Defibrination syndrome

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Summary

Three cases of defibrination syndrome and bleeding tendency are described. In each case the aetiology was completely different but thrombocytopenia and fibrinogenopenia were present together. This combination is invariably due to diffuse intravascular clotting and it is suggested that these simple investigations should be asked for in cases of unexplained shock, acute renal failure of obscure origin, severe intravascular haemolysis, septic abortions, etc.

Heparin would appear to be of value in these cases of defibrination.

However, if there is no thrombocytopenia, defibrination may be due to excessive fibrinolysis. This should be treated with anti-fibrinolytics only when an underlying clotting defect has been excluded.

Introduction

Defibrination syndrome and diffuse intravascular clotting have been the subject of many articles, symposia and monographs (Hardaway, 1966; McKay, 1965; *Thrombosis et Diathesis Haemorrhagica*, 1967). Rosner & Ritz (1966) have listed forty different causes of defibrination but do not include malaria. Lasch, Roka & Heene (1966) classified various causes of defibrination into two: (1) diffuse intravascular clotting, and (2) excessive fibrinolysis. They found that platelets and certain platelet factors were reduced if defibrination was due to coagulation, while fibrinogen breakdown products were excessive if the defibrination was due to excessive fibrinolysis. However, intravascular clotting can produce excessive fibrinolysis and thus complicate the picture (Merskey *et al.*, 1964). In such a case, if the clotting tendency is overlooked and fibrinolysis inhibitors administered, the underlying hypercoagulable state may be dangerously aggravated.

In this paper three cases of defibrination syndrome and renal impairment each with thrombocytopenia and fibrinogenopenia are described. One of these cases was due to a heavy infection by *Plasmodium falciparum*.

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Case reports

Case No. 1

A man aged 57 years had been well until 3 weeks before admission. He had two attacks of dyspnoea each lasting for 1 hr and separated by 1 week, and vague abdominal pain. When admitted on 17 July 1966 he had severe pain in his legs and bloody diarrhoea. He was very ill and dehydrated. Purpura was present over the abdomen and there was a left black eye. Pulse, 160/min, fibrillating; blood pressure 85/50 mmHg. Femoral pulses were present but dorsalis pedis pulses were very faint. He was unable to move his legs which were hyperaesthetic, cold, blue and slightly oedematous. Bilateral crepitations were present in the chest. He had central abdominal tenderness but no guarding. Next day the purpura was more extensive and much bruising had occurred at the sites of venepuncture. His laboratory investigations (Table 1) indicated the presence of acute renal failure and defective coagulation. In spite of pressor drugs, hydrocortisone and antibiotics, his condition remained unchanged. In 24 hr he passed 300 ml of albuminous urine. Heparin and peritoneal dialysis were started on 19 July 1966 but he died 2 days later.

Necropsy was performed 22 hr after death: The body was well nourished but covered with widespread petechiae. The left toe was gangrenous. The parietal peritoneum showed blotchy haemorrhages. Both cardiac ventricles were hypertrophied and there was a fibrinous pericarditis. Masses of ante-mortem thrombus were present in the atrial appendages and left ventricle. The thoracic aorta showed a few atheromatous plaques but the entire abdominal aorta was partly filled with an organizing adherent cylindrical thrombus (Fig. 1) forming knuckle-like projections into the orifices of the main renal arteries. The upper branch of the left pulmonary artery and the terminal branches of the right pulmonary artery contained impacted thrombi. Femoral and other vessels were normal. The bronchi contained a little mucus. The liver (1150 g) and spleen (250 g) were congested. The splenic flexure of the colon was infarcted.

TABLE 1

	Case 1 (1966)		Case 2 (1966)		Case 3 (1965)	
	17 July	20 July	30 May	20 June	31 January	10 February
Haemoglobin (g/100 ml)	15.7	10.7	14.9	12.0	14.0	10.0
White cell (mm ³)	17,000	8,000	5,000	Normal	23,000 (Eosin. 7660/mm ³)	15,000 (Eosin. 4420/mm ³)
Platelets (mm ³)	40,000	20,000	10,000	310,000	12,000	28,000
RBC morphology	Fragmented ++		90% contained <i>P. falciparum</i>	Normal	Fragmented RBC+	Normal
Reticulocytes (%)	8	10			4	
Direct Coombs' test	Negative				Negative	
Prothrombin time (control 11 sec)	60		120	11	15	11
Fibrinogen level (mg/100 ml)	20		20	250	50	250
Fibrinolysis	Normal	Normal		Normal	Normal	
Thromboplastin generation time (control 7 sec)	15			7	8	
Deficient factors	II, V, VIII, X			None	V, X	
Blood urea (mg/100 ml)	384	452	92	22	56	58
Na (mEq/l)	130	122	143	Normal	Normal	—
K (mEq/l)	6.4	5.6	9.1	Normal	Normal	—
Cl (mEq/l)	85	83	97	Normal	Normal	—
HCO ₃ (mEq/l)	18	16	14	Normal	Normal	—
Bilirubin (mg/100 ml)	1.0		1.9			
Liver function tests	SGOT 620	Normal	Normal		Normal	Normal

Histology. Section of the heart showed thrombi, oedematous myocardium and several venules containing masses of fibrin, but no active inflammatory changes. The lungs showed focal bronchopneumonic consolidation.

