ACUTE HAEMOLYTIC ANAEMIA AS A COMPLICATION OF TYPHOID FEVER

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Haemolytic anaemia as a rare complication of typhoid fever was first recognized by Osler in 1895.[1] Since then, however, less than 40 authentic cases have been described in the medical literature.[1-16, 20] We wish to report a patient who had typhoid fever and presented with acute intravascular haemolysis.

CASE REPORT

A 36-year-old Bantu labourer was admitted to the Karl Bremer Hospital on 11 March 1963. He had been in good health until 3 days previously when he fainted on arriving home from work. He subsequently passed much red blood per rectum and felt weak and feverish. The next day he remained in bed with progressive malaise and headache and noticed that his urine had become 'like black coffee'. At no time did he experience rigors, vomiting, diarrhoea or significant abdominal pain. On the third day of his illness he again passed blood per rectum and was admitted to hospital.

The patient had come from the Transkei a year previously. His past history and further clinical interrogation revealed nothing else of note, except 'kidney trouble' in 1954. No typhoid contacts could be traced.

Clinical Examination

An ill, well orientated man of normal build presented with a temperature of 102°F and a respiration of 24/min. There was mild scleral jaundice but no significant adenopathy, bleeding tendency, splinter haemorrhages or skin rashes.

Cardiovascular system. BP 150/90, pulse 84/min. (good volume), heart normal.

Abdomen. Mild peri-umbilical tenderness but no masses or peritoneal irritation; liver was just palpable but spleen not clinically enlarged; rectal examination showed melaena but no other abnormality; proctoscopy was normal. The rest of the clinical examination was non-contributory.

Urine. Dark red colour. Microscopy: abundant epithelial cells but no red cells, pus cells or cylinders. Chemical tests: protein +++; orange sugar reduction with Benedict's reagent; bile and urobilinogen not demonstrated; porphyrins absent. Spectroscopy: oxyhaemoglobin present.

Peripheral blood. Hb. 5·8 G/100 ml.; PCV 16%; MCHC 36%; leukocyte count 30,000/cu.mm. (lymphocytes 14%, neutrophils 77%, staff cells 4%, metamyelocytes 5%, occasional myelocytes); normoblasts 4/100 leukocytes; reticulocyte count 5·4%; platelets 289,000/cu.mm.; ESR 40 mm./1st hour. Westergren. Red cell morphology showed severe anisocytosis, large numbers of spherocytes, 'triangular cells' and fragmented microcytes.

Special Investigations

1. *Haematology.* (11 March 1963) Serum spectroscopy showed oxyhaemoglobin bands but no methaemoglobin, sulphaemoglobin or carboxyhaemoglobin. Schumm's test was negative. (12 March) L.E. cell investigation negative. Heinz body preparation negative. Direct and indirect Coombs' tests were negative at 37°C and 22°C. Bone-marrow aspiration showed hyperactive normoblastic erythropoiesis and hyperactive myelopoiesis.

2. *Blood biochemistry.* (12 March) Blood urea was 16 mg./100 ml. Serum proteins: Albumin 4·5 G/100 ml., Globulin 3·2 G/100 ml. (increased α 1, β and δ globulin). Bilirubin 2·7 mg./100 ml. (direct 0·5 mg./100 ml., indirect 2·2 mg./100 ml.); direct Van den Berg reaction negative. Transaminase (SGPT) 64 Cabaud units/ml. Alkaline phosphatase 2·4 Bodansky units/100 ml. Thymol turbidity 2 units, thymol flocculation 0 unit and zinc turbidity 4 units. Cholesterol 111 mg./100 ml. (15 March) Fasting blood sugar 152 mg./100 ml.

3. *Blood Wassermann & VDRL* tests were negative.

4. *Agglutination tests* (12 March) Widal negative, Brucella negative, Weil-Felix negative, Paul-Bunnell negative.

5. *Blood cultures. Salmonella typhi* were isolated on March 11, 12 and 14, but on 15 March no growth could be obtained.

