PSEUDOTUMOUR IN CHRISTMAS DISEASE

OPERATIVE AND MEDICAL MANAGEMENT

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Pseudotumour of haemophilia is a well-recognized though rare condition. A large tumour-like mass develops slowly, either spontaneously or else following trauma. The femur is the most commonly involved site[1] though several other bones have been affected, e.g. ilium,[14] tibia,[9] olecranon and thumb.[10] Of 26 patients known to have had this disease, 12 died following surgery, and 3 without surgery.[11]

Enormous dimensions may be reached, and acceleration of the process appears to follow attempted aspiration. Sometimes the enlargement ceases, and the pseudotumour may then remain unchanged for very long periods of time. More usually, relentless growth results in pressure effects, and infection of the clot may occur. A misdiagnosis of sarcoma or osteomyelitis is frequently made.

The patient reported here suffered from proven 'Christmas' disease, and his pseudotumour had been present for about 3 years before admission to Groote Schuur Hospital.

MATERIAL AND METHODS

A human factor IX concentrate designated 'CSB' was supplied by the Paris Centre National de Transfusion Sanguine.[17] It varied in strength, and a check assay was carried out on each batch before use, in all instances agreeing closely with Dr. Soulier's assays. It is supplied as a powder which should preferably be kept at 4°C and is readily soluble in normal saline. There were no local or general reactions to 'fraction CSB'. This has now been replaced by a concentrate designated 'PPSB'.[17]

Blood samples before infusion were taken through the existing needle, and immediate post-infusion samples from the other arm 10-15 minutes later.

Methods

Lee and White clotting time, one stage prothrombin time, thromboplastin generation test, and Christmas factor assays were done by the methods of Biggs and Macfarlane.[6]

Case History

A.T., a White male aged 21 years, was referred to this hospital on 12 June 1962 with a grossly enlarged left thigh. He had been shown to have Christmas disease by Dr. Merskey in 1956, having bled from the umbilicus on the 10th day of life, and had thereafter suffered numerous bleeding episodes including haemarthroses.

Three years before his admission a haematoma had developed without any trauma on the medial aspect of the left thigh. This had grown slowly and had not been treated for the first 2½ years, by which time the thigh measured 28 in. in circumference. Attempts were then made elsewhere to aspirate the mass. Thereafter it appeared to increase more rapidly in size, and the haematoma extended along the left flank to the axilla. He had received 27 pints of blood during 1962 before his admission.

Two weeks before admission pressure necrosis of the skin above the left knee occurred, and a blood clot exuded (Fig. 1). He had recently become jaundiced.

He had 2 brothers. One was haematologically normal, but the other died of haemorrhage following dental extraction at the age of 6 years. There was no family history of haemophilia.

On examination he was pale, jaundiced and pyrexial. The striking finding was the enormous swelling of the left thigh (circumference 36 in.) which superficially resembled a sarcoma (Fig. 1). There was a one-finger hepatomegaly. Other systems were normal. The haemoglobin was 7·0 G/100 ml. and both bilirubin and urobilinogen were present in the urine.

X-ray of the left femur showed a curious deformation of the shaft, and radiating septa of calcification extending deeply into the haematoma (Fig. 2).

Investigations. Hb. 7·0 G/100 ml. VPRC 20%. MCHC 35. WBC 9,200/cu.mm., polymorphs 82, lymphocytes 18. Platelets 220,000/cu.mm. Quick one-stage prothrombin time 16 secs. Lee and White clotting time 9 min. Thromboplastin generation test: gross defect of serum factors. Serum total bilirubin 3·1 mg./100 ml.; conjugated bilirubin 2·0 mg./100 ml.; serum albumin 2·7 G/100 ml.; globulin 2·9 G/100 ml.; serum alkaline phosphates 16·6 KA units. Zinc turbidity 9 units, thymol turbidity 1 unit. Blood urea 18 mg./100 ml. Plasma haptoglobins absent.

He was diagnosed as suffering from pseudotumour complicating Christmas disease, with probable homologous serum jaundice. It was possible that a mild ABO incompatibility during his numerous transfusions had depleted the haptoglobins.

Treatment was at first expectant. It was not possible to raise his Hb. above 7 G/100 ml. by tranfusions. Steady loss of blood and serum from the area of necrosis continued, which could not be controlled by either plasma or serum intravenously, at 2 l./day. His one-stage prothrombin time improved slowly to 12 seconds following intravenous vitamin K.

