Acute myelofibrosis and acute myeloblastic leukaemia

Idiopathic myelofibrosis is a myeloproliferative disorder with characteristic clinical, haematological and pathological findings, which include a chronic course, prominent splenomegaly, normocytic normochromic anaemia, many teardrop cells, reticulocytosis, thrombocytosis, a few immature erythroid and myeloid elements in the blood, and myelofibrosis. While acute leukaemia seems to be associated with this disease,¹ the aetiological role of the latter, radiotherapy, and chemotherapy cannot be determined. Five cases of acute myelofibrosis, reported by Lewis and Szur,² were associated with no significant poikilocytosis, thrombocytopenia, absence of splenomegaly, 1-2% myeloblasts in peripheral blood, myelofibrosis, and poor prognosis. We report here a case of simultaneous acute myelofibrosis and acute myeloblastic leukaemia, since it raises some questions about their relation to the spectrum of myeloproliferative disorders and illustrates difficulties in their management.

Case report

A 57-year-old woman was an inpatient for a complaint of abdominal pain, polyuria, and polydipsia for two weeks. She was a pale, obese woman with no fever, lymphadenopathy, bone tenderness, or hepatosplenomegaly. Laboratory results showed blood glucose 13.53 mmol/l (246 mg/100 ml); haemoglobin concentration 9.8 g/dl; platelet count 100 000/ μ l; leucocyte count 13 800/ μ l, with 38% neutrophils, 1% bands, 47% lymphocytes, 2% metamyelocytes, 1% myelocytes, 10% myeloblasts, 1% erythroblasts, and no significant erythrocyte abnormalities. An iliac crest biopsy showed adipose and dense collagenous tissue contiguous with mature bony trabecles; the intertrabecular spaces contained compact cellular tissue composed of irregular bundles of fibroblasts, numerous megakaryocytes, and sparse erythromyelopoietic cells in varying stages of maturation, but predominantly in immature forms. The megakaryocytes were irregularly enlarged and frequently showed bizarre nuclear configuration. Staining by silver impregnation method showed abundant reticulin fibres. The touch preparation from the biopsy specimen and the scanty aspirated material contained 50% myeloblasts with Auer bodies in a few. The sugar water test was negative. Acute myelofibrosis and acute myeloblastic leukaemia was diagnosed.

She was treated with cytosine arabinoside (65 mg/m² intravenously daily); 6-mercaptopurine (15 mg/m² by mouth daily); allopurinol (100 mg by mouth thrice daily); and tolbutamide. After eight days the chemotherapy was interrupted because of severe pancytopenia. During the ensuing 12 months she received cytosine arabinoside (100 mg/m² intravenously twice a week)

and 6-mercaptopurine (100 mg/m² by mouth four days a week). The haemoglobin concentration remained between 7.5 and 10.0 g/dl; platelet counts between 100 000 and 200 000/ μ l; and leucocytes between 2400 and 10 000/ μ l, with up to 600/ μ l myeloblasts. Red cell morphology was unremarkable except for macrocytosis.

Thirteen months after diagnosis she had fever, pallor, petechiae, no lymphadenopathy or hepatosplenomegaly. The haemoglobin concentration was 9.3 g/dl, leucocytes 92 500/ μ l with 4% neutrophils, 3% bands, 3% lymphocytes, 2% promyelocytes, and 88% myeloblasts. Blood smear revealed appreciable diminution of platelets, macrocytosis, and Auer rods in some myeloblasts. Despite treatment with cytosine arabinoside, cyclophosphamide, vincristine, and prednisone she died.

Discussion

The short duration of symptoms; absence of splenomegaly; and red cell abnormalities, thrombocytopenia, and myelofibrosis are compatible with a diagnosis of acute myelofibrosis. The considerable increase of myeloblasts (50%) in the bone marrow with Auer rods was considered sufficient evidence for the diagnosis of acute myeloblastic leukaemia.³ This picture could be explained on the basis of a stem-cell abnormality resulting in proliferation of myeloblasts as well as fibroblasts in the marrow. Alternatively, as Sanerkin suggests, we were dealing with acute leukaemia and reparative myelofibrosis.⁴ Unfortunately, technical difficulties prevented us from obtaining cytogenetic studies in this case. If identical chromosomal abnormalities could be demonstrated in the myeloblasts and the fibroblasts, this would constitute a cogent argument in favour of a common abnormal stem cell.

