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Removal of Abnormal Clone of Leukaemic Cells by Splenectomy

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Summary

A patient with chronic myelocytic leukaemia positive for the Philadelphia (Ph[1]) chromosome underwent splenectomy in the "terminal phase" of his disease. Chromosomal analysis of a marrow aspirate obtained during the operation showed nothing abnormal. Material from the spleen, however, showed the absence of a C chromosome and the presence of a "marker" chromosome in all metaphases examined. The patient did well for almost three years after splenectomy, and serial cytogenetic studies of marrow specimens showed the Ph[1] chromosome to be the only significant abnormality. Six months before death from recurrent blastic transformation aneuploidy was found in a marrow specimen. Subsequently additional abnormalities, including cells with two Ph[1] chromosomes, were detected. The karyotypic abnormalities found in the splenic specimen, however, never recurred.

Introduction

Chronic myelocytic leukaemia (C.M.L.) is usually characterized by the Philadelphia (Ph[1]) chromosome in cells of myeloid origin. With rare exceptions[1] this is a constant feature, being found in overt disease, during excellent clinical and haematological remissions, and in the terminal stages. Ph[1]-positive cells may become established in the spleen[2 3] and other extramedullary sites.[4]

In some patients the Ph[1] chromosome is the only karyotypic abnormality detectable throughout the course of the disease. Additional cytogenic abnormalities, however, may appear as the patient enters the terminal stage. These include changes in the number of chromosomes, the appearance of "marker" chromosomes, and the presence of cells containing two Ph[1] chromosomes.[5 6] Occasionally such aberrations appear before any clinical or haematological deterioration is apparent; if so, they are of serious prognostic import. There is an increasing body of evidence that haematological deterioration and death in C.M.L. results from the proliferation of one or more increasingly abnormal clones of leukaemic cells, and that the karyotypic abnormalities seen in the terminal phase constitute overt evidence of this process.

We report the case of a patient who underwent splenectomy in the "terminal phase" of C.M.L. and whose subsequent course suggested that this procedure eliminated the abnormal clone of cells responsible for his deteriorating haematological condition.

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Case Report

A 32-year-old black steel worker was diagnosed in March 1968 as a case of C.M.L. after bleeding profusely following a tooth extraction. His W.B.C. was 247 × 10^9/l (65% neutrophils, 2% lymphocytes, 1% eosinophils, 2% basophils, 12% myelocytes, 17% promyelocytes, 1% myeloblasts); platelets were 110 × 10^9/l; and haemoglobin was 11 g/dl. His spleen extended 17 cm below the costal margin and he had subcutaneous nodules 2 cm in diameter in both thighs. Appearances on bone marrow and splenic biopsy were consistent with the diagnosis; no fibrosis was seen in the biopsy specimen. Aspiration of the subcutaneous nodules yielded myelocytes and normoblasts. Leukocyte alkaline phosphatase score was zero. Chromosomal analysis of bone marrow cells revealed the Ph[1] chromosome but no other abnormalities.

The patient was included in a comparative study of mitobronitol and busulphan. His initial treatment was with mitobronitol, which decreased the W.B.C. and spleen size but caused pronounced thrombocytopenia requiring transfusions. He was then treated with busulphan from July to November 1968. This induced a good remission except for the development of recurrent thrombocytopenia. The haemoglobin and W.B.C. became normal and the spleen impalpable. Subsequently he received maintenance therapy with mitobronitol. His course was complicated by thrombocytopenia, which required frequent discontinuance of the drug or reduction of the dose, producing wide fluctuations in the W.B.C. Nevertheless, the haemoglobin remained normal, the spleen was not felt, and differential counts showed no blasts or promyelocytes.