He ran a high fever, and his jaundice deepened. One week after admission paralysis of the left leg and gangrene of the left foot developed. He appeared terminal. Prednisolone, 40 mg./day, was then given in an attempt to improve hepatic function, and his general condition and jaundice improved dramatically.

Following correspondence with Dr. Biggs of Oxford, and most helpful advice from her, it was discovered that a concentrate of human Christmas factor was commercially available from Dr. J. P. Soulier of Paris ('fraction CSB'). It was decided to amputate the patient's leg under cover of this concentrate, as there seemed no chance of survival with conservative management.

Disarticulation at the hip was performed by Prof. J. H. Louw on 24 June 1962. Supplies of concentrate were rather limited, and were withheld until this procedure was completed in order to conserve supplies. Loss of blood was replaced up to this point by transfusion. A dose equivalent to 3 l. of plasma was then given, with immediate haemostasis (Figs. 3 and 4).

Thereafter doses of concentrate were given in accordance with assay results and haemostasis remained adequate for 6 days, though blood levels and the half-life were below expectation so that more concentrate had to be given than was anticipated. A proteus was cultivated from the depths of the blood clot in the amputated leg (Fig. 5). On the 3rd day he developed klebsiella pneumonia, and staphylococcal septicaemia on the 6th day. For these infections the appropriate antibiotics were given by mouth or intravenously.

An insignificant haemorrhage from the wound on the 4th day was followed by a larger bleed on the 6th day. By the 8th day it was apparent that the half-life of the concentrate was well below expectation. A summary of doses given and the life of the concentrate at a late stage showed that the fall-off at 6 hours was 61% (Table I). In view of this, no further con-

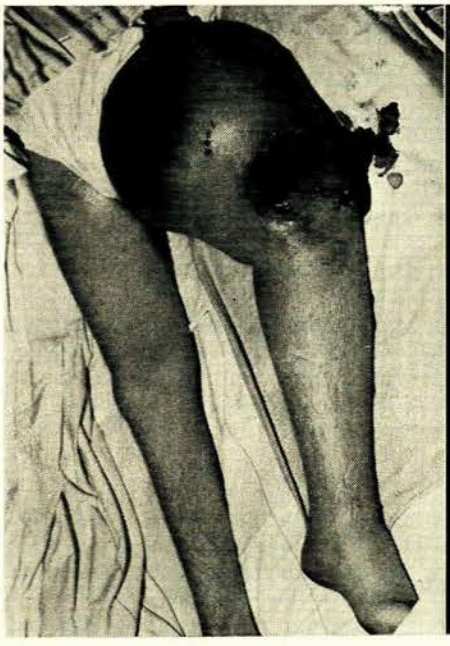
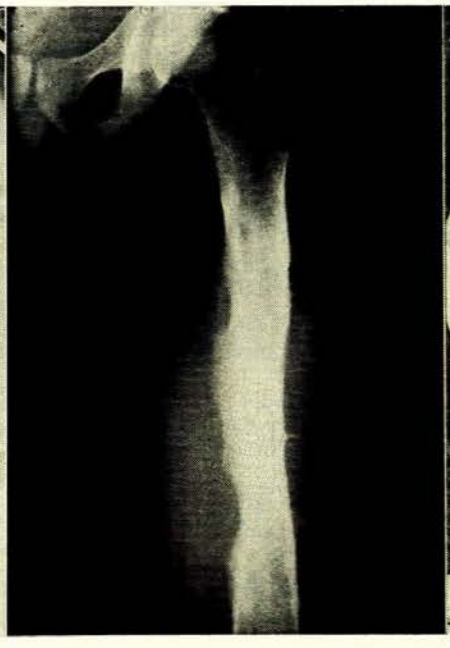


Fig. 1. See text.



