FATAL AGRANULOCYTOSIS DURING TREATMENT WITH CHLORPROMAZINE

BY

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Although only recently introduced, chlorpromazine is already a widely prescribed drug. Serious complications encountered during its use should therefore be made known. The aim of this note is to record the clinical details of a patient who died of agranulocytosis during a course of treatment with chlorpromazine.

Literature

Mild and transient leucopenia during the early weeks of treatment with this drug is well recognized (Andersen, 1954), but fully developed agranulocytosis has seldom been recorded. Lomas (1954) drew attention to a 69-year-old woman who developed agranulocytosis after receiving 6 g. of chlorpromazine in 41 days. The total leucocyte count fell to 680 per c.mm., of which only 11% were polymorphs. The drug was withdrawn and prophylactic penicillin was administered, but after 10 days there was still no improvement in the blood count. The patient was then given five injections of 50 mg. of cortisone. Subsequently the white blood count rapidly became normal. A second case was reported from Denmark by Munch-Petersen (1954). His patient was a 71-year-old woman who was given 10.6 g. of chlorpromazine in 48 days. On the 46th day of treatment she developed diarrhoea and on the 48th her temperature rose. The white-cell count was 800 per c.mm., of which 14% were polymorphs. The patient was treated with repeated blood transfusions, folic acid, and prophylactic penicillin. In spite of a mild bilateral bronchopneumonia she made slow but steady progress, and nine days after the initial blood examination the white-cell count was again normal. A third example has been recorded in Norway by Giacobini and Lassenius (1954) in a 57-year-old woman who was treated with a combination of chlorpromazine and promethazine. The latter antihistaminic drug was used to enhance the sedative effect of chlorpromazine and to guard against any untoward sensitivity reactions. This latter device was notably unsuccessful. On the 40th day of treatment the patient complained of pain in the limbs and lassitude, and on the 45th day a blood count showed 900 leucocytes per c.mm., of which 200 (22%) were polymorphonuclears. The patient was treated with blood transfusion and penicillin, and recovered well. A fortnight after the discovery of agranulocytosis no abnormality could be found in the white-cell count.

All these patients were women, all were of middle or old age, and all recovered. All developed agranulocytosis at about the sixth week of treatment with chlorpromazine, and in none were there any warning signs of sensitivity to the drug. The patient described below differs from them in that she was a young woman, her illness proved fatal, and clear-cut clinical evidence of sensitivity to chlorpromazine preceded the development of agranulocytosis by an interval of 2½ weeks.

Case History

The patient was a married woman aged 38. She had first consulted a psychiatrist in 1943, when she was 27. A diagnosis of hysteria was made, and she subsequently attended the psychiatric out-patient department fairly regularly for a number of years. Her symptoms during this time were very numerous, and no organic cause for them could be found. They did not improve. In 1951 she was admitted to hospital in an hallucinated and maniacal state, which necessitated her early transfer to a mental hospital. There was little or no response to a course of electric

convulsion therapy, and she ultimately returned home. Between 1951 and 1954 she complained frequently of lassitude, syncope, excessive menstrual loss, and pain involving most parts of the body. These symptoms could be temporarily controlled only by frequent changes in treatment. Many remedies were therefore used. They included compound tablets of codeine; sodium salicylate and potassium citrate in simple mixtures; aspirin, phenacetin, and caffeine tablets; "hypon" tablets; and "amenorone" tablets. None of these preparations is known to depress the activity of the bone marrow. Amidopyrine and the sulphonamides were not used.

On August 17, 1954, treatment with chlorpromazine was recommended. The initial dose was 25 mg. three times daily, and this was doubled nine days later, the patient receiving 150 mg. daily on and after August 26. On August 28 she complained of lassitude and fever, and her temperature was 101.2° F. (38.4° C.). Although examination revealed no obvious cause for the fever it was thought best to treat her with procaine penicillin intramuscularly for three days. The fever lasted only two days. On September 1, however, 14 days after the treatment with chlorpromazine had started, she complained that she was passing pale faeces and dark urine. Jaundice was confirmed on clinical examination. Like the fever, this also was short-lived, and on September 4 was barely discernible. On September 6 a third complication arose: an irritating rash developed on the limbs. Two days later the presence of a discrete maculo-papular erythema was confirmed: it involved all four limbs, but particularly the thighs and calves. On September 10 the rash had gone. Up to this point treatment with 150 mg. of chlorpromazine daily had been continued without interruption. It was now continued throughout 2½ weeks of relatively good health. On September 27, however, after receiving 5.475 g. of chlorpromazine in 41 days, the patient developed ulceration of the gums and tongue and her temperature rose to 101.2° F. (38.4° C.). An immediate blood count showed 900 white cells per c.mm. (polymorphonuclear leucocytes 10%, lymphocytes 90%). A diagnosis of agranulocytosis was made. Treatment with chlorpromazine was stopped at once, and the patient was immediately admitted to hospital.

On admission the patient lay still and resented examination. Her temperature was 100° F. (37.8° C.), pulse 100, and respirations 22. Her tongue was dry and furred. There were numerous small ulcers on the mucous membranes of her tongue and pharynx. The gums were also ulcerated. There was no pallor of the mucous membranes, and no jaundice, rash, oedema, or enlargement of the lymphatic glands. The heart and lungs were normal; the liver and spleen could not be felt; and the urine contained neither albumin nor sugar.

In spite of the withdrawal of chlorpromazine and the prophylactic injection of 500,000 units of penicillin intramuscularly twice daily, the patient did not improve. An irregular fever between 99 and 101° F. (37.2 and 38.3° C.) was maintained, and ulcerative stomatitis persisted. Daily blood counts, the results of which are given below, showed a persistent grave granulopenia.