In February 1970 recurrent splenomegaly was noted and mitobronitol was abandoned. Treatment with cytarabine, carmustine, busulphan, and cyclophosphamide failed to re-establish stable control; modest numbers of blasts and promyelocytes appeared in the peripheral blood, the haemoglobin fell to 11-12 g/dl, and the spleen increased in size. Blasts in a marrow aspirate, however,

remained below 5%. On 24 September the spleen extended 21 cm below the costal margin, the W.B.C. was 129 × 10^9/l (2% blasts, 3% promyelocytes), and the platelets were 32 × 10^9/l. A bone marrow aspirate was reported as showing "early myeloblastic transformation" (blasts 15·4%, promyelocytes 21·6%) and the patient was referred to us. He was given loading doses of hydroxyurea (0·05 g/kg) to control the rising W.B.C., and on 29 September splenectomy was performed. The spleen (which had decreased in size with hydroxyurea) weighed 1800 g and contained many immature myeloid cells and a few normoblasts but no megakaryocytes. The postoperative course was uneventful and the platelet count rose to over 200 × 10^9/l.

The patient was then treated with a demecolcine-mercaptopurine combination[7] and entered an immunotherapy programme for C.M.L.[8] An excellent remission was achieved and he remained in a good haematological and clinical condition for almost three years in a programme of "rotating" maintenance chemotherapy with two-drug combinations. In June 1973 routine bone marrow aspiration showed aneuploidy but an otherwise normal marrow. Five weeks later immature cells were detected in the peripheral blood and bone marrow aspiration showed 17·6% myeloblasts. His haematological and clinical condition deteriorated rapidly, with anaemia, thrombocytopenia, fever, subcutaneous nodules, and bone pain. He responded poorly to various antileukaemic agents and died on 12 December. Necropsy showed pseudomonal bronchopneumonia and extensive leukaemic infiltration of viscera and lymph nodes.

CHROMOSOMAL STUDIES

Chromosomal studies (direct method) of marrow were performed on nine occasions. In conjunction with splenectomy (29 September 1970) chromosomal analyses were performed on both a bone marrow aspirate (obtained at operation) and material from the spleen. The table gives the findings of cytological and chromosomal examinations of the marrow and spleen during the illness. Before splenectomy marrow aspirates usually showed florid leukaemia. This was presumably because thrombocytopenia prevented the use of enough chemotherapy to achieve better control of the disease. Nevertheless, the percentage of myeloblasts was normal until 24 September 1970. Chromosomal studies showed no abnormalities other than the presence of a single Ph¹ chromosome.

On 29 September the bone marrow showed unequivocal improvement after chemotherapy with an agent not previously used. Chromosomal analysis of the marrow aspirate showed no appreciable change from previous studies (fig. 1). The splenic karyotype, however, was grossly abnormal. All 22 mitoses examined contained a submetacentric marker chromosome replacing a chromosome of group C (6-12). In addition some mitoses contained an abnormality of the second G-22 chromosome, which appeared as a smudge (fig. 2).

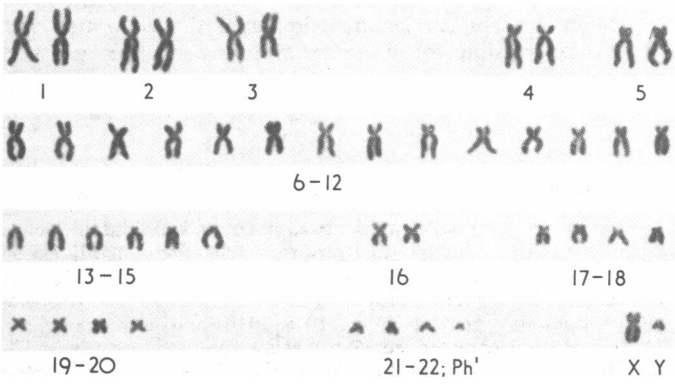

FIG. 1—Typical karyotype from bone marrow aspirate obtained at splenectomy.

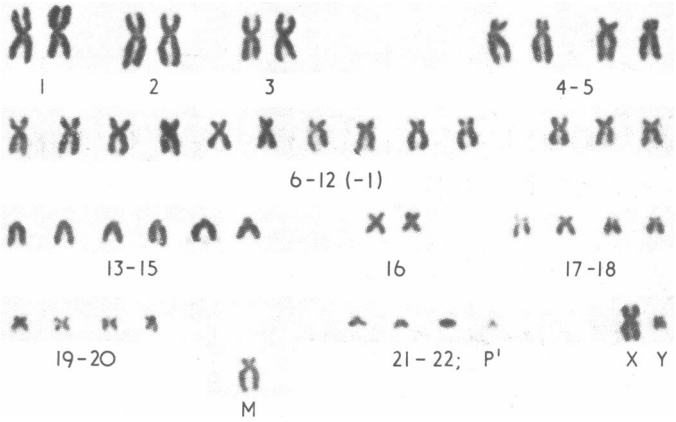

FIG. 2—Karyotype from spleen showing missing C-group chromosome marker chromosome (M), and "smudged" G-22 chromosome.