When acute myeloblastic leukaemia supervenes in myeloproliferative disorders, it carries a very poor prognosis. In spite of suboptimal doses of chemotherapeutic agents, given because of compromised marrow reserves, our patient survived for 13 months. More information is needed to establish the natural history and optimal therapeutic strategy in such cases. This case forms additional evidence for the concept of the myeloproliferative disorders.⁵

¹ Modan, B, *Clinics in Haematology*, 1975, 4, 427.

² Lewis, S M, and Szur, L, *British Medical Journal*, 1963, 2, 472.

³ Beard, M E J, and Fairley, G H, *Seminars in Hematology*, 1974, 11, 5.

⁴ Sanerkin, N G, *Journal of Clinical Pathology*, 1964, 17, 541.

⁵ Dameshek, W, *Blood*, 1951, 6, 372.

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Cellular marrow tissue with irregular bundles of distorted fibroblasts, intermingled megakaryocytes, and sparse hematopoietic cells. (H and E, $\times 200$).

Prescribing of tranquillisers and barbiturates by general practitioners

In clinical practice with problems of addiction one becomes aware of the many people who have become dependent on psychoactive drugs. One becomes aware, too, not only of the ease with which such patients can obtain repeat prescriptions but also of the apparently lax criteria sometimes used for initially prescribing these compounds. For this reason I have conducted a study of the prescribing habits of some general practitioners.

Method and Results

A new housing-estate community in the north-east of England at some distance from a major centre was chosen for study. This estate had one pharmacy, and there were three general practices, which yielded most of the prescriptions studied. Prescribed items on prescriptions brought to this centrally-placed pharmacist were classified into those containing psychoactive compounds and "organic" compounds. (An organic prescription item is when the item is commonly used for physical disease—for example, digoxin, phenobarbitone, antacids, steroids, etc.) Analgesic preparations and cough suppressant agents were separately classified and will be the subject of another report. Each prescription item was categorised into one of two groups depending on whether it was written by the doctor or the receptionist. October 1975, January 1976, and March 1976 were the months chosen for the study and the prescription form sampling intensity was one in two, one

in ten, and one in three, respectively. In October 792 prescription forms were studied (1201 prescription items), in January 255 (413), and in March 616 (979).

In the three individual months 1663 prescriptions were examined (2593 prescription items): 344 (13.2%) of these items were for tranquillisers such as diazepam or tricyclic compounds such as imipramine, while 50 (2%) were for barbiturates either of the short-acting type or as contained in some antacid mixtures or so-called migraine remedies. The actual numbers of barbiturate prescription items in the tested sample were 20 in October, 5 in January, and 25 in March. Examination of the table shows that patients receiving anxiolytic treatment, antidepressive treatment, and sedative measures had their prescription items written more often than not by the receptionist.

Percentage of prescriptions written by receptionist

	October 1975	January 1976	March 1976
"Organic" prescriptions ..	23	22	22
Anxiety depression ..	66	60	65
Barbiturates ..	80	80	72

Discussion

Many factors must contribute to whether prescriptions are written by the general practitioner or the receptionist. The more a treatment is simply palliative and the less the doctor feels he has to contribute by frequent reassessment of the condition, the more likely it is that the patient will receive repeat prescriptions. For barbiturates this occurs in 72-80% of occasions. Around this central theme other factors such as excessive pressure of work and the cultural expectation of "a pill for everything" impinge. The treatment by most doctors and psychiatrists of patients with life difficulties by the single expedient of tablets encourages the population to regard physiological responses to stress as pathological processes.

The extraordinarily high percentage of receptionist-written prescription items (of psychoactive drugs) and its constancy from month to month possibly indicate a chronic failure of the medical profession to respond adequately to their patients' need of counselling, marriage guidance, and family therapy. In the short term it seems likely that many doctors require education in helping and persuading their patients to give up their dependence on tablets. These results conducted in one housing-estate community confirmed the clinical impression that patients obtain repeat prescriptions too easily.

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Infection with penicillinase-producing gonococcus

Gonococci that are relatively insensitive to penicillin have been recognised for many years. A few strains that are highly resistant owing to the production of penicillinase have recently been found in the USA.^{1,2} Phillips described a strain isolated in London,³ and Turner *et al*⁴ found several in Liverpool. We describe two further patients whose infections were due to a similar organism.

