10^9/L and a platelet count of 262 x 10^9/L. A reticulocyte count was 3.1%. Bone marrow aspiration showed a hypercellular marrow with marked erythroid hyperplasia and dyserythropoiesis. An iron stain showed increased iron in the fragments, and an occasional ring sideroblast (2%) was seen. Megakaryocytes were present in normal numbers. There was no excess of blast cells. In view of the stable clinical course, cytotoxic therapy was not felt to be indicated and the patient returned to Brazil with a recommendation to be managed with blood transfusions as required.

Patient 3

A 14-year old girl presented in July 1981 with a history of malaise, weakness, and amenorrhea for several months and abdominal pain over the preceding week. On examination, she was pale and febrile (38.4°C). There was no lymphadenopathy, but hepatomegaly (4 cm) and splenomegaly (7 cm) were noted. A full blood count showed a hemoglobin of 7.5 g/dL, a mean cell volume of 93 fL, a nucleated cell count of 69 x 10^9/L (neutrophils 7%, lymphocytes 12%, monocytes 57%, metamyelocytes 2%, normoblasts 22%) and a platelet count of 21 x 10^10/L. Serum lysozyme was 36.8 μg/mL (normal range: 2.5–7.5 μg/mL) and urinary lysozyme was nil. Bone marrow aspiration yielded a hypercellular marrow with erythroid hyperplasia and dyserythropoiesis. An iron stain showed the presence of abnormal sideroblasts, though no ringed sideroblasts were seen. Myelopoiesis was decreased and there was an infiltration with monocytoid cells (32%) and blast cells (14%). Treatment was instituted with courses of daunorubicin, cytosine arabinoside, and thioguanine (DAT). Remission was achieved in November 1981, but, despite maintenance chemotherapy, blood and bone marrow relapse occurred in May 1982. Re-induction with DAT was unsuccessful, but a second remission was achieved following a bone marrow transplant from a histocompatible brother at the Royal Marsden Hospital. A second relapse occurred in May 1983. A third remission was obtained and the patient was given a second bone marrow transplant in August 1983. However, further relapse occurred and she died in January 1984.

From the Department of Haematology, John Radcliffe Hospital, Oxford, the Department of Medical Genetics, Churchill Hospital, Oxford, and the Department of Haematology and the Department of Cytogenetics, City Hospital, Nottingham, United Kingdom. Submitted March 5, 1984; accepted March 31, 1984.

Address reprint requests to Dr D.J. Moir, Department of Haematology, Milton Keynes Hospital, Eaglestone, Milton Keynes, Bucks., United Kingdom.

© 1984 by Grune & Stratton, Inc.

0006-4971/84/6401-0032$03.00/0
CYTOGENETIC STUDIES

Bone marrow cells were obtained from posterior iliac crest aspirates. Chromosome preparations were made by standard techniques from both direct preparation and methotrexate synchronized cultures. G-banding was carried out by a trypsin-Leishmann technique.

Case 1

Bone marrow preparations on the dates given produced the following results: (Feb 18, 1980): ten cells 46,XY, t(1;3); (Oct 27, 1980): 20 cells 46,XY, t(1;3) (p36;q21); (May 21, 1981): five cells 46,XY, t(1;3) (p36;p21); (April 7, 1982): ten cells 46,XY, t(1;3) (p36;q21); (March 17, 1983): ten cells 46,XY, t(1;3) (p36;q21).

Analysis of PHA-stimulated blood lymphocytes from peripheral blood on May 5, 1981 showed a normal constitutional karyotype.

Case 2

Bone marrow analysis on Feb 1, 1983, showed 34 cells 46,XX, t(1;3) (p36;q21) and one cell 44,XX, -8, -11 (chromosomes 1 and 3 normal).

Case 3

Bone marrow analysis on July 13, 1981, showed ten cells 46,XX, t(1;3) (p36;q21).

Peripheral blood analysis on the same date showed (unstimulated) ten cells 46,XX, t(1;3) (p36;q21).

Figure 1 shows partial karyotypes from each of the three cases.

DISCUSSION

The features of the myelodysplastic disorders include refractory cytopenias, macrocytosis, monocytosis, and a cellular marrow with evidence of dyspoiesis, often involving all three major cell lines. Blast cells may or may not be increased. Recently, the FAB cooperative group have made proposals for the classification of this heterogenous group of diseases. The first two cases reported here clearly have some form of myelodysplastic disorder. Patient 1, however, is not easy to classify, with features both of refractory anemia with excess of blasts (RAEB-type 3, FAB) and chronic myelomonocytic anemia (CMML-type 4, FAB). Patient 2 falls into the refractory anemia category (RA—type 1, FAB), with a small percentage of blast cells.

Fig 1. Partial karyotypes, from each of the three cases, illustrating the translocation t(1;3) (p36;q21). The karyotype from case 1 was photographed from the marrow taken on May 21, 1981.
ringed sideroblasts in the marrow. Both of these patients are relatively young and both have had a relatively stable clinical course. The diagnosis for patient 3 is more difficult; in this case, the clinical presentation was more acute and a diagnosis of acute myelomonocytic leukemia (AMML) is probable. Nevertheless, myelodysplastic features, including marked monocytosis and appreciable erythroid hyperplasia with dyserythropoiesis were present, and this case may represent a transformed myelodysplastic disorder. The incidence of a myelodysplastic phase preceding AMML in childhood is not uncommon and may be as high as 17%.

Our three patients were all shown to have, as the sole cytogenetic abnormality, a translocation between chromosomes 1 and 3. Abnormalities of chromosomes 1 and 3, including monosomy, trisomy, and various deletions and translocations, have been described in lymphoproliferative and myeloproliferative disorders and other human cancers. However, translocations between chromosomes 1 and 3 have rarely been reported. A review of the literature has shown that such translocations have been described in acute non-lymphocytic leukemia, in myeloma, and in acute myeloblastosis. These translocations had various breakpoints and in three cases, additional abnormalities were present. The cases described in this article are the first to be reported with breakpoints 1p36 and 3q21. The breakpoints appear to be identical in all three cases (Fig 1); this is therefore a new specific translocation.

The significance of specific translocations in the pathogenesis of neoplasia has recently been discussed. In some cases, it appears that the translocation, and possible subsequent activation, of an oncogene is important. This has been well demonstrated in Burkitt’s lymphoma, where the oncogene, c-myc, has been shown to be translocated from its normal position on chromosome 8 to a site within the immunoglobulin-coding region on chromosome 14. There is now some evidence to suggest that the activation of two oncogenes (transforming and immortalizing) may be necessary for complete tumor development. This may be of relevance when considering the chromosomal abnormalities in preleukemic states. It is possible that alternative combinations of activation may account for differences in clinical presentation. Recently, a new oncogene, c-N-ras, has been assigned to chromosome 1, and an oncogene, c-raf, is known to be localized to chromosome 3. The exact subregional localization of these oncogenes has not yet been established, and it would be of considerable interest to know whether either of them is involved in the 1;3 translocation described here.

ACKNOWLEDGMENT

We thank Professor Sylvia Lawler for the initial cytogenetic studies on Patient 1, done at the Royal Marsden Hospital (Feb 18, 1980). We also thank Dr P. Emerson and Professor D. J. Weatherall for allowing us to report details of patients under their care.

REFERENCES

A new translocation, t(1;3) (p36;q21), in myelodysplastic disorders

DJ Moir, PA Jones, J Pearson, JR Duncan, P Cook and VJ Buckle