CHRONIC IDIOPATHIC AGRANULOCYTOSIS

Report of a Fatal Case Treated with Corticotrophin (ACTH)

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In 1922 Schultz described the clinical picture of a fatal necrotizing throat infection usually occurring in elderly females. Since then many cases of agranulocytosis (as it was named) have been described, the majority due to secondary marrow intoxication with chemical agents containing a benzene grouping. The primary or idiopathic variety still remains a mysterious malady, occurring at all ages, especially in females, and about whose causation little is understood.

Since 1934 only 30 cases or so have been recorded in the United Kingdom. There has been no survey of the whole subject in this country for the past 10 years, apart from the contribution of Adams and Witts in 1949, when five cases were described and discussed.

Treatment remains problematical. Many forms have been tried and are well known. They include splenectomy, irradiation, nucleotides, glutathione, liver extract, the various components of the B complex of vitamins, especially pyrodoxine, folic acid and cyanocobalamin, transfusion of whole blood or its constituents, especially leucocyte cream, bone marrow and leukaemic extracts. The greatest advance so far has been the use of antibiotics and in particular penicillin, which helps to prevent those infections previously proving fatal.

Due to the paucity of suitable cases, reports of the effect of ACTH have been few in number, especially in regard to the idiopathic variety. Its use in the following case, which was observed over three years, is therefore described.

Case Report

K.M.C., a housewife aged 53 years, was first admitted on 30.9.52 as a case of pneumonia. She had complained of pain in the right side of the chest for two days.

Shortly after the death of her son in 1943 she developed pains in the hands, knees, ankles and feet, which were ascribed to rheumatoid arthritis and treated as such. She had taken various proprietary brands of aspirin up to nine tablets daily to relieve these pains without much success.

In 1951 she was treated for septic feet.

On Examination

T. 102°. P. 124. Resp. 42. Depressed and ill. Dry, furred tongue. Edentulous. Tachypnoea. No rash, glands, or ulceration. Both lung fields showed multiple crepitations, especially in right mid zone. B.P. 135/85. Heart sounds normal. Hands soft, pale and smooth with little evidence of articular thickening. Some saphenous varices present.

Investigations

X-ray chest 2.10.52. Patchy consolidation right lung field. Sputum: no predominant organism isolated. No acid-fast bacilli present.

On admission: white cells 1,600. No granulocytes, only a few premature cells.

Blood group 'O' Rh positive.

Sternal marrow film 11.10.52: no granulocytes. Only a few myelocytes. 42 per cent. lymphs. Normoblasts +.

Treatment

Benzyl penicillin, 1,000,000 units intramuscularly six-hourly for 38 mega units. Chlorotetracycline, 500 mg. six-hourly for five days. Sodium pentose nucleotide, 5 ml. twice daily for four days I.M. Aq. gentian violet, 1 per cent. to mouth. One pint compatible and cross-matched blood. Heparin, 10,000 units I.M. six-hourly for 2,800,000 units. Pyrodoxine, 100 mg. I.V. for four days. Ascorbic acid, 1,000 mg. daily.

Progress

Initial improvement occurred, apart from a herpetic eruption of the lip. The chest cleared by 8.10.52, but numerous small shallow ulcers of tonsillar fossae and palate developed. She was frail and weak. By 27.10.52 the ulceration was worse. On 3.11.52 a blood transfusion of one pint whole blood was given. Four days later pitting oedema of left leg developed with tenderness in Scarpa's triangle. By 11.11.52 both the leg and

mouth had improved. Progress, if any, was still very slow, but by 10.12.52 she had recovered sufficiently well to go home. The leg was still swollen and an elastic stocking was ordered.

Follow-up

1.1.53 to 6.6.53. Has felt well, apart from occasional headaches and hot flushes. No ulceration present. B.P. 150/90. Weight 11 st. 5 lb. Oral oestrogens prescribed.

29.7.53. Readmitted to hospital with right-sided abdominal pain for three days. C.S.U.: pus cells and *B. coli*. W.C.C. 2,800. Polys 12 per cent. Discharged well on 28.8.53 after treatment with citrates and oxytetracycline.

28.11.53 to 27.2.54. Vague aches, headaches, hot flushes, but looks and feels well. Weight 13 st. Meibomian cyst of eyelid present. W.C.C. 1,400. Polys 10 per cent.

24.10.55. Defaulted from out-patients' during

the first half of 1955 and then readmitted to hospital with headache, coryza and increasing cough for seven days. Treated at home with sulphatriad. T. 102. P. 124. Resp. 24. Flushed. Right nostril ulcerated. Bilateral basal crepitations. Increasing pallor, lethargy, weakness, necrotic ulceration of the tongue and dysphagia occurred.

She died 17 days after admission and three years, 2/12 after originally seen. No post-mortem performed, but cause ascribed to bronchopneumonia despite negative X-ray findings.

Investigations

25.10.55. Chest X-ray clear! C.S.U. normal. W.C.C. 500/cu. mm. No granulocytes.

4.11.55. W.C.C. 600/cu. mm. No granulocytes.

25.10.55. Hb 99 per cent. R.B.C. 4,800,000/cu. mm.

4.11.55. Hb 75 per cent. R.B.C. 3,880,000/cu. mm. Group 'O' Rh positive.

7.11.55. Sternal marrow puncture; the marrow is erythropoietic and shows red cell precursors. No platelet deficiency. The predominant cell is a small lymphocyte: cells of the granulocyte series almost completely absent, a rare promyelocyte and eosinophil are seen.

The picture suggests an actual aplasia of granulocytic system. The lymphocytes are small and mature. There is no accordance with a leukaemic state.

