THROMBOTIC MICROANGIOPATHIC HAEMOLYTIC ANAEMIA

BY

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Introduction

The syndrome of thrombotic microangiopathic haemolytic anaemia is rare and almost all the cases reported have been in adults. Very few cases occurring in childhood have been reported and the youngest recorded case was 22 months old (Craig and Gitlin, 1957).

We report the clinical and pathological details and the response to treatment of a child aged 21 months, who was seen at the Austin Hospital, Melbourne.

Case Report

J.L., a male child aged 21 months, was admitted to the Austin Hospital, Melbourne, with a week's history of malaise, anorexia, fever and a suggestion of pain, tenderness and mild swelling of both wrists and ankles. Six days before admission a red, blotchy urticarial rash was noted over the diaper area but this faded after three days.

He had had similar but milder symptoms following immunization with triple antigen, also following a course of sulphonamide, and one mild attack appeared spontaneously. These early episodes lasted only a few days. There were no significant past illnesses and the family history was not relevant.

On physical examination he was flushed and unco-operative. The temperature was 103° F., the pulse 164 and respirations 28 per minute. A fine purpuric rash diffusely involved the face and both upper extremities. Both wrists were swollen and tender and movement was restricted by pain; in addition, there was mild swelling of both knees and ankles. A mild tonsillitis and an otitis media were present. A provisional diagnosis of anaphylactoid purpura of the Schönlein type was made and he was treated with aspirin.

During the first week in hospital his temperature ranged between 99° F. and 103° F. (Fig. 1). The blood examination showed the haemoglobin to be 9 g. % (60%), the white cell count 20,000 per c.mm., with 70% neutrophils (showing a marked shift to the left), 25% lymphocytes and 5% monocytes; the red cells and platelets were normal, and no lupus erythematosus cells (repeated examinations), glandular fever cells or malarial parasites were seen; the reticulocyte count was less than 1%.

Examination of the sternal marrow revealed no abnormality. The clotting and prothrombin times were normal but clot retraction was poor. The Paul-Bunnell and Coombs tests were negative. Repeated blood cultures and agglutination tests, the Mantoux and Casoni tests and the Wassermann and Kahn reactions were all

FIG. 1. —Temperature range during first admission.

negative. Liver function tests, the blood urea and the serum proteins and electrophoresis were normal. The cerebrospinal fluid was normal as were radiographs of the chest and long bones. The throat swab grew a β haemolytic streptococcus.

The rash reappeared during the second week and the temperature, malaise and irritability persisted. A four-week course of aureomycin did not affect the temperature.

One month after admission the spleen became palpable and there was a mild generalized lymphadenopathy. At this stage the white blood count rose to 32,400 per c.mm. but the haemoglobin did not fall. After three months of hospitalization his temperature subsided spontaneously and being quite well he was allowed to go home. He remained well for the next six months when he developed a rash, resembling erythema marginata, on his arms and chest. Six weeks later the swinging temperature recurred and on one day his joints became painful. Similar episodes recurred weekly until he was readmitted three weeks later because of persistent pyrexia, irritability and a disinclination to move his limbs.

Examination at this stage revealed a fine generalized red papular rash, slight generalized lymphadenopathy and a temperature of 103° F. (Fig. 2.) The haemoglobin was

FIG. 2.—Temperature range during second admission.

11 g. % (74%); white cell count 24,600 per c.mm. with 60% neutrophils, 4% eosinophils, 33% lymphocytes and 3% monocytes; reticulocytes 12%. The platelets were 100,000 per c.mm.; this was the lowest figure obtained, and the count the next day was normal. In addition the red cell fragility in hypotonic saline was slightly increased and spherocytes were observed for the first time. The serum bilirubin was 3.2 mg./100 ml. and urinary urobilinogen was markedly increased and the faecal urobilinogen excretion per day was 300 mg.

The white blood count gradually rose to 56,000 per c.mm. in the next four weeks; the marked shift to the left and the presence of 8% myelocytes rendered the blood picture leukaemoid. The haemoglobin level waxed and

waned in association with a fall and rise in the reticulocyte count, which reached 15% at one stage. The spherocytes increased in number and became a permanent feature.

The possibility of thrombotic microangiopathic haemolytic anaemia was suggested by one of us (N.P.O.) and a combined axillary lymph node and pectoral muscle biopsy was taken. Sections of the muscle showed no abnormality. Sections of the lymph node revealed reactive hyperplasia only, but striking changes were observed in the small calibre vessels in the pericapsular region (Fig. 3.) One vessel was almost completely occluded by a mass of hyaline material. There was a breach in the vessel wall with resulting haemorrhage into the perivascular tissues. There was no perivascular reaction whatsoever. Other vessels were occluded and in the thrombi could be seen endothelial cells, fibroblasts and the clefts of recanalization. Some vessels showed endothelial hyperplasia and others subendothelial accumulation of hyaline material. These histological findings confirmed the diagnosis. Sections were stained by Weigert's, Mallory's P.T.A.H., Biebrich scarlet-aniline blue and Pearse's P.A.S.-orange G-haematoxylin stains, and most of the thrombi were partially positive for fibrin.

Cortisone therapy was started, with initially 25 mg. of cortisone acetate twice daily by mouth. The improvement was dramatic; his temperature subsided in 10 hours and although occasionally elevated in the next two weeks this was never above 100° F. When the dose was increased to 50 mg. b.d. the temperature remained completely normal. Equally dramatic was the clinical improvement; his personality completely changed, he became co-operative, his appetite returned and he immediately wanted to get out of his cot. Before this he was quite miserable and inconsolable. With 50 mg. b.d. he developed features of Cushing's syndrome and prednisolone 5 mg. t.d.s. and later 5 mg. b.d. was substituted for cortisone acetate. Since that time he has required between 5 and 10 mg. of prednisolone daily; the mother has now learnt from his general demeanour and from his temperature chart (which she has kept assiduously) how much cortisone is required. The constant aim is to stop cortisone therapy but at this stage a remission has not been obtained. Clinically, however, he is very well indeed and physical examination reveals no abnormality.

