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Splenectomy in Chronic Myeloid Leukaemia
A Case Report and Review

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SUMMARY

We report the case of a man with chronic myeloid leukaemia, whose disease had undergone transformation and whose life was threatened. Splenectomy was performed, and two years later he is alive and well, taking no anti-leukaemic therapy. Since splenectomy he has had one severe attack of malaria, and one episode of jaundice thought to be due to viral hepatitis. He discontinued his malaria prophylaxis one year ago and has not been ill since.

Splenectomy as a last resort will benefit some patients with chronic myeloid leukaemia after transformation, and elective splenectomy should be considered in the management of patients with this disease. However, final unequivocal proof of the value of elective splenectomy is still awaited.

INTRODUCTION

Chronic myeloid leukaemia is a disease characterised by a greatly elevated total white blood count, the majority of which are mature granulocytes. In the chronic form of the disease the total of blasts and promyelocytes in the peripheral blood is less than 30%. The bone marrow shows increased myelopoeisis. Clinically the most striking feature of chronic myeloid leukaemia is splenomegaly.

Before any treatment was available the median survival was 19 months (Minot 1924). Splenic

irradiation increased this figure to 28 months, and the advent of busulphan therapy to 39.5 months (MRC 1968). Busulphan is still the most useful drug, and can be started in a dose of 4 mg./day. When the wbc has fallen to 10 -20,000, busulphan may either be stopped, and restarted if the wbc climbs over 30,000 (Wintrobe 1974) or may be given continuously to keep the wbc at 7-12,000 (Spiers 1974 a). This usually requires 0.5-4 mg./day. Initially when leukamic tissue is being destroyed rapidly there is increased uric acid production, and allopurinol may be given to reduce the risk of uric acid nephropathy. Other side effects of busulphan include marrow toxicity with thrombocy topenia, gynaecomastia, and pulmonary fibrosis. Almost all patients respond to busulphan with a reduction in wbc, decrease in spleen size and symptomatic improvement. The disease then enters into a controlled phase, which lasts on average 36 months. Then the disease undergoes "transformation" (Baikie 1966, 1969). Usually more primitive blast cells accumulate in the bone marrow and peripheral blood and the spleen increases in size again, causing pain and associated with splenic infarct, haematoma, abscess or rupture. (Canellos 1971, 1975). This blastic transformation of CML is resistant to busulphan therapy and untreated is usually rapidly fatal – half the patients are dead within one month of its onset (Karanas and Silver 1968). Response to single drug treatment is rare, and combinations of drugs are usually employed (Hayes and Ellison 1969; Foley 1969). 20 - 30% of patients treated with vincristine and prednisolone achieved complete remission (Canellos 1971; Marmont and Damasio 1973). More recently a seven-drug combination was described which gave good remission in 4 cases out of 9 with a median survival of more than 9 months from the onset of blast crisis (Speirs 1974 b).

On the other hand transformation of the disease may take the form of hypersplenism (Karanas and Silver 1968) with pancytopenia and death usually occurs from bleeding episodes related to the thrombocytopenia (Baikie 1966). In this type of patient transfusion of blood and platelets offers palliation but no drug therapy is effective.

CASE HISTORY

A.T., male, b. 1952, of Chadiza district, Eastern Province. Chewa tribe.

He presented at another hospital in November 1972 with epistaxis. Pallor and splenomegaly were noted. Hb was 7.0 G/dl, wbc 201,600/cu mm and platelets 52,000/cu mm. On the peripheral blood film acute lymphoblastic leukaemia was diagnosed and he was given prednisolone and cyclophosphamide and 3 pints of blood. One month later his wbc was still 198,000 and he was referred to UTH in Lusaka. Examination revealed palatal petechiae and the spleen reached the umbilicus. The Hb was 13.9 G/dl, platelets 60,000 and wbc 110,200 with differential; neutrophil polymorphs 64%, myelocytes 27%, eosinophils 1%, monocytes 4% and lymphocytes 4%. The bone marrow report confirmed the diagnosis of chronic myeloid leukaemia and treatment was started with busulphan. During 6 weeks as an in-patient at UTH, his platelet count rose to 88,000 and his wbc fell to 52,000. He was discharged in February 1973 taking busulphan 4 mg/day and on review at the end of March 1973 his wbc was 14,000, platelets 61,000 and busulphan was discontinued.