These karyotypic abnormalities were never seen again. On 29 June 1973, when haematological values were consistent with complete remission, aneuploidy was observed in all metaphases. On 6 August nine out of 11 cells examined contained 51 chromosomes including two Ph¹ chromosomes.

Discussion

These findings are consistent with the hypothesis that (*a*) a grossly abnormal clone of leukaemic cells originated and was proliferating in the spleen, while less abnormal cells were multiplying in the marrow; (*b*) the abnormal clone was eliminated by splenectomy; and (*c*) combination chemotherapy and immunotherapy resulted in a prolonged remission once the more malignant clone of cells had been removed.

Unfortunately karyotypic analysis was not carried out in conjunction with marrow aspiration on 24 September 1970, when a sharp increase in the percentage of myeloblasts was recorded.

Marrow Cytology and Chromosomal Analyses

Date	Cellularity	Myeloblasts (%)	Promyelocytes (%)	No. of Mitoses with and without PR¹*				
				No. of Chromosomes:				
				44-	45	46	47	51
11/3/68	4 +	3·2	19·6			27+,3−		
14/11/68	2 +	4·2	6·0					
13/11/69	4 +	0·8	3·2			8 +,2−		
11/2/70	4 +	2·0	9·4					
7/7/70	4 +	4·6	15·0					
24/9/70	4 +	15/4	21/6					
29/9/70	2 +	3·0	15·4	3 +	2 +	14 +	1 +	
						(No other abnormalities)		
29/9/70 (spleen) ..				2 +	2 +	18 +		
						(Missing C and marker chromosome in all mitoses)		
5/10/70					3 +, 1−	21 +		
27/10/70	3 +	5·4	34·4		4 +	21 +		
6/11/70		7·4	17·2		1 +	6 +		
18/2/72	2 +	2·0	10·2		1 +	26 +		
29/6/73	1 +	1·4	5·4	1 +			10 +,2−	
6/8/73	2 +	17·6	19·6			2 +		9 + +
8/11/73	1 +	31·0	28·2					

* + = Single Ph¹. + + = Double Ph¹. − = No Ph¹ seen.

Possibly these may have been of splenic origin, containing the abnormal karyotype, and were eliminated by the brief but effective course of hydroxyurea before splenectomy. If so, one would assume that the marrow had not then been colonized by the abnormal clone. It appears highly unlikely that so short a course of hydroxyurea would have had a permanent effect on an established population of cells in marrow while leaving the splenic clone easily demonstrable. Large numbers of neoplastic cells may enter the marrow from other sites without establishing a proliferating population there. We have seen four patients with disseminated lymphoproliferative disease[9] and one with "blastic" myeloid metaplasia of the spleen (unpublished data) in whom marrow remission followed local radiation therapy or splenectomy.

Aggressive treatment of myeloblastic transformation may temporarily eliminate clones of leukaemic cells with karyotypic abnormalities,[10] but such remissions are usually short-lived and the abnormal karyotype often recurs within weeks.[11] In our patient, in contrast, the abnormal clone of cells shown in the spleen disappeared permanently after splenectomy. Karyotypic abnormalities were again found during the last six months of life, but these were different from those seen originally. Nevertheless, cytogenetic examination on 29 June 1973, when the patient appeared to be in complete remission of leukaemia, predicted the rapid haematological and clinical deterioration that was observed a few weeks later.

Attempts to reverse the terminal episode of myeloblastic transformation were unsuccessful. This is consistent with our experience that Ph[1]-positive patients who develop additional karyotypic abnormalities are much more refractory to treatment of the blastic state than patients who retain the original chromosomal pattern.

