A CASE OF THROMBOTIC THROMBOCYTOPAENIC PURPURA SURVIVING FOR FOUR YEARS

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SYNOPSIS

A case of thrombotic thrombocytopaenic purpura is described. He was successfully treated with blood transfusions, steroids and dipyridamole and is alive and well more than four years later. The actions of antiplatelet drugs are reviewed and it is suggested that their efficacy and freedom from side-effects merit their use as drugs of first choice in our present state of knowledge.

INTRODUCTION

Thrombotic thrombocytopaenic purpura (TTP) is an uncommon disease of young adults with a peak incidence in the third decade (Wintrobe 1974). Females are affected slightly more often than males in the ratio 3:2 (Amorosi & Ultmann 1966). The number of published cases since the original case was described by Moschcowitz in 1925 is over 300 (Amir & Krauss 1973). The mortality is high: 80% die within 3 months and less than 10% survive for longer than a year (Wintrobe 1974). The original diagnostic triad of thrombocytopaenic purpura, haemolytic anaemia and neurological manifestations has now been expanded to a pentad with the inclusion of renal disease and fever. The triad, however, remains a satisfactory basis for diagnosis (Amorosi & Ultmann 1966).

The disease differs from the haemolytic-uraemic syndrome of childhood in respect of the older age group involved, the higher mortality and in the larger number of organ systems affected (Wintrobe 1974).

This paper reports a case of the disease in a middle-aged adult who was treated with platelet transfusions, steroids and dipyridamole and who was successfully maintained in remission for a year and five months until his relapse. He was then successfully re-treated.

CASE REPORT

History

A 50 year old Chinese male clerical assistant was admitted to hospital on 4.12.74 with a ten-day history of generalised weakness and anorexia. The first two days of his illness were marked by diarrhoea. He had had eight bowel motions during the two days and the stools had been watery and yellowish-brown with no blood or mucus in them. The motions were not accompanied by colic or tenesmus. He had been told on the day of admission that he was jaundiced and had

been passing tea-coloured urine during the previous two days. There was no history of nausea, anorexia or vomiting and no history of self-medication or of exposure to chemicals. He was a social drinker and had no previous history of jaundice or petechiae. He had not had any injections during the past few months.

Clinical Examination

Examination revealed a mildly obese patient who was pale with a temperature of 37.5°C and a tinge of conjunctival jaundice. The liver was just palpable below the costal margin and was not tender. There were no petechiae, the spleen was not enlarged and there was no lymphadenopathy.

The heart rate was 88/min. and regular with a grade 2/6 ejection murmur heard all over the praecordium and the blood pressure was 110/60. The lungs were clinically clear and there was no neurological abnormality.

Initial Investigations

Haemoglobin	5.6 g/dl
Packed Cell Volume	19.0%
Reticulocytes	10.0%
White Blood Cell Count	12,300/ul
Differential Count:	
Polymorph	75%
Lymphocyte	23%
Monocyte	1%
Eosinophil	1%
Platelet Count	30,000/ul

ESR: 25 mm in 1st hour (Westergren)

The peripheral blood film showed neutrophil leucocytosis with some myelocytes. Red cells showed mild anisocytosis and poikilocytosis with some fragmented cells, spherocytes and normoblasts. Platelets were diminished.

The urine examination was negative except for a trace of albuminuria. There was no haemosiderin in the urinary deposit and there was no occult blood or ova in the stools.

Bone marrow examination showed a regenerating marrow with secondary megaloblastosis.

Investigation of Haemolytic Anaemia

Red Cell Fragility was slightly increased with haemolysis commencing at 0.6% (Normal 0.55%) and completed at 0.25% (Normal 0.2%).

Glucose 6-phosphate dehydrogenase was present.
Haemoglobin electrophoresis was normal.
Direct Coombs Test was negative.
VDRL was non-reactive.
Lupus erythematosus cells were absent.