He remained on no medication for 1 year and then reported to St Francis' Hospital on 7.3.74 when his spleen was noted to extend into the pelvis. His Hb was 10.8 G/dl, platelets 190,000 and wbc 59,200. Busulphan was re-started, and his wbc initially rose to 150,000 and then fell to 126,000 and he was discharged on busulphan on 25.3.74. His haematological indices as an out-patient are summarised in table I. On 24.4.75 his wbc has fallen to 1,200 whilst the Hb and platelets remained normal, and busulphan was stopped.

He was then admitted to another hospital on 24.5.75 with epistaxis, bleeding from the gums and anaemia. He was given 5 pints of blood over the next two weeks but his Hb remained 3.7 G/dl and he was referred to St Francis' Hospital on 10.6.75. On admission there was nose and gum bleeding and retinal haemorrhages. The initial Hb was 2.1 G/dl and the full indices are summarised in table II. During the course of this admission he required frequent transfusions, but his Hb and platelet counts stayed low. He developed cardiac failure and the rash of pellagra and his spleen increased in size. The Coombs' test was negative, and steroids had no effect on the thrombocytopenia, so it was decided to perform splenectomy for hypersplenism. The operation was performed by one of us (J.M.C.) on 16.7.75. Moderate oozing occurred from the splenic bed, but no special difficulty was encountered. Operative blood loss was 800 ml, and 3 pints of fresh blood were given during surgery. The spleen measured 30 x 15 x 15 cm. There were no post-operative complications – in particular no thrombocytosis, and steroids were tapered off. At discharge two weeks post-operatively he felt well, and was not in cardiac failure. He had no bleeding tendency and his transfusion requirements were markedly reduced. The course of this admission is summarised in table II.

Since discharge in August 1975 he has had three further admissions. At the end of August 1975 he had an attack of malaria with haemolysis and temporary slight jaundice. His Hb fell to 6.8 G/dl and he was given 4 pints of blood which brought the Hb up to 9.0 G/dl. His wbc then was 15,100 and platelet count 100,000. He was started on proguanil.

On 20.9.75 his Hb had again fallen to 6.6 G/dl and he was given 4 more pints of blood. His Hb rose to 12.1 G/dl on that occasion.

In November 1975 he was admitted with jaundice, deranged liver function tests, nose bleeding and an enlarged tender liver. The course of the disease was like that of viral hepatitis, and since he had received 29 pints of blood in the previous 22 weeks it was thought that virus B hepatitis was likely. His haematologic values from August 1975 up to the present time are summarised in table III.

For 17 months now he has remained fully fit, taking no medicine, and has completed his course at teacher training college.

DISCUSSION

The first splenectomy for leukaemia was

recorded in 1866 (Bryant 1866), but for 100 years the procedure was attended by such a high morbidity and mortality, especially when performed late in the disease after transformation had occurred (Bednarek 1976), that it was looked upon as a desperate measure (Fisher 1952; Holt 1966). Recently, however, the operative morbidity and mortality have been lowered (Stryckmans 1974) and various authorities have recommended splenectomy for troublesome symptoms related to splenomegaly (Strumia 1966; Mittelman 1970) or for hypersplenism with refractory cytopenias (Meeker 1967, Canellos 1972). A recent report published in 1976 (Gomez 1976) describes 60 cases of splenectomy in CML, most of whom were already in transformation, with varying degrees of hypersplenism in some and frank