Discussion

The first example of this syndrome was described by Moschcowitz (1924, 1925). Probably no more than 40 proven cases have been reported since. According to Symmers and Barrowcliff (1951) this syndrome occurs in both sexes at any age. The youngest case recorded so far was a child, aged 22 months, reported by Craig and Gitlin (1957). All cases to date have died, two-thirds of them in six weeks or less. Examples of a prolonged course are few, the longest being that of a young man reported by Brown and Norman (1946). Another

FIG. 3.—Section of the arteriole in the pericapsular region of the lymph node, showing a hyaline thrombus, rupture of the vessel wall and haemorrhage into the surrounding tissues. Haematoxylin and eosin. $\times 700$.

case running a course of three and a quarter years was reported by Meacham, Orbison, Steele and Schaefer (1951).

The onset of the syndrome is usually sudden. Typically it is characterized by fever, purpura and haemolytic anaemia. Multifarious, fluctuating neurological disturbances often occur terminally and are of little diagnostic consequence, and death results, usually in two to four weeks.

Abnormal laboratory findings include thrombocytopenia and anaemia often associated with a raised reticulocyte count. Leucocytosis is usual and may be leukaemoid in type. The bleeding time is prolonged and clot retraction defective but the coagulation time is usually normal.

The case is of interest for several reasons: it is the youngest one on record, the mode of presentation although acute was by no means fulminating and the illness has been protracted. Frank neurological signs have been absent from the start, although there was a marked personality change consisting of extreme misery and complete lack of co-operation even after months in hospital. With a fall in the temperature the patient became quite quickly a happy and co-operative child. On one day only was the platelet count down to 100,000 per c.mm., but this was normal the next day and subsequently. Anaemia was never at any time severe, the lowest haemoglobin level recorded being 9 g. % (60%).

The clinical presentation with fever, leucocytosis, marked joint symptoms, an urticarial rash and a mild purpura, has been recorded before.

Evidence of hypersensitivity, as illustrated here, to pertussis-diphtheria-tetanus antigen and sulphonamides is not infrequent in this syndrome and reactions to iodine compounds, sulphonamides, and penicillin have been reported. Many consider this syndrome to be related to the so-called collagen diseases. We felt that the symptomatology was consistent with that of disseminated lupus erythematosus, but L.E. cells were not demonstrated. There is a good deal of pathological evidence to support this view. Verrucous endocarditis and disseminated lupus erythematosus have been reported in association with thrombotic microangiopathy. Symmers and Gillett (1951) have also reported a case of polyarteritis nodosa in which widely disseminated lesions of thrombotic microangiopathy were also present. Beigelman's (1951) concept of the aetiology of disseminated lupus erythematosus, polyarteritis nodosa, and thrombotic microangiopathy is that of a hyperergic response occurring at different sites in the vessel wall; a maximal response in the perivascular mesenchyme produces disseminated lupus erythematosus, a

maximal response in the media produces polyarteritis nodosa, and a maximal response in the intima produces thrombotic microangiopathy. Similar lesions can be reproduced in animals by the Schwartzman phenomenon.

The thrombotic lesions, which are confined to the smallest calibre vessels, occur more frequently and are more numerous in the myocardium, the capsular zones of the adrenals and in the renal cortex. The hepatic and adrenal sinusoids are not involved. There has been, in the past, much speculation as to the exact nature of the occlusive thrombi. Although it was generally accepted that these thrombi were composed of agglutinated platelets, there was no definite proof. Craig and Gitlin (1957) reviewed the literature at length and discussed the inadequacy of the standard staining procedures for fibrin. Using fluorescein-labelled rabbit anti-human fibrin serum, they showed that the thrombi were composed of fibrin. Also with this fluorescent antibody technique, they failed to demonstrate platelets in the thrombi.

The names given to this syndrome in the past have been unsatisfactory. While some have stressed the thrombocytic nature of the thrombi and others the thrombocytopenia, they all lose sight of the characteristic haemolytic anaemia. Moschcowitz's syndrome was suggested as a title, but being eponymous it is not entirely satisfactory. Symmers (1952) suggested the name of thrombotic microangiopathic haemolytic anaemia or, for short, thrombotic microangiopathy, which is descriptively accurate and wisely omits controversial and inconsistent features. It is to be hoped that this title finds general acceptance.

The prognosis in the present case must obviously be guarded. Cases living longer than this one have been reported but have invariably terminated fatally. However, the response to steroid therapy is the encouraging feature of this case. The recorded cases have almost always been so acute that therapy has not been successful. A.C.T.H. and cortisone have been used and splenectomy has been performed but without benefit. We feel that in this case cortisone proved of decided value in inducing the second remission. Reduction of prednisolone below 5 mg. b.d. results in elevation of the temperature, malaise and joint soreness within three days. We have persistently tried to discontinue therapy but the reappearance of pyrexia and symptoms has been prompt.

Summary

The youngest case (21 months) of thrombotic microangiopathic haemolytic anaemia is recorded. The child is alive and well after two years.

The clinical and pathological findings are given in detail. The nature of the occlusive thrombi is discussed.

The names accorded this syndrome are discussed and the title, thrombotic microangiopathic haemolytic anaemia, or for short, thrombotic microangiopathy, is supported.

Steroid therapy has been of inestimable benefit and no doubt has been life-saving. As yet it has not been possible to discontinue the maintenance

dose of prednisolone. The prognosis must obviously remain guarded.

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