Progress and Treatment

The clinical picture was that of acute intravascular haemolysis. In the absence of a satisfactory diagnosis, no specific therapy was instituted except for a blood transfusion of 4 pints. The patient appeared remarkably well in spite of significant pyrexia (99·5°F - 105·5°F) and a rising blood urea—45 mg./100 ml. (13 March); 64 mg./100 ml. (15 March); 104 mg./100 ml. (16 March). However the urine output remained satisfactory and on 26 March the blood urea had fallen to 48 mg./100 ml.

The haemoglobinuria decreased rapidly and disappeared on the third day after admission. All clinical signs of haemolysis cleared in the course of a week, and the haemoglobin stabilized at 11 G/100 ml.

On the 5th day after admission severe rectal haemorrhage recurred, necessitating a blood transfusion of 8 pints. On the same day the Microbiology Department reported isolation of *Salmonella typhi* from blood cultures taken on admission.

Immediate treatment with chloromycetin (500 mg. 4-hourly for 3 days followed by 500 mg. 6-hourly) was instituted and 5 days later the patient was apyrexial.

The glycosuria and raised blood sugar values suggested diabetes mellitus. On a 1,200-calorie diabetic diet the glycosuria disappeared and the blood sugar fell to 74 mg./100 ml. (26 March).

No further complications were noted and on 27 March he was transferred to the City Hospital for Infectious Diseases, where he made an uninterrupted recovery.

Subsequent follow-up was not possible as the patient returned to the Transkei after discharge from hospital.

DISCUSSION

The occurrence of haemolytic disease in the course of typhoid fever might not be as rare as is generally thought. Osler[1] found 1 case among 1,500 typhoid patients, but Huckstep[20] in 1962 recorded an incidence of 2%, while Berman *et al.*[12] found an incidence of 5·9% in 1945. McFadzean and Choa[14] reported the rather similar figure of 4·6% among the Chinese of Hong Kong in 1953; they remarked on the absence of haemolysis in paratyphoid A, B and C. Nevertheless Ruggieri[16] as recently as 1961 reviewed the world literature and could find no more than 32 reported cases of haemolytic anaemia from salmonella infections, and at least 5 of these are doubtful instances.[4-7]

The mechanism of haemolysis is not clear. As happened in our case, at least 50% of the reported instances of acute typhoid haemolysis with haemoglobinuria occurred during the first week of illness, when bacteraemia is known to be maximal. However, the salmonella is normally an anhaemolytic organism. Although early work by Friedberger and Vallen[17] in 1923 did suggest that bacteriophage interaction may render the salmonella haemolytic under certain experimental conditions, this is unlikely as a spontaneous occurrence. McFadzean and Choa[14] noticed that haemolysis did not parallel the severity of infection but outlasted the pyrexial illness. A large proportion of their cases also had a positive Coombs' test and seemed to respond to ACTH rather than to antibiotics. They therefore sug-

gested an underlying auto-immune aetiology, possibly associated with the lymphoid hyperplasia of typhoid fever. Our patient was Coombs-negative and the haemolytic crisis cleared after a blood transfusion in the presence of undiminished pyrexia. Rapid disappearance of clinical haemolysis as well as repeated large blood transfusions, necessitated by recurrent intestinal haemorrhage, hindered satisfactory appraisal of the haemolytic process. However, the investigations performed showed no cause for haemolysis besides the obvious systemic infection. Heinz bodies suggestive of 'drug-induced' haemolysis were not demonstrated, but the glucose-6PO_4-dehydrogenase content of his erythrocytes was not estimated. McFadzean and Choa[14] considered ACTH of great therapeutic value in their cases, but Ruggieri[16] reported a disappointing response to prednisone. Nevertheless, one feels that steroid therapy should be instituted in this condition, as its value is well established in fulminating typhoid.[18]

The present case illustrates the protean manifestations of atypical typhoid fever. In addition to the haemolytic episode the patient presented with severe intestinal haemorrhage during the first week of illness. The persistent leucocytosis and tachycardia can be partially attributed to the acute blood loss and haemolytic reaction. Diabetes mellitus is not a recognized complication of typhoid, but latent diabetes may be unmasked by the stress of any severe systemic illness.[19]

SUMMARY

A case of typhoid fever is reported, which presented with acute intravascular haemolysis and melaena during the first week of illness. The literature on typhoid haemolysis is briefly reviewed; the association is possibly less uncommon than is generally thought.

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