Serum Bilirubin	0.7 mg/dl (0.3 — 1.1. mg/dl)
Total Protein	6.8 g/dl (6.6 — 8.7 g/dl)
Serum Albumin	4.0 g/dl (3.5 — 4.8 g/dl)
Alk. Phosphatase	7 K.A. units/dl (3 — 13 K.A. units/dl)
SGPT	25 IU/L (Normal < 30IU/L)
Blood Urea	31 mg/dl (10 — 50 mg/dl)

Coagulation Studies

Partial Thromboplastin Time:
Patient: 79 secs. Normal less than 100 secs.

Kaolin Cephalin Clotting Time
Patient: 42 secs. Normal less than 65 secs.

Prothrombin Time (Quick)
Normal: 14 secs. Patient: 16 secs.

Thrombin Clotting Time:
Normal: 12 secs. Patient: 17 secs.
Corrected with Protamine sulphate (1/80) to 10 secs.
Ethanol gelation test was negative.
Protamine sulphate test (1/10) was negative.
Serial Thrombin Time was normal.

Fibrin Degradation Product (TRC):
11.4 ug/ml (Normal 3.5 ug/ml)
Factor VIII: 175% (Normal 80 — 180%)
Factor V : 92% (Normal 70 — 200%)
ELT : 385 mins. (Normal)

Comment: The findings are inconclusive but may suggest early phase of DIVC.

Subsequent Progress & Management (See figure)

The fourth to sixth hospital days were marked by slightly blood-stained sputum and the patient was febrile (maximum temperature 38.5°C) during the sixth to ninth hospital days. The lungs remained clear to auscultation and there was no radiological abnormality. However, beta haemolytic streptococci were grown from the sputum and a course of tetracycline (as indicated by the sensitivity tests) was given. His sputum gradually cleared.

Two units of fresh blood were transfused on the seventh day, the post transfusion haemoglobin being 7.9G/dl. Prednisolone was started at a dosage of 15 mg 6-hourly from the tenth day.

The platelet count, which had been 30,000/ul on admission, dropped to 10,000/ul on the 9th day but platelet transfusion was considered inappropriate at that time.

The situation changed significantly on the 14th hospital day when he was found to have petechial haemorrhages chiefly in the lower limbs. He was conscious but showed no response to questions or commands and had a mimimal right-sided hemiparesis. There was no neck stiffness and Kernig's sign was absent. The pupils were equal and reacted to light.

6 units of platelets were transfused as an emergency measure and his neurological signs showed a remarkable remission on the 15th day and the improvement was maintained for 3 days.

He was given 2 units of packed cells on the 16th day and 2 units of fresh blood on the 17th day. The reticulocyte count on the 16th day was 20% and the haemoglobin was 6.6G/dl. The post-transfusion haemoglobin on the 18th day was 10.4G/dl.

On the 18th day he was noted to be drowsy and sweating excessively and his condition remained the same over the next 18 days with poor response to commands and monosyllabic answers to questions. Towards the end of this period he became rational and

HOSPITAL DAY	PLATELETS x10³/ul	G. Hb/dl	DIPYRIDAMOLE mg/day	PREDNISOLONE mg/day	UNITS TRANSFUSED
1	30	5.6			
7					2 (fresh blood)
9	10				
10		7.8		60	
14				↓	6 (platelets)
16	30	6.6			2 (packed cells)
17					2 (fresh blood)
19				45	
21				30	
22				20	
23				15	
24				10	
25	55	9.2		↓	
30				7.5	
36	95		300	20	
37			↓	30	
39	75	9.9		↓	
44			400		
52			↓	45	
59	225	9.3		↓	
61				30	
66				20	
67	400			↓	
73			300		
76			200		
80			100	15	
83	280		50		

FIGURE 1. Progress and Therapeutic Measures during the period of first hositalisation

complained of blurring of vision in the right eye and numbness in the right leg. (This illustrates the feature of fluctuating, neurological signs which is characteristic of the disease). Ophthalmic examination revealed the following:

Right eye: Visual acuity 6/60. Diffuse retinal haemorr hages of the dot-and-blob type peripherally and flame-shaped near the posterior pole. There was also a sub-hyaloid haemorrhage with macular oedema.

Left eye: Visual acuity 6/6. Small areas of haemorrhage seen near the disc.

Vitmains K and C were started at doses of 10mg t.d.s. and 100 mg t.d.s. respectively on the 38th day.

