Uncontrollable bleeding due to Hypofibrinogenemia in a case of acute Myelo-monocytic Leukaemia

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HYPOFIBRINOGENEMIA is a fairly well documented but rare complication of acute leukaemia (Rosenthal et al, 1955; Pisciotta and Schulz 1955; Didisheim et al, 1964). Although acute pro-myelocytic leukaemia has been the usual recognised variety (Hillestad, 1967; Rosenthal 1963; Pittman, 1966) to give rise to this complication, other cytologic varieties have also been found to cause this (Baker et al, 1964; Hirsh et al, 1967). There still exists considerable uncertainty as to the exact mechanism or mechanisms by which a fibrinopenic state may complicate acute leukaemia. Knowledge of such mechanism is very important from the point of view of management as the method of treatment may depend on its nature.

Recently, such a rare complication was encountered in the University Hospital, University of Malaya, and the details of the patient are reported below to illustrate the various diagnostic difficulties and problems in management. This happens to be the only case with such a complication among 35 adult acute leukaemic patients seen and treated in this hospital between May 1968 and April 1970.

Case Report

J.S., a 20-year-old Eurasian bachelor was admitted to the University Hospital on 30th July, 1969, with complaints of swollen, bleeding gums for ten days and a warm, tender, reddish swelling of the right forearms below his elbow for three days. He had never had any similar bleeding tendencies before; however, five days prior to admission, he had sustained a minor cut over his right great toe from which he had bled for nearly 24 hours. There was no associated fever, sore throat, bone pains or easy bruising of the skin. There was nothing significant in his past, family or personal history. He had not been exposed to any radiation, chemicals or drug therapy.

On examination, he was found to be of fairly satis-

Table I. Results of Peripheral Blood Counts

Days after admission	1	3	4	6	8	10	13	17
1. Hb. (G/100 ml)	7.9	8.6	9.9	8.6	6.3	4.6	7.3	3.3
2. PCV (%)	23	26	31	23	20	15	21	9.5
3. MCHC (%)	34.4	33.2	31.9	37.4	31.4	30.6	34.8	34.7
4. Platelets (x 10^3/ul)	12	22	22	12	6	11	16	7
5. Leucocytes (/ul)	1,600	900	1,100	1,500	2,100	1,600	3,800	1,100
6. Diff. Leuc. Count (%)								
Blasts	20	22	46	38	41	86	59	20
Metamyelocytes	1	0	0	0	0	0	0	0
Neutrophils	16	16	40	18	12	6	9	30
Eosinophils	1	0	0	0	0	0	0	0
Lymphocytes	62	50	14	44	47	8	32	50
Nucleated R.B.C.	1	0	0	1	0	4	0	0
Degenerate Cells	0	12	0	0	0	0	0	0
7. Reticulocytes (%)	0.5				0.5	2	0.3	

factory general condition, although moderately pale and slightly icteric. There were no purpuric spots over his body nor had he any large lymph nodes. Both his upper and lower gums were swollen and haemorrhagic but his teeth were quite healthy. There was no evidence of pharyngitis or tonsillar involvement. He had a slightly warm, tender, fluctuant, oval, red swelling (measuring 8 cm. by 4 cm.) over the lateral aspects of his right upper forearm, and this was without doubt a haematoma. The right elbow joint was not affected. Examination of his cardiovascular, respiratory and nervous systems revealed no abnormality. His optic fundi were normal. On abdominal examination, however, his liver was just palpable but the spleen could not be felt. With such a short history and the physical findings, a provisional diagnosis of an active coagulation abnormality secondary to an acute leukaemic process was made and a number of investigations were carried out.

Investigations

The haematology results are tabulated in **Table 1.**

Urine Examination: Protein and sugar nil. Trace of urobilinogen present.

Microscopy: Rbc 36/ul. Wbc 3/ul.

Faeces: Occult blood positive.

Uric Acid 4.8 mg/100 ml. Serum proteins 6.9 gm/100 ml.

Albumin 4.0 gm/100 ml. Globulin 2.9 gm/100 ml. Alpha-l-Globulin 0.40 gm/100 ml. ALpha-2-Globulin 0.90 gm/100 ml.

