Purpura fulminans with haemolytic anaemia

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Summary

A 10-month-old female infant with purpura fulminans is reported. The patient had clotting abnormality compatible with consumption coagulopathy. Histopathological examination revealed the presence of microthrombi. Heparin was effective in correcting the clotting defects. The infant also suffered from microangiopathic haemolytic anaemia. She died 17 days after the onset of the illness from infection in spite of antibiotic therapy.

PURPURA fulminans is a rare but catastrophic and often a fatal disease of children with a mortality rate of over 90%. Death usually takes place within the first 48–72 hr. The survivors frequently suffer from a serious morbidity, and limb amputation is commonly required (Charkes, 1961; Fishbein, 1969). A preceding infection such as chickenpox, measles, scarlet fever, streptococcal pharyngitis, meningococcaemia and exanthems frequently occurs (Dunn, 1951; Chambers, Holyoke and Wilson, 1952; Bauhasin, 1964; Allen, 1966; Cram and Soley, 1968). The onset of the illness is abrupt with the appearance of ecchymotic purpuric areas, mostly in the lower extremities, with a striking symmetry. The purpuric areas progress rapidly, becoming dark in colour and end with tissue necrosis and gangrene. The trunk and upper extremities are rarely involved. Melaena, haematuria, involvement of the lung, spinal cord and sciatic nerve have been observed (Allen, 1966; Brown and Nelson, 1967; Dudgeon *et al.*, 1971). Apart from the characteristic external manifestations of the illness, the patient may suffer from fever, chill, haemorrhagic shock and coma.

Many authors have commented upon similarities between purpura fulminans and Schwartzman phenomenon as seen in experimental animals. These similarities are based on histological and laboratory studies. Histological examination in purpura fulminans has shown microthrombi of the small blood vessels with perivascular infiltration of the involved area (Heal and Kent, 1953). The blood clotting mechanism of these patients reveals defects similar to those seen with the so-called hypercoagulable state and purpura fulminans has been included in the growing list of conditions characterized by Disseminated Intravascular Coagulation (DIC). Little (1959) has suggested the descriptive eponym, Post-infectious Intravascular Thrombosis with Gangrene. On the assumption that thrombosis and consequent consumption of clotting factors is the basic defect in purpura fulminans, heparin with its antithrombin activity has been used in management.

This communication describes a 10-month-old female infant with a typical clinical picture and characteristic laboratory findings. In addition, at onset of the illness she was found to have a profound microangiopathic haemolytic anaemia.