TABLE I

Date	24.	4.	15.	29.	11.	25.	13.	10.	15.	20.	26.	6.	4.	24.
	11.	1.	1.	3.	3.	3.	4.	5.	6.	8.	10.	1.	3.	4.
	72	73	73	73	74	74	74	74	74	74	74	75	75	75
Hb G/dl	7.0	13.9	13.5	15.7	11.1	11.2	13.6	13.9	11.4	9.5	12.1	12.4	13.4	10.7
Platelets, x 1,000	52.8	60	93	61	210	150								250
WBC x 1,000	201	110.2	65.6	14.7	147	126.7	36.6	14.8	9.5	5.2	23.5	16.5	8.7	1.2
DEFFERENTIAL %														
Neutrophil Polymorphs	64	56	57	30										
Myelocytes		27	25	3	30									
Metamyelocytes			2	2	20									
Promyelocytes					8									
Blasts			1		6									
Lymphocytes		4	6	36	2									
Eosinophils, Monocytes, Basophils		5	10	2	4									
Blood (pints)	3													
Busulphan Mg/day		6	4	0	3	6	6	6	6	4	4	2	2	0
Notes		UTH	UTH		SFH	SFH								
		LUSAKA			KATETE									

TABLE II

Date	10.	20.	29.	3.	10.	14.	16.	17.	24.	31.	2.
	6.	6.	6.	7.	7.	7.	7.	7.	7.	7.	8.
	75	75	75	75	75	75	75	75	75	75	75
Hb G/dl	2.1	3.7	7.7	6.8	6.3	11.2		12.3	7.9	8.2	9.3
Platelets, x 1,000	12.5		60	70	60	60		80	80	140	
WBC x 1,000	3.6			1.7	1.6	1.6		9.2	10.8	2.8	
DIFFERENTIAL %											
Neutrophil Polymorphs	72	64								70	
Myelocytes	4	25								18	
Metamyelocytes	8	8								5	
Promyelocytes		3								3	
Blasts	2									1	
Lymphocytes	2										
Eosinophils, Monocytes, Basophils	12								3		
Blood (pints)	2	2	4	2	2	4	3				2
Notes		1.		2.			3.				4.

Notes: 1. Digoxin for cardiac failure 2. Steroids started 3. Splenectomy 4. Discharge from hospital

TABLE III

Date	18. 8. 75	28. 8. 75	20. 9. 75	17. 11. 75	4. 12. 75	3. 1. 76	14. 2. 76	23. 4. 77
Hb G/dl	9.9	6.8	6.6	12.4	10.1	12.1	14.4	14.8
Platelets, x 1,000	120	100	80	140	250	200		100
WBC x 1,000	3.6	15.1	4.5	4.2	8.1	7.1	7.2	5.8
Differential %								
Neutrophil Polymorphs	74	40	44	48				79
Myelocytes	14	30	28	15				3
Metamyelocytes	10	18	6	24				
Promyelocytes		4	10	6				
Blasts		1	3					
Lymphocytes	2		2	2				15
Eosinophils								
Monocytes		7	7	5				3
Basophils								
Blood (pints)		4	4					
Notes		1.	2.	3.				4.

Notes: 1. Malaria
2. Admitted for transfusion
3. Hepatitis
4. Fully fit

blastic disease in others. Of the 56 patients who were dead at the time of the report the median survial time after operation was only 6 months, and only 10 survived 1 year. However, one patient lived for 9 years after the operation and the authors conclude: "In half the patients short term haematologic and clinical improvement is obtained . . . . In a small but measurable minority substantial and prolonged benefit is achieved". The patient reported here comes into this category.

Thus, whilst it is accepted that busulphan improves the quality of life during the controlled phase of chronic myeloid leukaemia, it does not greatly postpone the onset of transformation. Furthermore, there is no simple standard treatment which is effective once transformation has occurred; and the overall survival time from diagnosis has not been greatly prolonged. Current research is therefore being directed towards finding methods of delaying the onset of transformation of the disease, and these will be reviewed briefly here.