Beta-1 and Beta-2-Globulin 1.05 gm/100 ml. Gamma-Globulin 0.25 gm/100 ml.

Total Bilirubin 2.3 mg/100 ml. Conjugated 0.2 mg/100 ml.

Unconjugated 2.1 mg/100 ml. S.G.O.T. 9 I.U./Litre.

S.G.P.T. 12 I.U./Litre.

Direct and Indirect Coombs Test negative. Bone Marrow Examination: Marrow was aspirated readily from the sternal manubrium. The films contained small grossly hypercellular particles and trails. Primitive cells predominated and were mostly blast cells with highly irregular nuclear and cytoplasmic structure. Although highly irregular and often having a monocytoid structure, the cells were almost all strongly peroxidase positive. They also showed weak, diffuse PAS reaction in the cytoplasm. Azurophil granules and Auer bodies occurred in many of the primitive cells. Myelocytes and metamyelocytes (including eosinophil) were present, but mature polymorphs were very scanty. The alkaline phosphatase score of the mature polymorphs was rather low (42), with predominance of low-scoring cells (score 0 = 65%, score 1 = 30%, score 2 = 3%). Erythropoiesis was relatively inconspicuous and showed macronormoblastic and some megaloblastiform features.

Megakaryocytes were very rare. Occasional lymphocytes and plasma cells were seen as well as abnormal haemohistio-blast-type reticulum cells. Iron was moderately abundant in the stores. This was an acute leukaemia of the myeloid series. There was very considerable structural variation, so that this most closely conformed to the Naegeli-type para-myeloblastic leukaemia or myelo-monocytic leukaemia. Serum Iron 224 ug/100 ml. Unsaturated Iron Binding

Table 2. Results of Coagulation Tests

Days After Hospital Admission	1	6,	10	11	13	Normal Values
1. Bleeding Time (mins) (Duke)	> 18				> 30	0–10
2. Clotting Time (mins) (Lee & White)	> 21				> 30	5–11
3. One-Stage Prothrombin Time (sec)	29	26	18			14
4. Prothrombin Activity (%) (based on dilution curve)		20	31			100
5. Thrombotest (%)	17	40	42			100
6. Tests for overactive fibrinolysis (a) Clot Lysis Time (Hrs)		6–10				No Lysis
(b) Thrombin Titre Test		Strongly Positive				
7. Fibrinogen (mg/100 ml)		120	100	100	50	150–400
8. Thromboplastin Generation Test		Normal	Normal			
9. Circulating Anticoagulants		Absent				

Capacity 141 ng/100 ml. Total Iron Binding Capacity 365 ug/100 ml. Folic Acid 6.8 ug/ml. B_{12} 3782 pg/ml. Unsaturated B_{12} Binding Capacity 4600 pg/ml. Bleeding Time more than 18 minutes. Clotting Time more than 21 minutes.

Chest X-ray: Heart size normal. Lung fields clear. The results of other investigations are given in **Table 2,** which includes the results of the various coagulation studies. All these tests were carried out by standard methods as recommended by Dacie. Plasma fibrinogen levels were estimated by turbidimetric method.

The diagnosis of acute myelomonocytic leukaemia was therefore confirmed by these laboratory tests, and there was no doubt that this patient had a rather serious coagulation disorder arising from his leukaemia.

The patient was transfused with 1.5 litres of fresh whole blood (F.W.B.) on the second day of his admission **(Fig. 1)** and the gum bleeding seemed to be slightly less the day after although he started developing spontaneous bruises all over his body. He was started on Prednisolone (1 mg/Kg.) 15 mg. four times a day and 6 Mercaptopurine (2.5 mg/Kg) 50 mg. three times a day, both orally, on the third day. Two more units of fresh blood of 500 ml. each were administered the same evening. His gum bleeding was slightly less. However, it continued to ooze for the next 48 to 72 hours, at the end of which, on the 6th