Meanwhile, dipyridamole was started at a dose of 100 mg t.d.s. on the 36th day and increased to 100 mg 6-hourly on the 44th day. Also on the 36th day prednisolone, which had been tailed down to 2.5 mg t.d.s., was increased to 5 mg q.d.s. His neurological state and general condition began to improve the day after dipyridamole was started. Meanwhile he developed an infected perineal haematoma which burst in a few days and for that he was covered with parenteral Ampicillin and Cloxacillin. The dipyridamole was reduced to 100 mg t.d.s. on the 73rd day and to 50 mg over the next week.

His general condition remained satisfactory and he was discharged home on the 83rd hospital day (24.2.75) when his platelet count was 280,000/ul and his perineal wound was clean. The therapeutic regime on discharge was:

Dipyridamole 50 mg OM
Prednisolone 5 mg t.d.s.
Vitamin C 100 mg t.d.s.
Vitamin K 10 mg t.d.s.

Outpatient Management

He remained asymptomatic with a platelet count of 220,000 when seen a week later. Dipyridamole was then taken off and he was maintained on prednisolone 5 mg t.d.s. which was later tailed off and discontinued over the next 6 weeks. The vitamins were not prescribed after his first outpatient attendance. His general condition and platelet counts remained satisfactory during the 10 months following discharge.

However, when seen on 26.1.76, his haemoglobin was 9.8 G/dl and the platelet count was 55,000/ul. He felt well and refused admission and was therefore started on dipyridamole as an outpatient at a dose of 100 mg t.d.s. He was also given prednisolone 5 mg t.d.s. When seen a week later, his haemoglobin was 10.8 G/dl and platelets 100,000/ul. A month later, his platelets were 60,000/ul and the haemoglobin 11.7 G/dl. The reticulocyte count was 3%. Over the next nine months his platelet counts ranged from 150,000/ul to 235,000/ul and he was taken off steroids and dipyridamole in November and December, 1976 respectively. He remained well for a year and five months after treatment was discontinued.

RELAPSE

Clinical Findings

He was re-admitted on 23.5.78, three years and five months since first seen, with a three-day history of jaundice, tea-coloured urine, dark stools and exertional dyspnoea. There had been no self-medication and he had not taken any alcohol since his previous admission.

He was febrile, pale and jaundiced and there were petechiae and ecchymoses over the abdomen and thighs. The liver edge was 3cm below the costal margin and the spleen was palpable to a depth of 2cm. The blood pressure was 150/70mm Hg. The other systems including the central nervous system were normal.

Investigations

Hb 6.8 G/dl, TW 15,000/ul, Platelets 20,000/ul, Reticulocyte count 40%.

Peripheral blood film: Nucleated RBC 25/100 WBC, macrocytes, densely stained microcytes, polychromatic cells +, poikilocytes+.

Partial Thromboplastin Time/Prothrombin Time: Normal.

Direct Coombs Test: Negative.

L.E. Cells x 2: Negative

Liver Function Tests: S. Bilirubin 3.0 mg/dl
SGPT 9.7 I. U/L (Normal $<$ 30 I.U./L)

Urine test for bile: Nil

Urobilin: Trace

Urobilinogen: +

Blood urea 60 mg/dl.

Treatment and Progress

He was given intravenous hydrocortisone 100 mg 8-hourly from the second to the fifth hospital day. Prednisolone was started on the third hospital day at 5 mg tds and increased to 10mg qds on the fifth day. The drug was tailed down from the 14th day until he was getting 5mg bd at discharge on the 34th day. 1 unit of fresh blood was transfused on the third day.

He soon improved and was discharged on the above dose of prednisolone and dipyridamole 75mg tds.

He was well when reviewed as an outpatient. When seen on 5.3.79 his Hb was 13.6G/dl and the platelet count was 180,000/ul. His treatment then was dipyridamole 75mg b.d. and prednisolone 5 mg OM.

Discussion

Rational treatment should be based on an understanding of the aetiology. There is agreement that the nodal point of the disease is a microangiopathic coagulopathy primarily involving platelet consumption (Amorosi and Karpatkin 1977; Amorosi and Ultamann 1966; Zacharski et al 1976).