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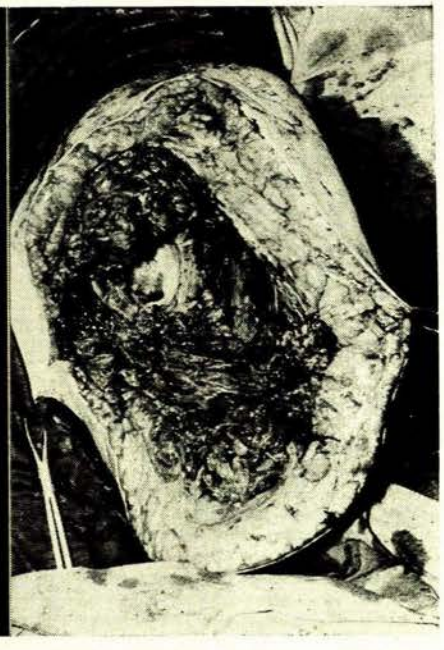

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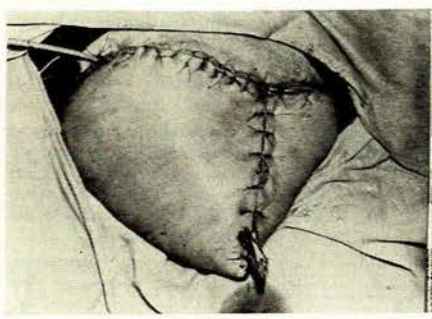

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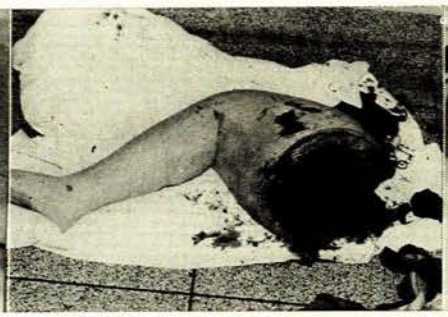

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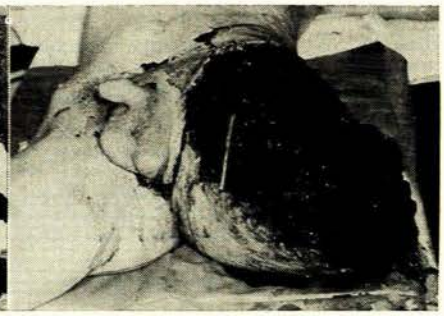

Fig. 6. See text.

centrate was given from the 8th day onwards, but 2 l. or more of plasma were continued daily.

TABLE I. FALL-OFF RATE AT 6 HOURS

From	*To*	*Fall-off*
%	%	%
34	11	68
24	11	54
27	11	59
25	8	68
18	5	72
15	8	47
		Average: 61

On the 17th day a massive haemorrhage tore open the healing wound. Further supplies of concentrate had now come to hand, and secondary suture was performed by Mr. W. Roberts. Once more adequate haemostasis was obtained, but coliform organisms and a staphylococcus were cultivated from the open wound (Fig. 6).

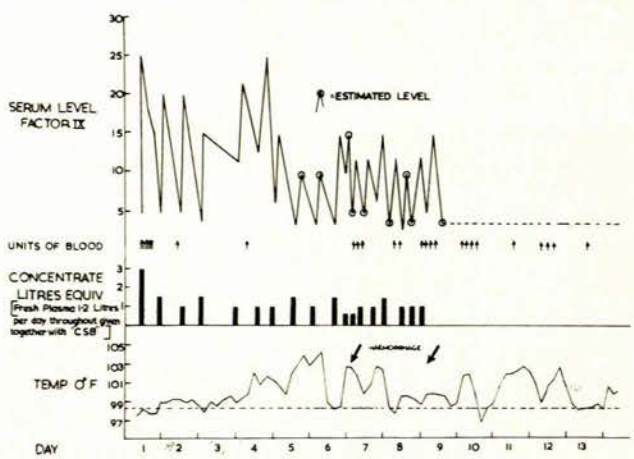

Fig. 7. See text.

While supplies of concentrate lasted, haemostasis was adequate. Dr. Biggs, of Oxford, kindly contributed her emergency dried supply of concentrate as well, but nevertheless supplies ran out on the 25th day (Fig. 7). On the 26th day haemorrhage again disrupted the wound and it was apparent that further surgical procedures would be ineffective. Dr. J. P. Soulier suggested the use of epsilon amino caproic acid (EACA) and through the courtesy of Lederle Laboratories a large supply of this drug was obtained on the 24th day, and was given in doses rising to 24 G daily by the 26th day. From the time of the second haemorrhage there was a steady blood loss of 500-1,000 ml. daily, and it did not seem that EACA or plasma checked this at all.