Treatment

Penicillin : chlortetracycline.

8.11.55. Soluble corticotrophin, 25 mg. six-hourly I.M. for *three days* before death.

Discussion

There seems little doubt that the case described conforms to the clinical and pathological picture of idiopathic aplastic agranulocytosis. It would appear that the first symptoms (fleeting pains) commenced some time after 1943, which would suggest that the duration of the illness was approximately 12 years. The fact that aspirin was used *after* the onset of the joint pains makes this unlikely as the causal factor. It is of interest that the patient's illness started after a severe mental shock, namely, the death of her son. Whether such shock acts as a trigger mechanism, in predisposed adults at any rate, is conjectural. Although most cases occur in adults, the condition does occur in early infancy, e.g. two years (Bruck, 1947; Moncrieff, 1951). However, at this early age it may well be that the *infection* which usually acts as a precipitating factor could be the cause rather than the result of the granulopenia, due to the immature condition of the infantile bone marrow.

A further similar personal case occurring in an adult female aged 57 years may be interposed here. She was admitted on 25.5.52 suffering from staphylococcal septicaemia. An initial white cell count showed 330 white cells with no granulocytes. Eleven days later the count had risen abruptly and permanently to 21,200, of which 78 per cent. were granulocytes, 27 per cent. being immature. Treatment included penicillin, chlortetracycline and pentnucleotide.

Witts classified the disease amongst the aplastic anaemias, but as their cause is equally obscure this is of little help in treatment. Most of the recorded cases occur in females, but whether this means that the female sex hormone in whole or part acts as a marrow depressant under certain circumstances is disputed.

Most of the cases are fatal nowadays as a result of the disease itself rather than from secondary infections, which are controlled by antibiotics. Despite this, it seems that sufferers can survive

for many years; thus Spaet and Damshek record a case in a woman of 63 years who survived for 25 years. The present case as mentioned probably lived for 12 years.

In a disease of such varying course and long duration it is natural that attempts should be made to classify it on a 'chronological' basis. Thus acute fulminating, chronic insidious, relapsing and cyclical varieties have been described. I myself (1946) postulated a critical level of leucopenia below which symptoms might occur. However, a study of recorded cases would seem to point to chance rather than any specific pathological factor as the cause of the variations.

The course of the illness bears some resemblance to the reticuloses, especially leukemia and Hodgkin's disease, both of which are characterized by relapses and remissions. Whether some similar malignant cellular process is the cause is debatable.

It is difficult, therefore, to prognosticate in a given case. A month after the original admission of the present case her condition appeared as grave as the day on which she died, yet this occurred three years later! The results of treatment, too, are difficult to appraise. Credit for cure or remission is usually given to the last treatment employed.

Nowadays, when in doubt, cortisone or corticotrophin is widely employed after all else has failed. Cortisone stimulates haemopoiesis, so that this somewhat rationalizes its use in haematology, although its mechanism is unknown. Corticotrophin was used as a last resort in this case *three years* after the original diagnosis. The soluble as distinct from the gel variety was employed because it was considered that absorption would be quicker. Intermittent intramuscular dosage (25 mg. six-hourly) was felt to be as effective as the continuous intravenous method.

Although it was intended to continue it, if effective, for an indefinite period, perhaps on a maintenance dose basis, *three days* later the patient's condition was no better and she died before any real assessment of its value could be made. Whether this result was due to 'too little being given too late' is questionable, because of the unpredictable nature of the malady. Some spontaneous recovery of her marrow function had occurred by 27.12.54, when the white cell count rose to 2,600, Polys 20 per cent. It is conceivable that if corticotrophin had been employed at this time any recovery may have been ascribed to its use. It would seem, however, that if the marrow is or becomes aplastic, as in the present instance, then no form of stimulation would be of any avail. Whether cortisone itself would have been better than corticotrophin is also conjectural. It is possible that the adrenal glands were so depressed by the long-continued effects of the illness that

they were unable to be stimulated. What the effect of agranulocytosis is on these glands, I do not know. However, it might seem in retrospect more rational to use cortisone rather than corticotrophin in this and similar states.

Martenson and Vikbladh (1954) discussed the serum protein findings in a woman of 49 years who had thyrotoxicosis in 1948 followed by granulopenia for six years. Studies showed a pathological protein fraction constituting 30 per cent. of total proteins which immigrated at the same rate as gamma globulin and which agglutinated normal leucocytes, especially neutrophils. They therefore postulated that neutropenia is the result of auto-immunization, causing intravascular destruction of leucocytes. Two other cases, however, did not show the same phenomenon. Whether the thyrotoxicosis, too, was a factor also remains disputable. If an allergic basis were postulated, the use of cortisone and ACTH might be rationalized still further. However, one swallow does not

make a summer and no firm conclusions can be drawn from a single case. Its use, therefore, remains *sub judice*.

Summary

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BIBLIOGRAPHY

- ADAMS, E. B., and WITTS, L. J. (1949), *Quart. J. Med.*, **18**, 173.
 BRUCK, E. (1947), *Amer. J. Dis. Child*, **73**, 186.
 LIBRACH, I. M., and CRONIN, R. G. (1946), *Brit. med. J.*, **2**, 897.
 MARTENSON, J., and VIKBLADH, I. (1954), *Blood*, **6**, 632.
 MONCRIEFF, A. (1951), *Arch. Dis. Child*, **26**, 438.
 SPAET, T. H., and DAMESHEK, W. (1952), *Amer. J. Med.*, **1335**.
 SCHULTZ, W. (1922), *Deutsch. Med. Wchschr.*, **48**, 1495.
 WITTS, L. J. (1936), *Proc. R. Soc. Med.*, **29**, 671.

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