The trigger factor is not known for certain. There is some subintimal deposition of PAS — positive material and endothelial damage (Amorosi and Karpatkin 1977; Lerner et al 1967). There is no vasculitis (Amorosi and Ultmann 1966). The vascular damage could be of auto-immune origin although there has been no proof of this to date. Also, transfusion of plasma from TTP patients to normal people does not produce thrombocytopaenia unlike in Idiopathic Thrombocytopaenic Purpura (Zacharski et al 1976). Many patients have a prodromal stage of respiratory or gastro-intestinal illness as in our patient and bacterial or viral agents have been suspected to have been the cause but no proof of these suspicions has been obtained.

The anaemia is of the microangiopathic haemolytic type (Wintrobe, 1974) and the coagulation does not primarily involve fibrinogen. Fibrinogen levels are normal and fibrin degradation products are only slightly elevated (Lerner et al 1967; Giromini et al 1972; Zacharski et al 1976).

Steroids with splenectomy is a therapeutic regime that has been reported to be successful. (Goldenfarb and Finch 1973). This response would favour an auto-immune basis for the disease. Steroids have a lympholytic effect and also are bound to lymphocytes so that the latter lose the ability to interact with platelets, phagocytose or synthesise antibody (Zacharski et al 1976). Splenectomy removes a very vascular organ which would trap damaged corpuscular elements. Against this must be weighed the report of TTP in a previously splenectomized patient and the known anti-platelet effect of anaesthetic agents (Zacharski et al 1976). Failures on this regime are also known (Amorosi and Karpatkin 1977) and the dangers of steroid therapy have to be remembered.

Following up on the possibility of a toxic substance damaging the endothelium and/or the platelets, exchange transfusions have been employed with a fifty-four percent success rate (Bukowski et al 1976).

The two operative procedures described here have disadvantages: they are not uniformly successful, they carry an appreciable risk in a patient with a bleeding diathesis and cannot be carried out where skilled surgical and medical teams are not available (as in peripheral hospitals).

In this context, the success of anti-platelet drugs with or without corticosteroids as in our patient and in others is heartening (Amorosi and Karpatkin 1977; Rossi et al 1974). We now have a simplified outline of the events in

platelet aggregation (Pitney 1972). Initial damage exposes the collagen of the subendothelial tissue to which platelets adhere. The adherent platelets, damaged vessel walls and red cells then liberate ADP which causes primary platelet aggregation. The exposed sub-endothelial tissue releases thromboplastin which results in thrombin formation. The thrombin and a labile prostaglandin intermediate, convert the primary platelet aggregate to an impermeable platelet plug containing fibrin. Platelets in the non-aggregated state are wrinkled due to the energy released by ATP when this is converted to ADP. Where there is an excess of ADP, this conversion is inhibited and there is less energy available to the platelet membrane which therefore does not contract or wrinkle. Aggregation is then facilitated.

The role of anti-platelet drugs in preventing aggregation is explained by Amorosi and Karpatkin (1977) and can be understood by their actions at the various stages of the above sequence.

Platelet adherence to the vessel wall is strongly inhibited by sulphinpyrazone which is also a mild inhibitor of the platelet release reaction. The latter reaction is potently blocked by aspirin which acetylates prostaglandin synthetase. Dipyridamole raises the cyclic AMP levels of the platelets by inhibiting cyclic AMP phosphodiesterase. These high cyclic AMP levels are associated with inhibition of Primary and Secondary Platelet Aggregation. Cyproheptadine is bound to the platelet membrane, inhibits serotonin uptake and depresses Primary Platelet Aggregation. This drug was found to be the most effective prophylactic to thrombus formation under experimental conditions.

Lerner et al (1967) report successful treatment of a patient with steroids and clinical dextran. They suggest that dextran plays its part by coating platelets and vascular endothelium and thereby preventing aggregation.

Controlled clinical trials rather than anecdotal reports should ideally be the basis of treatment. Such trials are difficult in a disease such as TTP which is rare and of variable severity. Until further information is available it seems reasonable to use one or more anti-platelet drugs which are safe and appear to be effective. In view of its safety and proven efficacy in clinical situations we would stress the value of dipyridamole.

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