Date	Hb %	R.B.C. per c.mm.	W.B.C. per c.mm.	Polymorphs %	Platelets per c.mm.
27.9.54			900	10	
28.9.54	83		1,600	10	
29.9.54	83	3,800,000	1,500		
1.10.54			1,400		
2.10.54	70		900	15	290,000
4.10.54			800	5	

On October 2 profuse diarrhoea developed, and from this point the patient rapidly deteriorated. Next day she developed right lower lobar pneumonia which failed to respond to 2,000,000 units of penicillin intramuscularly, 500 mg. of oxytetracycline intravenously, and 2 g. of oxytetracycline

intramuscularly, all given within 24 hours. On October 4, one week after admission to hospital and seven weeks after starting treatment with chlorpromazine, the patient died. Permission for necropsy was not granted.

Comment

For two reasons it is difficult to avoid the conclusion that chlorpromazine was responsible for this fatal agranulocytosis. Firstly, the agranulocytosis developed six weeks after the first dose of chlorpromazine; this interval corresponds with that noted in other recorded cases. Secondly, the agranulocytosis followed definite evidence of sensitivity to chlorpromazine. Transient fever, jaundice, and skin rashes are well recognized as complications of treatment with chlorpromazine. The other drugs used before treatment with chlorpromazine began can scarcely be incriminated. They do not carry the reputation of toxicity towards the bone marrow, and they had been taken frequently and harmlessly by this same patient on previous occasions.

This case suggests that evidence of sensitivity to chlorpromazine should be treated with respect. Fever, jaundice, and skin eruptions during the early weeks of treatment should be taken as danger signals and should compel repeated examination of the blood, if not withdrawal of the drug. Ulcerative stomatitis, particularly if it occurs at about the sixth week of treatment, should be an absolute indication for the immediate cessation of chlorpromazine therapy.

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CYST FORMATION SEVEN YEARS AFTER A CUTIS GRAFT REPAIR OF HERNIA

BY

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The use of skin in the repair of hernia was suggested more than forty years ago in Germany (Loewe, 1913), and was first applied clinically to post-operative incisional herniae (Rehn, 1914). It did not come into any general use for inguinal herniorrhaphy until Mair (1945) published his paper. The possibility of cyst formation due to the persistence of epithelial or glandular elements was not noted in the first two series of cases published (Mair, 1946; Marsden, 1948), but was stressed by Strahan (1950) in a series of 413 cases. Strahan found nine definite cases of cyst or sinus formation, with a number of others in which the presence of a cyst was suspected but not proved by actual operation. Most of the cysts in Strahan's series were small; but two were large, and his Case 3 is very similar to the one reported here.

Case Report

A railway worker aged 48 first developed a left inguinal hernia in 1946. The hernia was operated on in May, 1947, and the transcript of the rather brief operation note reads as follows: "Left inguinal incision. Poor musculature. Direct inguinal hernia. Cutis graft repair performed. Patient to remain in bed three weeks." The patient stated that he had made an uncomplicated recovery after operation, and that he had not returned to his job, which entailed heavy lifting, until August, 1947. He remained quite free from symptoms and from any sign of recurrence until June, 1954—more than seven years after the operation—when he began

to complain of pain in the groin, radiating into the testicle, and later noticed a swelling under his operation scar. He was examined by a surgeon, who diagnosed recurrent left inguinal hernia.

Examination showed a heavily built overweight man with protuberant abdominal wall rather heavily laden with fat. There was a well-healed oblique operation scar in the left inguinal region, and beneath it an elongated smooth solid swelling lying in the long axis of the inguinal canal. It was not reducible, but appeared to have some impulse on coughing. A diagnosis of incarcerated omentum in a recurrent hernial sac was made—the details of the previous operation being overlooked through an over-hasty perusal of a rather illegibly written case record.

At operation the first feature noticeable was the unusually dense fibrotic obliteration of the normal layers of the inguinal musculature. The swelling was obviously solid, and, after it had been separated from the spermatic cord and dissected up, it became apparent that it stopped short

at the internal ring and had no communication with the peritoneal cavity. The swelling, which measured 7 cm. in length and nearly 3 cm. in greatest diameter, was removed intact. Its removal left a potential weakness in the posterior wall of the inguinal canal, which was repaired with silk sutures after a relaxing incision in the anterior rectus sheath.

The patient made an uncomplicated recovery after operation, and left hospital with no evidence of any recurrent herniation.

The swelling, when examined after removal, proved to be a cyst, with walls varying from 2 to 5 mm. in thickness. It contained a waxy inspissated material, and several dark hairs, one of which was an inch (2.5 cm.) in length, were seen lying free in it. Histological examination of the cyst wall showed a well-formed squamous epithelial lining, with a connective-tissue backing resembling normal dermis, though without its papillary structure. The size and shape of the cyst are well shown in the photograph.

Comment

Apart from the cases mentioned by Strahan in his large series, only two cases have been reported in this country of cyst formation after buried skin-graft operations (Clarke, 1952; Powell and Ewing, 1952). Clarke made a thorough review of the relevant literature, and discussed the factors favouring cyst formation. His case, however, like most of the others, was a small cyst discovered coincidentally at operation for recurrent hernia. The possibility of the persistence of buried glandular elements was recognized by Rehn in his original paper. Experimental work by Zimches (1931) showed that a piece of skin inserted free into muscle tissue tends to curl up into a U shape and regularly to form an inclusion cyst; and even if sutured into position