Case report

K.R., a 10-month-old girl, was well until 10 days before admission to Mosul Children's Hospital, when she developed fever and cough. She responded initially to treatment with tetracycline but was admitted because of advancing ecchymosis of the right thigh. The past and family history were not contributory. Physical examination showed an acutely ill child with a temperature of 38°C; pulse, 100/min; respiration, 30/min; blood pressure, 80 mmHg and weight 7 kg. Positive findings were restricted to the right lower extremity where a large ecchymosis occupying most of the upper half of the thigh was situated on the medial side. Radial, femoral and popliteal pulses were palpable. The ecchymosis increased in size during the first 24 hr after admission and bullae developed at the periphery. The right thigh and leg were swollen. The patient looked toxic and moribund with oozing of blood from her mouth (Fig. 1). Laboratory data are given in Table 1. The peripheral blood film showed a large number of irregularly contracted and fragmented erythrocytes including triangular, helmet and pincered cells, an appreciable number of nucleated red cells and polychromasia (Fig. 2). These findings suggested that intravascular coagulation with a concomitant haemolytic anaemia was in progress. The patient was transfused with 150 ml of fresh blood and a continuous intravenous drip was started containing heparin 100 iu/kg body weight 4 hourly plus penicillin and chloromycetin. Twenty-
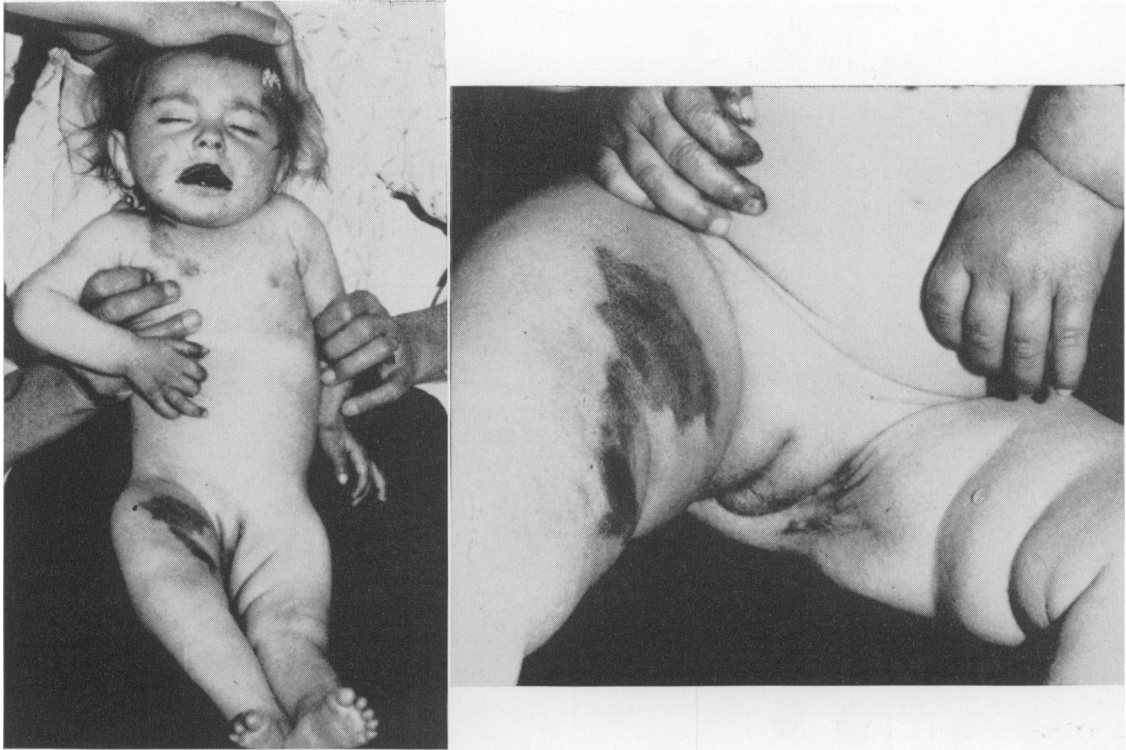
FIG. 1. Photographs of the patient on the second hospital day.

TABLE 1. Laboratory data

	Before heparin therapy	After heparin therapy
Haemoglobin	4·3 g/100 ml	14·3 g/100 ml
Packed cell volume	15%	47%
Mean corpuscular haemoglobin concentration	29%	30%
Reticulocyte count	10%	1%
White blood cell count	8200/mm³	5000/mm³
Red blood cell morphology	Marked fragmentation	Occasional distortion
Platelet count	50,000/mm³	120,000/mm³
Bleeding time	Excessively prolonged	6 min
Clotting time	> 1 hr	15 min
Prothrombin time	150 sec (control, 15 sec)	17 sec (control, 15 sec)
Partial thromboplastin time	360 sec (control, 60 sec)	106 sec (control, 65 sec)
Plasma fibrinogen	20 mg/100 ml	250 mg/100 ml

four hours from the onset of therapy she was less toxic with a normal temperature and the oozing of blood from the mouth had ceased. Seventy-two hours from the onset of therapy, coagulation studies, urinanalysis, blood urea, SGPT activity, serum protein electrophoresis and X-rays of the chest, right femur and leg, were normal (Table 1).