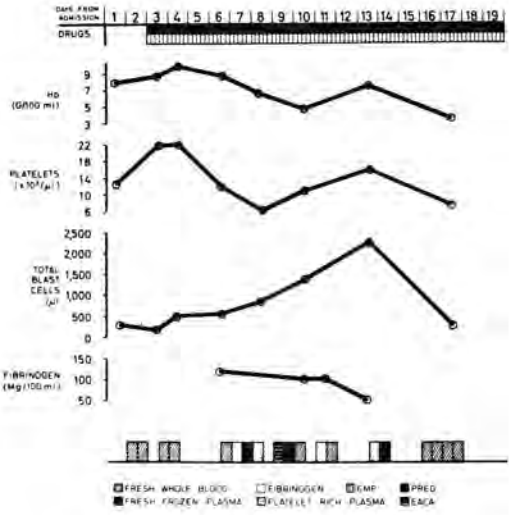

Fig. 1: Progress of the patient

day, he was given another unit (500 ml.) of fresh whole blood. At this stage, it was confirmed that his plasma fibrinogen was low and the next day he was given two units of fresh frozen plasma (F.F.P.) and six units of fibrinogen of 2 grams each intravenously over six hours. Although slightly less, the bleeding,

Table 3. Thromboplastin Generation Test to Screen the Plasma Coagulation Factors Activity.

Reagents	Incubation Time at 37°C (mins)					
	1	2	3	4	5	6
	Clotting Time in Secs. of the Substrate Plasma					
Normal Plasma) Normal Serum) Lipoid)	30	13	12	10	10	10
Patient's Plasma) Normal Serum) Lipoid)	27	12	12	11	10	10

The second T.G.T. also showed identical results

however, continued and he was given two units of platelet-rich plasma (P.R.P.) the day after as his platelet count was extremely low. On further evidence to treat him very cautiously with a modest amount of E.A.C.A. and he received 12 grams of E.A.C.A. (Amicar) intravenously over a 12-hour period on the ninth day after admission. This was followed by the administration of three units of F.F.P. and one litre of fresh whole blood, and his bleeding improved to a considerable extent. On the eleventh day, he was given another eight grams of fibrinogen over four hours and this was followed by two further units of fresh whole blood. His clinical condition remained unchanged but unfortunately it started deteriorating again two days later. He continued to bleed from his gums and fresh crops of purpura appeared on his body. Two units of P.R.P. were administered on the same afternoon. There was no great change and he received two more units of F.F.P. the following day. Unfortunately, no more fibrinogen could be made available, and as he was not responding to any form of treatment at all, the outlook seemed absolutely hopeless. His fibrinogen level continued to drop and his peripheral platelet count was only 7000/ml. Despite almost continuous fresh blood transfusion over the 16th, and 17th post-admission days, he had a fairly large intra-cranial haemorrhage as evidenced by extensive fresh bilateral haemorrhages in his vitreous and fundi on the evening of the 18th day. He vomited out some blood and gradually sank into coma. Bouts of melaena and passage of blood-stained urine followed. Oozing from nose and gums continued and he ultimately expired in his sleep on the 17th of August, 19 days after admission to hospital. No post-mortem examination could be carried out.

Discussion

In 1955, Rosenthal and his colleagues reported the development of hypofibrinogenemia in seven patients with acute promyelocytic leukaemia (Rosenthal et al, 1955). Later in 1963, he published his observations on more detailed studies of 17 patients with similar illness whom he had seen over the previous nine years. Almost all his patients had a very fulminating short illness, poor response to therapy, and were dead within a few weeks due to massive intracranial or gastro-intestinal haemorrhage (Rosenthal, 1963). Since then, this complication has been noted by various other workers interested in this field, and cytologic types other than the "acute promyelocytic" variety have also been reported to have this complication (Hirsh et al, 1967).

Current opinion views the fibrinogenopenia in acute leukaemia as resulting from:—

(a) Excessive consumption or utilisation of fibrinogen by multiple micro-thrombi in a disseminated intravascular hypo-coagulate state (Rosenthal, 1963; Baker et al, 1964; Didisheim, 1964; Verstraete et al, 1965; Pittman et al, 1966).