A final supply of Dr. Soulier's concentrate came to hand on the 35th day, and was used, but recurrent haemorrhage continued from the chronically infected wound.

In the last fortnight of his life he complained of tenesmus and pain in the left iliac fossa. He died following a massive haemorrhage on 10 September 1962.

He had received 179 pints of blood and 330 units of plasma during his period of hospitalization.

At postmortem examination there was recent rupture of the femoral artery at the wound and an extensive infected haematoma along the left iliac vessels to the retroperitoneal area. A proteus was isolated showing the same sensitivities as that which had been found at the disarticulation (to kanamycin and chloramphenicol) and coliform organisms with the same range of sensitivity were also found.

DISCUSSION

Pseudotumour is a rare complication of haemophilia, 26 cases having been reported up to 1962.[11] Because of the rarity of the condition, recognition is often delayed while alternative diagnoses such as sarcoma and osteomyelitis are pursued. Recognition depends on a high degree of awareness.

The pathogenesis of this curious condition is uncertain, many having commenced without trauma. There seems to be a constant relationship to bone, and possibly the cyst commences subperiosteally or within the medullary cavity. Slow and inevitable extension is the rule, with compression of adjacent bone and soft-tissue fibrosis, locule formation, and calcification, and no true capsule is formed.

The greatest hazard these patients have to face is undoubtedly infection. This leads almost inevitably to septicaemia and death. Our patient's pseudotumour had become infected before he arrived, presumably through the area of necrotic skin above the knee (Fig. 1).

It would appear to be unwise to attempt aspiration of these haematomata. Full aseptic technique may prevent immediate infection but the cyst is under pressure and the puncture wound may not heal, infection then occurring readily. Should a haematoma be inadvertently aspirated, it would appear necessary to proceed rapidly to radical excision. Infection following aspiration is reported on several occasions in the literature.[13,14]

TREATMENT

Haemophilic haematomata will often resolve if intensive intravenous plasma therapy is used (2 l. or more per day). However, beyond a certain indefinable point resolution does not occur, and surgery is then essential.

It is now generally accepted that the level of the deficient factor must be brought above 25% and maintained there

for 10 - 14 days after the operation.[7] This can only be done if concentrates are used. Human concentrates appear to be safe and non-antigenic. Their use is of necessity confined to large centres where plasma levels can be regularly measured and the patient should be transferred to such a centre for surgery.

In calculating the dosage of concentrates, it is necessary to take into account the half-life of the factor concerned, the size of the compartment into which it dilutes, and the basal metabolic rate of the patient. The accepted half-life of factor VIII appears to be 12 hours, and of factor IX about 24 hours.[4,5,12] The factor VIII compartment appears to be the circulating plasma volume so that doses of AHG can be directly related to the calculated plasma volume. The factor IX compartment, however, appears to equal 3 times the plasma volume,[5,12] so that requirements are 3 times greater per dose than those of AHG. The longer half-life makes for less frequent doses.

The rise of 13·3%/litre of Dr. Soulier's concentrate is in close agreement with the rise of 12·2%/litre found by Biggs and Macfarlane[7] using their own concentrate of factor IX (Table II).

TABLE II. SERUM FACTOR IX INCREMENT AFTER INFUSION OF 'FRACTION CSB'

	Dose of plasma equivalent (ml.)	*Level %*		
		Before	*After*	*Rise %*
	2,000	(5)	21	16
	2,000	13	34	21
	1,000	11	24	13
	1,000	11	27	16
A	1,000	(11)	25	14
	500	8	18	10
	500	5	14	9
	500	(5)	15	10
	500	4	10	6
	500	3	10	7
	500	6	17	11
	10 litres			133

= 13·3% rise per litre.

A. These are sequential dosages at 6-hourly intervals. The bracketed figures indicate estimated levels.

The patient's blood levels of factor IX were initially far lower than those recommended by Biggs. This was no doubt due to the Gram-negative infection found at operation, which had caused an elevation of the BMR, and thus shortened the half-life of 'fraction CSB' from the 24 - 30 hours found by Loeliger and Hensen[12] to about 12 hours initially in this patient. There was, it is true, a very small haemorrhage from the wound on the 4th day, when levels were at all times above 10% but the first major haemorrhage occurred on the 6th day, by which time the half-life had decreased to 5 hours, and the highest levels attained were of the order of 10% (Fig. 8).