Effect of density of inoculum on MIC of penicillin in first isolate from case 2

Inoculum (20 µl)	Penicillin concentration (mg/l)								
	100	50	25	12.5	6.25	3.125	1.56	0.78	0
McFarland No 1	++	++	++	++	++	++	++	++	++
10 ⁻¹	-	+	+	+	++	++	++	++	++
10 ⁻²	-	-	-	-	-	-	50 colonies	+	+
10 ⁻³	-	-	-	-	-	-	-	12 colonies	+
10 ⁻⁴	-	-	-	-	-	-	-	-	30 colonies

++ = Confluent growth. + = Semiconfluent growth. - = No growth.

Case reports

Case 1—A 36-year-old man attended the Whitechapel clinic on 17 August 1976 complaining of urethral discharge for a day after recent sexual contacts in Liverpool. Gram-negative diplococci were seen in a stained smear, and he was given 1.5 g talampicillin and 2 g probenecid. Two days later his smear was still positive and he was re-treated with 3 g ampicillin and 2 g probenecid by mouth and 2.4 megaunits procaine penicillin intramuscularly. On 23 August gonococci were still present and further intercourse was denied. He was given 2 g kanamycin. When seen five days later he said that his discharge had stopped and then recurred; gonococci were still present, and 500 mg doxycycline was given. On 2 September he had no discharge, and smears and cultures were negative. He did not reattend.

Case 2—A 20-year-old girl came to the clinic on 28 August 1976 as a contact of the first patient, with whom she had had intercourse the previous day. She had no symptoms but gonococci were found in a cervical smear. Despite 3 g ampicillin and 2 g probenecid urethral and cervical smears still showed gonococci on 2 September. She was given 2.4 megaunits of procaine penicillin, but four days later gonococci were still present in the cervical smear. After further treatment with 2 g kanamycin smears and cultures were negative on 9 and 15 September.

Bacteriological studies—Gram-negative, oxidase-positive diplococci with the colonial morphology of gonococci were isolated three times in case 1 and twice in case 2. All these isolates produced acid from glucose but not from maltose, lactose, or sucrose. They gave bright fluorescence with an antigenococcal conjugate, and the coagglutination test result was positive.

Sensitivity tests—Plate dilution tests on brain-heart infusion agar with 10% horse blood were performed with inocula of about 10⁴ colony-forming units of three isolates from case 1 and two from case 2. All gave identical results. After 48 hours' incubation the minimum inhibitory concentrations (MICs) were: penicillin >0.5 mg/l, ampicillin >0.5 mg/l, streptomycin >500 mg/l, tetracycline 0.5 mg/l, and spectinomycin 10 mg/l. Strains from both patients were sensitive in disc tests to kanamycin and co-trimoxazole. Higher concentrations of penicillin were inoculated with 20 µl of tenfold dilutions of suspensions adjusted to the opacity of a McFarland No 1 tube. With strains from both patients the MIC varied with the size of the inoculum. Results with the first isolate from case 2 are shown in the table. Isolates of both strains produced a red coloration in the chromogenic cephalosporin test for beta-lactamase.⁵

Comment

The gonococci isolated from these patients were highly resistant to penicillin; results of in-vitro tests suggested that this was due to penicillinase production. Gonococcal sensitivity test results are seldom available before treatment failure is apparent, and the choice of antibiotic for re-treatment depends on knowledge of the sensitivity patterns of strains in local circulation. Whether these strains are freaks or are in general circulation remains to be determined. Fortunately they are still susceptible to other agents. Those so far tested have been sensitive to spectinomycin and tetracycline. Until more is known about their prevalence and properties, these two antibiotics seem likely to be effective when an initial treatment with penicillin has failed.

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¹ Ashford, W A, Golash, R G, and Hemming, V G, *Lancet*, 1976, **2**, 657.
² Golash, R G, *et al*, *Lancet*, 1976, **2**, 793.
³ Phillips, I, *Lancet*, 1976, **2**, 256.
⁴ Turner, G C, Ratcliff, J G, and Anderson, D, *Lancet*, 1976, **2**, 793.
⁵ O'Callaghan, C H, *et al*, *Antimicrobial Agents and Chemotherapy*, 1972, **1**, 283.

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