(b) Accelerated digestion destructive of fibrinogen as a result of: (i) primary overactive fibrinolytic activity (Cooperberg and Neiman, 1955; Pis-

ciotta and Schulz, 1955; Fisher et al, 1960; Lee, 1962) or (ii) increased fibrinolysis secondary to coagulopathy (Fletcher, 1962). or

(c) Failure of fibrinogen production in the liver.

In many instances, it is not possible to determine which of these processes are responsible for the bleeding or whether they are all involved at the same time (Wintrobe, 1967; Fearnley, 1969).

There is no doubt that the severe, uncontrollable bleeding in this patient was mainly due to hypofibrinogenemia secondary to a fulminating acute leukaemia, although the associated thrombocytopenia must have contributed to it.

Fibrinogen deficiency due to hepatic involvement is a rare condition and it has been reported in cases of severe liver disease such as acute yellow atrophy (Conley, 1951). In those cases, the degree of parenchymal liver damage is usually quite gross. Although this patient was mildly jaundiced initially, his hepatic function and urinary findings were more suggestive of haemolytic rather than a hepatic jaundice. The transaminase and serum albumin were also normal and interestingly enough his jaundice improved later. Thus it seems unlikely that hepatic dysfunction contributed significantly to the deficiency of fibrinogen.

Thus one is left with the two other possible causes by which this complication might have arisen.

It has been suggested that the coarse granules in the leukaemia cells, probably produce "thromboplastin-like substance" (Pittman et al, 1966) and thus precipitate diffuse intravascular coagulation. A number of factors such as fibrinogen, prothrombin, factors V and VIII are 'consumed' fairly rapidly by the numerous micro-thrombi formed and a considerable number of circulating platelets is also absorbed to make the situation worse. This is the so-called consumptive-coagulopathy or defibrination syndrome.

On the other hand, a fibrinopenia may occur as a result of excessive activation of the plasminogen plasmin system and accelerated fibrinolysis. It is also possible that both are co-existent, the coagulative process giving rise to secondary fibrinolytic activity (Rodriguez – Erdman, 1965).

In the present case, it was extremely difficult to determine whether the fibrinogen deficiency was primarily coagulative or fibrinolytic. Since the fibrinolytic process was definitely over-active and there was no evidence of any gross reduction in plasma factors V and VIII (see the results of T.G.T. in Table 3), one would tend to think that the process was basically fibrinolytic. However, prothrombin and coagulation factors like V and VIII can also be reduced by excessive digestion by fibrinolysins, (Fearnley, 1969). A low plasma plasminogen level would have provided more concrete evidence in favour of a primary fibrinolysis (Flute, 1964), had this been estimated.

A prolonged one-stage prothrombin time, not necessarily reflecting a hypoprothrombinaemic state, is quite characteristic in any situation with fibrinogen deficiency. On the other hand, due to reasons given already, a true prothrombin lack may occur in these conditions.

The prognosis in these cases of acute leukaemia is extremely gloomy as response to any form of therapy is usually negligible (Rosenthal, 1963; McNicol and Douglas 1964). However, the use of anti-fibrinolytic agents, such as epsilon-amino caproic acid (E.A.C.A.), has been known to be of value in cases with excessive fibrinolysis (Nilsson et al, 1966) or, on the other hand, Heparin may be useful in the control of bleeding secondary to diffuse and intravascular thrombosis (Verstraete et al, 1963; von Francken et al, 1963). In any case, these patients must receive ample quantities of fibrinogen, fresh frozen plasma, fresh whole blood and platelet concentrates in addition to their anti-leukaemia drugs. This patient was given a small amount of E.A.C.A. and that therapy was discontinued because the evidence in favour of his having a primary fibrinolytic process was not very convincing and there would also be a theoretical risk of precipitating further thrombosis with E.A.C.A. (Rachmilewitz, 1967). Unfortunately, all other measures taken did not help him very much and he expired even before his anti-leukaemia therapy could become adequately effective.

Summary

Fatal bleeding due to fibrinogen deficiency and overactive fibrinolysis as a complication in a case of acute myelo-monocytic leukaemia is described. The pathogenesis of this complication, especially in relation to this patient, is briefly discussed.