1. Drugs

Some cases are unusually sensitive to busulphan and develop marrow aplasia at a dose that would be quite safe for most patients. The mortality of these cases is high, but some survivors have had remissions lasting several years after the episode (Stryckmans 1974). This has led several authors to question whether marrow aplasia should be deliberately induced to secure longer remissions (Galton 1969; Perreau 1969). It has also been suggested that the drugs useful for treating blast crises might be employed prophylactically in the controlled phase of the disease, and two, four and seven drug combinations are under investigation (Spiers 1974 a).

2. Immunotherapy

The aim of immunotherapy is to enhance the patient's immunological reaction to his own leukaemic cell antigens, either specifically by vaccination with these antigens or non-specifically using BCG. In one series, 15 patients with well-controlled CML were vaccinated with BCG and living cultured myeloblasts. These patients had considerable prolongation of survival and delay of transformation when compared to retrospectively matched controls (Sokal 1973). This finding, however, was not confirmed in another group of 14 patients (Ramachandar 1975).

3. Extra-corporeal irradiation of the blood (ECIB)

In this technique blood is withdrawn from the patient and irradiated to kill the less mature leucocyte precursors. The leucocyte count falls transiently (Schiffer 1966) and cytokinetic studies indicate that bone marrow activity may actually be speeded up by this process (Chan 1966; Ernst 1971).

4. Leucapharesis

Blood withdrawn from the patient is centrifuged to remove leucocytes and then re-transfused. The procedure is difficult to perform technically and only yields a slight transient fall in wbc, which takes only 2 - 3 days to recover to former levels (Buckner 1969). Leucapharesis alone does not give satisfactory control of the disease (Hadlock 1975).

5. Splenectomy

There are several theoretical reasons why splenectomy early in the disease might be of benefit. Splenectomy would reduce the total mass of leukaemic tissue, and would correct any hypersplenism and splenic red cell pooling. Cytogenetic differences have been described between splenic leucocytes and those in the bone marrow (Spiers and Baikie 1968; Mittelman 1974). Splenic cells have the Philadelphia chromasome and may have other chromasomal abnormalities as well (Zaccaria 1975). Leucocytes from the spleen may have greater proliferative activity than bone marrow cells (Gabraith 1969; Brandt 1969 a, b), and if these more anaplastic clones can be removed, the management of the disease might be easier. Furthermore, splenic problems late in the disease are common, and splenectomy then is acknowledged to be hazardous, but will benefit a proportion

of patients. However, several patients who had undergone splenectomy early in the disease for a variety of indications have had haematological remissions without chemotherapy, (Cutting 1967), or unusually long survivals (Dubios-Ferriere and Radler 1967; Meeker 1967). These considerations prompted two trials of elective splenectomy during the controlled phase of the disease. The first report (Spiers 1975) on 26 patients suggests that the onset of transformation of the disease was significantly delayed by the procedure, and after transformation these patients were symptomatically less troubled, and required fewer transfusions of blood and platelets than non-splenectomised patients. Further, the response to intensive anti-leukaemic chemotherapy after transformation seemed to be better. The median survival time from operation for this group of patients had not been reached at the time of reporting, but two patients were still alive nearly 8 years after operation, with well-controlled disease.

A second report (Ihde 1976) on 32 patients observed generally for longer, showed that elective splenectomy prolonged the median survival from diagnosis to 60 months. Interestingly, if the operation was performed within one year of diagnosis, this effect was not observed. In neither series were there any post-operative deaths, and only one major complication was encountered. In this second series the response to two-drug combination chemotherapy after transformation was no better than in non-splenectomised patients, although transfusion requirements were less and splenic symptoms absent. Therefore, elective splenectomy performed more than one year after diagnosis, in the well-controlled phase of the disease significantly delayed the onset of transformation of the disease. However, a group which had been well-controlled for one year before operation might be expected to have a longer survival from diagnosis than the medial anyway. Therefore neither group of authors claim to have proven conclusively that elective splenectomy significantly delays the onset of transformation, although this is strongly suggested by the results in both series. A controlled trial is in progress to settle the question.

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