Owing to lack of supplies, we were unable to administer sufficient concentrate to bring him back to a safe condition, and he continued to bleed intermittently at these low levels.

The second course, after secondary suture, was more successful, in that there was no overt haemorrhage for the 8 days that supplies lasted, despite one 36-hour period when levels were at no time above 10%. At least in this patient, adequate haemostasis would seem to have been attained by intermittent levels of no more than 15%.

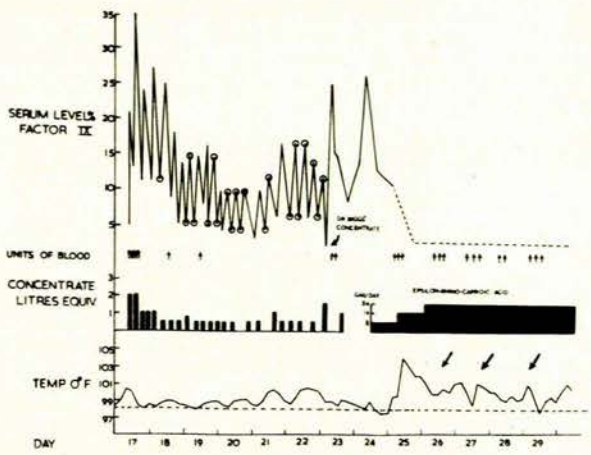

Fig. 8. See text.

Epsilon amino caproic acid (EACA) is a powerful inhibitor of fibrinolysis, apparently by direct inhibition of serum plasminogen activator.[8] It has been found to be of real value in haemophilia[15] but we unfortunately did not obtain supplies until haemorrhage had already disrupted the wound. It did not appear to help under these very adverse conditions. However it caused veins to clot that had been used for intravenous therapy so that it was not possible to use any vein more than once for infusions after the administration of EACA had begun. This may carry wider implications. Perhaps fibrinolysis is a continuing process in the normal patient, and is responsible for the clearing of small intimal clots after such minimal damage to vessels as occurs with venepuncture. Suppression of fibrinolysis would then lead to the rapid occlusion of such vessels.

Surgical technique in the haemophiliac carries special consideration. Gentleness, meticulous haemostasis and careful skin opposition are mandatory. A paste of concentrate applied directly to the wound surfaces at operation has been recommended.[11] This is thought to promote healing. It would seem reasonable to do this, if sufficient concentrate is available. Any clot that forms is a nidus for infection, which may delay healing and may tilt the balance towards haemorrhage at these times when the factor percentage falls towards 25%. Pressure does not help. It is the slow capillary ooze which is mostly to be feared. This will not be stopped by pressure, which will only force the blood into deeper planes, perhaps disrupting the wound and certainly delaying the healing process.

It is essential to avoid inspection of the wound unless this is absolutely necessary. There is always the danger of the adherent dressing, and its removal may cause haemorrhage. If disruption occurs it is best to avoid secondary suture if at all possible, allowing the wound to granulate from the bottom. For some reason granulation tissue does not bleed in haemophiliacs.[3] In our case, the open wound formed a large flat surface, and could not possibly have granulated, so that secondary suture was unavoidable.

Antibiotic therapy carries no special consideration, though intramuscular injections should not be given to haemophiliacs on general principles. It was possible to give the appropriate antibiotics by mouth or intravenously, with the exception of Colistin which is dangerous by the intravenous route and cannot be given orally.[2] To illustrate the great difficulty of eliminating infections in the presence of haematoma formation, it was not possible to sterilize his wound despite the use of antibiotics to which the infecting organisms remained sensitive until his death.

SUMMARY

A case of pseudotumour of the thigh in Christmas disease is described. The leg was amputated, but infection of the haematoma led to bleeding and shortened the half-life of administered concentrate. Secondary suture was followed by further bleeding, and sepsis around the femoral artery led eventually to its rupture and death from exsanguination. The medical and surgical management are briefly discussed.

We would like to thank Drs. R. Biggs and J. P. Soulier for their continued advice and assistance; Mr. J. R. Jordaan, South African Ambassador to France, for arranging for supplies of the concentrate to reach the airport on time; Lederle Laboratories who kindly donated a large supply of epsilon amino caproic acid; and Dr. J. G. Burger, Medical Superintendent of Groote Schuur Hospital, for willing advice and for permission to publish.

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