We have carried out simultaneous karyotypic analysis of spleen and marrow aspirates from five other patients undergoing splenectomy during the accelerated or blastic phase of the disease but have not identified other instances of such cytogenetic discordance. From our experience, which includes 30 patients subjected to splenectomy during the "terminal phase" of C.M.L., such gratifying responses are unusual. The present case, however, is probably not unique. Our series includes two other patients whose disease reverted to an easily controlled chronic state and who survived more than three years after splenectomy. Unfortunately, both were treated before we initiated chromosomal studies of splenic cells.

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SHORT REPORTS

Q Fever Presenting with Paroxysmal Ventricular Tachycardia

A description of myocarditis complicating Q fever[1] prompts us to report a patient who presented with recurrent ventricular tachycardia and was found to have Q fever.

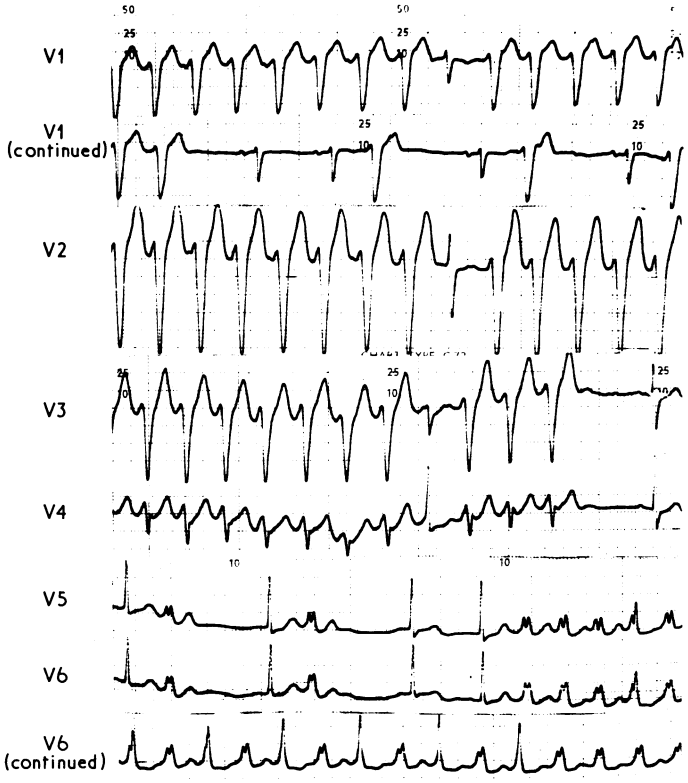
Case History

A 51-year-old insurance company manager, who occasionally visited farms, became febrile and had several rigors 10 days before admission. Two days after these, after some dizziness, he briefly lost consciousness. Over the next few days he began to feel better but the day before admission had two similar syncopal attacks. He looked pale and unwell and his pulse was 52 and irregular. The only other abnormality was a localized area of coarse crepitations at the left lung base. Blood pressure was 140/70. There was no evidence of congestive cardiac failure or endocarditis. E.C.G.s (see figure) showed frequent premature ventricular ectopic beats, paroxysmal ventricular tachycardia, and ST-T wave changes; haemoglobin was 13·1 g/dl; W.B.C. $7{\cdot}6\times10^9$/l, with normal differential count; E.S.R. 70 mm/hr; S.G.O.T. 34 units; blood cultures sterile. Chest *x*-ray film showed a small area of consolidation in the left lower zone, which cleared later. Phase II *Coxiella burnetti* titres were: <8, 1024, 2048 on days 1, 21, and 33, respectively.

A provisional diagnosis of viral myocarditis was made. The arrhythmia was difficult to control; it was treated initially with lignocaine and later with several combinations of other anti-arrhythmic drugs, including phenytoin, procainamide, and practolol, but was not fully controlled until 10 days later. He also had tetracycline for two weeks. The syncopal attacks were attributed to ventricular tachycardia and did not recur after admission. For several months he complained of palpitations after exertion but on follow-up at six months was completely well.

Discussion

Though ventricular ectopic beats may occur with any febrile illness, the nature, duration, and severity of this arrhythmia and the associated



E.C.G. showing premature ventricular ectopic beats, paroxysmal ventricular tachycardia, and ST-T wave changes.