The majority of the glomeruli were swollen and bloodless, and many of these exhibited conspicuous fibrin thrombi lying in the capillary tufts. A few glomeruli appeared individually almost completely infarcted as a result of plugging by fibrinous masses at the base of the tuft. These changes were similar to those seen in experimental and human Schwartzman phenomenon (McKay 1965; Skjorten, 1966). The spleen was congested. The liver showed venous congestion, haemosiderin-laden macrophages and early central lobular fibrosis. The aorta showed organizing thrombus and a few vasa vasorum also contained fibrin plugs. The testis (Fig. 2) showed fibrin thrombi in small vessels and capillaries. The brain, spinal cord, pancreas, adrenal, thyroid, pituitary and vertebrae were normal. Skeletal muscles showed haemorrhages.

Case No. 2

An Englishwoman, aged 40 years, developed pyrexia (102°F), vomiting and mild jaundice on 29 May 1966, 11 days after her arrival from Bulawayo. She was rested at home with a diagnosis of infective

hepatitis. On 30 May 1966 she was admitted to hospital in a collapsed state. Her blood pressure was 50/40 mmHg, pulse 100/min (regular) and temperature 101°F. Apart from bruising, especially at the sites of venepunctures, and hepatomegaly no other physical signs were detected. Blood for cross-matching failed to clot for over 1 hr. Laboratory investigations (Table 1) showed heavy infection with *Plasmodium falciparum* and defective coagulation. She was treated with intravenous chloroquine, heparin, hydrocortisone and pressor drugs. Fresh-frozen plasma (800 ml) was infused to replace the depleted coagulation factors. In the next 48 hr she made considerable clinical, haemodynamic and haemostatic recovery but her blood urea rose to 285 mg/100 ml. Heparin was discontinued and she had a peritoneal dialysis during the next 10 days with a slow return of her blood urea to normal. She was discharged well on 26 June 1966.

Case No. 3

A young Englishman, aged 18 years, was admitted to hospital on 31 January 1965 complaining of pyrexia, haemoptysis, rectal bleeding, a purpuric rash and painful right arm and both legs. Seven days prior to this he had had pharyngitis treated with tetracycline. On examination, he appeared very ill, pulse 100/min regular, blood pressure 125/80 mmHg.

FIG. 1. Aorta and kidneys with a large thrombus in aorta (Case 1).

Temperature 99.8°F. He had purpura on the legs, bilateral bronchial breathing and a pleural rub, but no hepatosplenomegaly. Cardiovascular and nervous systems appeared normal. Laboratory investigations (Table 1) showed thrombocytopenia, eosinophilia and defective clotting. A chest X-ray showed patchy opacities suggestive of infarcts. Sternal marrow puncture showed eosinophilia and plentiful megakaryocytes. Tests for platelet antibodies or viral antibodies were negative but his ASOT was 1500 units. He was considered to be suffering from diffuse allergic vasculitis. He received steroids and anti-coagulants (heparin for the first month) for 9 months during which attempted withdrawal resulted in purpura, thrombocytopenia and eosinophilia. On 28 February 1965 the platelets were $150,000/\text{mm}^3$, with normal eosinophils. In November 1965 after cessation of therapy, a phlebogram showed complete obliteration of the right femoral vein. Since then he has remained symptom-free.

Discussion

An acquired deficiency of coagulable fibrinogen may be due to lack of fibrinogen production by a severely diseased liver, destruction due to excessive fibrinolysis or interference by heparin. However, the commonest cause is excessive fibrinogen consumption in intravascular clotting (Merskey *et al.*, 1967). This, unlike liver disease and heparinaemia, is difficult to diagnose.

Lasch *et al.* (1966), found that a reduction of prothrombin, fibrinogen and Factors V and VIII was common to both diffuse intravascular clotting and excessive fibrinolysis; but thrombocytopenia

FIG. 2. Photomicrograph of testis (Case 1), showing fibrin thrombus in a small vein. Lendrum's stain, $\times 140$.

and reduction of platelet enzymes (e.g. adenosine triphosphatase) differentiated diffuse intravascular clotting from excessive fibrinolysis in which circulating fibrinogen breakdown products occurred excessively. Detection of platelet enzyme deficiency or increased fibrinogen breakdown products is beyond the scope of an average hospital laboratory, but the simple finding of co-existing thrombocytopenia and fibrinogenopenia nearly always indicates diffuse intravascular clotting. Thrombocytopenia and fibrinogenopenia were present together in these three cases. It seems probable that in Case 1 bronchopneumonia initiated a consumption coagulopathy resulting in a haemorrhagic diathesis.

The renal lesions and diffuse thrombosis in Case 1 resemble experimental lesions of Shwartzman phenomenon (bacterial endotoxin shock) (McKay, 1966), but in rabbits consumption coagulopathy has also been produced by mismatched transfusion, drugs, intravenous infusion of tissue extracts and thrombin (Penick *et al.*, 1958; Rodriguez-Erdmann, 1965). Also, irreversible shock and diffuse intravascular clotting have been produced in dogs by protracted venesection (Hardaway, 1966). In Cases 1 and 2, therefore shock may have been partly responsible for defibrination. Dennis *et al.* (1967) have shown depletion of coagulation factors in drug-resistant *Plasmodium falciparum* malaria and Hill, Knight & Jeffrey (1964) found thrombocytopenia in volunteers with quartan malaria. Thrombocytopenia and fibrinogenopenia in Case 2 would appear to be due to defibrination. In such cases, excessive haemolysis especially if intravascular can liberate sufficient erythrocytic thromboplastic material (Quick & Hickey, 1960) to produce intravascular clotting. In Case 2, heparin was discontinued after 48 hr but Dennis *et al.* (1967) have shown heparin and anti-malarials to produce a return to normal haemostasis much sooner than when anti-malarials were used alone in cases of blackwater fever. The role of heparin as the treatment of choice in such

bleeding diathesis is also illustrated by Case 3 in whom any attempted withdrawal resulted in thrombocytopenia and purpura.

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