Heparin therapy was discontinued on the eighth day and 24 hr later, surgical debridement of the lesions of the right thigh was performed. There was extensive sloughing and necrosis involving the skin, subcutaneous tissues and muscle layers. Coagulation studies before and after surgery were normal and the patient tolerated the procedure well without excessive bleeding. Histological examination of the removed tissues showed thrombosis of small blood vessels with perivascular infiltration, damage of vascular endothelium and tissue necrosis (Fig. 3). Culture from the material showed growth of *Staphylococcus aureus* sensitive to gentamicin which
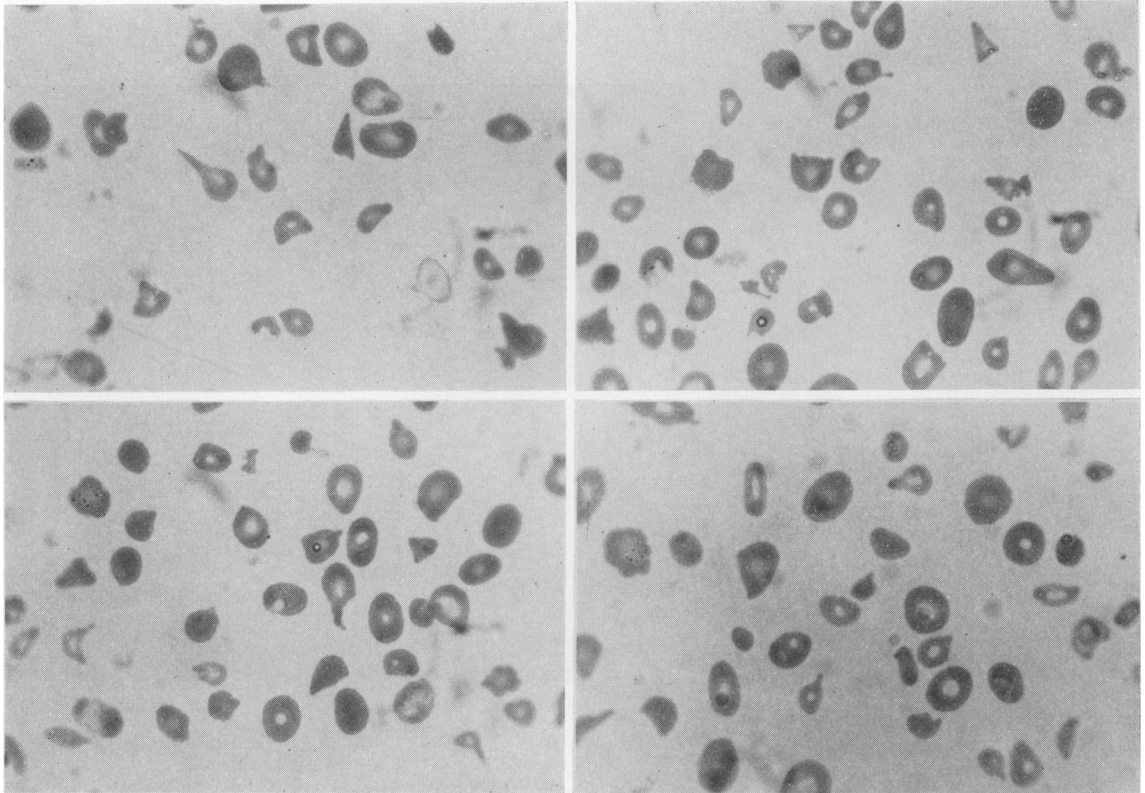
FIG. 2. Blood film of the patient before heparin therapy, showing fragmented and irregularly contracted erythrocytes (Leishman's stain × 630). (From different fields.)

was given from the twelfth day. One week after surgery she developed fever, lethargy and anorexia. On physical examination bilateral crepitations were heard and a diagnosis of septicaemia and pneumonia was made. Penicillin and chloromycetin therapy was resumed in addition to gentamicin but there was rapid deterioration in her general condition and she died 17 days after admission. Permission for autopsy was refused.

Discussion

Our patient fulfilled Hjort, Rapaport and Jorgensen's (1964) criteria for the diagnosis of purpura fulminans. (1) It is a disease of children; (2) it is preceded by a benign infection; (3) there is bleeding into skin after a latent period following the infection with rapid progression; (4) survivors after the critical period develop extensive skin necrosis following the blood coagulation abnormality with intravascular thrombosis; (5) thrombosis can be demonstrated in biopsy material from the involved area.

The aetiology of purpura fulminans remains unclear and the significance of the preceding infection

is uncertain. Deficiency of prothrombin, fibrinogen, platelets, factors V and VIII are the hallmark of the coagulation defects seen in cases of DIC (Rodriguez–Erdman, 1965). These deficiencies in the clotting factors have been repeatedly shown in recent studies with purpura fulminans (Little, 1959; Glass, 1962; Bauhasin, 1964; Allen, 1966; Antley and McMillan, 1967; Dudgeon et al., 1971). Our patient had prolongation of bleeding time, clotting time (more than 1 hr), prothrombin time ($2\frac{1}{2}$ min) and partial thromboplastin time (6 min) and a low platelet count 50,000/mm³ with a deficiency of fibrinogen (20 mg/100 ml) were found. Although facilities for factor V and VIII assays were not available, the pattern of tests is regarded adequate for the evaluation of DIC (Antley and McMillan, 1967, Dudgeon et al., 1971).