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References

1. Baker, W.G., Bang, N.U., Nachman, R.L., Raafat, F., Horowitz, H.I., (1964). Hypofibrinogenemic haemorrhage in acute myelogenous leukaemia treated with heparin. *Ann. Int. Med.* 61:116.
2. Conley, C.L., Ratnoff, O.D., Hartmann, R.C. (1951). Studies on afibrinogenaemia. *Bull. John. Hop. Hosp.* 88:402.
3. Cooperberg, A.A. and Neiman, G.M.A., (1955), Fibrinogenopenia and fibrinolysis in acute myelogenous leukaemia. *Ann. Int. Med.* 42:706.
4. Didisheim, P., Trombold, J.S., Vandervoort, L.E., Mibashan, R.S. (1964). Acute Promyelocytic Leukaemia with Fibrinogen and Factor V deficiencies. *Blood* 23:717.
5. Fearnley, G.R. (1969). Recent Advances in Blood Coagulation (Churchill, 1st. Ed.) : 242.
6. Fisher, S., Ramot, B., and Kreisher, B. (1960). Fibrinolysis in acute leukaemia. A case report. *Israel Med. Journal* 19:195.
7. Fletcher, A.P., Alkaersig, N., Sherry, S., (1962). Pathogenesis of the coagulation defect developing during pathological plasma proteolytic states. *J. Clin. Invest* 41:896.
8. Flute, P.T. (1964). Assessment of fibrinolytic activity in the blood. *Brit. Med. Bull.* 20:195.
9. Hillestad, L.K. (1957). Acute promyelocytic leukaemia. *Acta. Med. Scand.* 159:189.
10. Hirsh, J., Buchanan, J.G., De Gruchy, G.C., Baikie, A.G., (1967). Hypofibrinogenaemia without increased fibrinolysis in leukaemia. *Lancet* 1:418.
11. Lee, L. (1962), Reticuloendothelial clearance of circulating fibrin in the pathogenesis of the generalised Schawartzman reaction. *J. Exp. Med.* 115:1065.
12. McNicol, G.P., Douglas, A.S. (1964). Epsilonamino caproic acid and other inhibitors of fibrinolysis. *Brit. Med. Bull.* 20:233.
13. Nilsson, I.M., Andersson, L., Bjorkman, S.E., (1966). Epsilon – aminocaproic acid (EACA) as a therapeutic agent based on 5 years clinical experience. *Act. Med. Scand. Supp.* 448.
14. Pisciotta, A.V., and Schulz, E.J., (1955). Fibrinolytic purpura in acute leukaemia. *Am. J. Med.* 19:824.
15. Pittman, G.R., Senhanser, D.A., Lowney, J.F. (1966). Acute promyelocytic leukaemia. *Amer. J. Clin. Path.* 46:214.
16. Rachmilewitz, E.A., Schenker, J., Kropatkin, M.L. (1967). Defibrination Syndrome followed by Hypercoagulable state. *Throm. Diath. Haem.* 17:120.
17. Rodriguez-Erdman, F. (1965). Bleeding due to increased intravascular blood coagulation. *New Eng. J. Med.* 273:1370.
18. Rosenthal, R.L., Lee, S.L., Rosenthal, N., (1955). Hypofibrinogenaemia as a factor in haemorrhage in acute leukaemia. *Clin. Res. Proc.* 3:101.
19. Rosenthal, R.L. (1963) Acute promyelocytic leukaemia associated with hypofibrinogenemia. *Blood* 21:495.
20. Verstraete, M., Vermylen, C., Amery, A., Robyn, G. (1963). Heparin treatment of bleeding following intravascular coagulation. *Lancet*, 1:446.
21. Verstraete, M., Vermylen, C., Vermylen, J., Vandenbroucke, J. (1965). Excessive consumption of blood coagulation components as cause of haemorrhagic diathesis. *Am. J. Med.* 38:899.
22. Von Francken, I., Johansson, L., Oeson, P., Zetterquist, E., (1963). Heparin treatment of bleeding. *Lancet*, 1:70.
23. Wintrobe, M.M. (1967) *Clinical Haematology 6th Edn.* 960.