Heparin is regarded as the therapeutic agent of choice in the management of purpura fulminans (Rodriguez-Erdman, 1965; Antley and McMillan, 1967) and successful treatment has been reported by Little (1959) and others (Glass, 1962; Antley and McMillan, 1967; Hattersley, 1970; Dudgeon et al., 1971). We were able to correct the coagulation
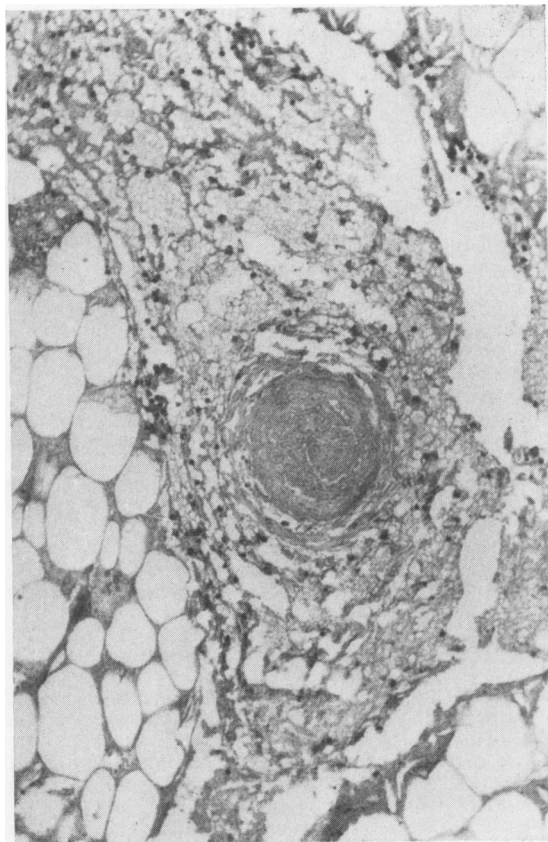
FIG. 3. Subcutaneous tissue from the affected area, showing thrombosis of a small blood vessel and cellular infiltration (haematoxylin and eosin × 252).

abnormality in this patient by using continuous intravenous heparin drip within 72 hr. Although 8 days of heparin therapy has been regarded adequate by Frederiks and Huffstadt (1970), others reported that premature cessation is followed by haemorrhage and clinical deterioration (Antley and McMillan, 1967; Hattersley, 1970).

Corticosteroids have been used in the treatment of purpura fulminans, although they seem not to be indicated since they potentiate the Schwartzman phenomenon. In practice they are found to provide no clinical benefit to successful therapy (Crawford and Riddler, 1959; van Creveld et al., 1965).

Treatment with blood and fibrinogen has been advocated and although this mode of therapy is theoretically contraindicated since it supplies substrates for intravascular thrombosis, the results vary from further deterioration to complete recovery (van der Horst, 1962; Bauhasin, 1964).

Low molecular weight dextran has been used successfully and the beneficial effects are attributed to coating of vessel walls and the blood elements with prevention of sludging (Patterson et al., 1965; Smith, 1967).

Morse, Rowe and Hartigan (1966) treated two cases by using antifibrinolytic agent (Epsilon amino-caproic acid) and both recovered. Excessive plasma fibrinolytic activity is seen with DIC and in these cases it is regarded as secondary or defensive fibrino-lysin with a protective role. Antifibrinolytic agents may be used in purpura fulminans, if it can be demonstrated that fibrinolytic activity is primary, since its use with secondary fibrinolysin consequent to DIC can be dangerous (Ratnoff, 1969; Seabaugh et al., 1971; Rodriguez-Erdman et al., 1971; McMillan, Weiss and Johnson, 1972).

Hyperbaric oxygen has been used with temporary improvement to save borderline necrotic tissues (Kuzemko and Loder, 1970; Dudgeon et al., 1971) and vitamins K, C and rutin have also been employed (Chambers et al., 1952).

Anaemia is frequently associated with purpura fulminans and is usually attributed to external loss and extravasation. This patient had severe anaemia which was secondary to blood loss and a micro-angiopathic haemolytic process. The evidence for this type of anaemia was the grossly distorted and fragmented erythrocytes, normoblastaemia and a high reticulocyte count. In our review of the literature on purpura fulminans, its association with micro-angiopathic haemolytic anaemia is mentioned only twice (Hollingsworth and Mohler, 1968; Dudgeon et al., 1971). However, if carefully sought, it may be determined more frequently in view of the known association with conditions characterized by intra-vascular coagulation and fibrin deposition (Brain, Dacie and Hourihane, 1962).

This patient died in spite of the fact that the clotting abnormality was corrected and surgical debridement satisfactorily tolerated. Septic death in purpura fulminans has been reported and secondary infections of the skin lesions by both Gram-negative and Gram-positive organisms have also been observed (Hollingsworth and Mohler, 1968; Dudgeon et al., 1971). The nature of this enhanced suscepti-bility to infection remains unknown.

Acknowledgments

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