Tohoku J. exp. Med., 1980, 132, 93–101

Studies on Blood Coagulation in Ulcerative Colitis and Crohn's Disease

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MORI, K., WATANABE, H., HIWATASHI, N., SUGAI, K. and GOTO, Y. *Studies on Blood Coagulation in Ulcerative Colitis and Crohn's Disease.* Tohoku J. exp. Med., 1980, **132** (1), 93–101 —— An investigation was made on 23 aspects of coagulation in 14 cases of ulcerative colitis, 5 cases of Crohn's disease and 3 cases of related diseases using a classification of increased and decreased coagulability. Of the 14 cases of ulcerative colitis, 10 were total colitis and 4 were left-sided colitis; 12 were on the active stage and 2 were in a state of remission. Treatment at the time of the investigation included prednisolone and/or Salazopyrin. In these cases, increased fibrinogen content, increased Factor VIII and Factor IX activity, increased platelet count, accelerated platelet aggregation rate and platelet retention rate were found. This hypercoagulability is thought to contribute to the clinical picture of these diseases and may prove useful as an index for determining the severity and prognosis of such cases and for deciding the indication for surgery. Furthermore, in cases where there is a marked increase in coagulability, combined anticoagulant therapy is thought necessary to improve the course of both ulcerative colitis and Crohn's disease. ———— ulcerative colitis; Crohn's disease; blood coagulation abnormality

Thromboembolism associated with ulcerative colitis or Crohn's disease in Japan was first reported by us (Kawamura et al. 1978) in an article entitled, "An autopsy case of a 32 year old man due to pulmonary thrombosis". Following that study we have undertaken studies on blood coagulation in cases of ulcerative colitis and Crohn's disease, the results of which are discussed below.

SUBJECTS

The subjects consisted of 14 patients with ulcerative colitis, 5 patients with Crohn's disease, and 3 patients with related diseases, all 22 were hospitalized or treated as outpatients in the Third Department of Internal Medicine, Tohoku University Hospital. The clinical types and stages of the lesions are summarized in Table 1.

Ten of the ulcerative colitis patients had total colitis and 4 had left-sided colitis; the disease was in an active stage in 12 and in remission in 2. One of the 5 Crohn's

Received for publication, July 18, 1979.

This paper was presented at the 64th Annual Meeting of the Japanese Society of Gastroenterology held in Sapporo on May 22–24, 1978.

This investigation was supported in part by the Grant for Specific Diseases from the Ministry of Health and Welfare.

TABLE 1. *The clinical type and stage of the lesions*

Disease	Name	Age	Sex	Classification	Clinical stage	Treatment
Ulcerative colitis	1. T.I.	28	F	Total colitis	Remission	Salazopyrin+ prednisolone
	2. N.I.	35	F	〃	Active	〃
	3. M.F.	65	F	Left-sided colitis	〃	Salazopyrin
	4. Y.K.	14	M	〃	〃	〃
	5. S.O.	10	M	Total colitis	Remission	〃
	6. Y.K.	74	F	Left-sided colitis	Active	Salazopyrin+ prednisolone
	7. C.H.	39	M	〃	〃	Salazopyrin
	8. Y.K.	12	M	Total colitis	〃	〃
	9. M.S.	22	M	〃	〃	Salazopyrin+ prednisolone
	10. H.T.	45	M	〃	〃	
	11. K.T.	22	F	〃	〃	Prednisolone
	12. H.S.		F	〃	Active (severe)	〃
	13. K.K.	24	F		〃	Salazopyrin+ prednisolone
	14. M.E.	11	F	〃	〃	Prednisolone
Crohn's disease	1. K.S.	15	M	Small and large intestine	Active	Salazopyrin
	2. T.S.	45	M	Small intestine	〃	〃
	3. H.E.	19	M	Small and large intestine	〃	〃
	4. Y.T.	19	M	〃		Salazopyrin+ prednisolone
	5. T.M.	27	M	〃	〃	〃
Others	1. K.S.	39	F	Non-specific multiple ulcers of small and large intestine	Abdominal pain and hypoproteinemia	
	2. M.T.	19	F	Suspected intestinal tuberculosis	Fever	Antituberculous drugs
	3. Y.H.	23	F	〃	Melena, diarrhea and anemia	〃

disease cases was examined 5 times during the course of the disease. One of the ulcerative colitis patients had not been treated at the time of this study, 3 had been given prednisolone only, 5 had been treated with Salazopyrin only, and 5 with both prednisolone and Salazopyrin. Of the Crohn's disease cases, 3 had been given only Salazopyrin and 2 Salazopyrin and prednisolone.

METHODS AND DETERMINATION OF HYPER- OR HYPOACTIVITY

The following methods were used in determining the blood coagulability and platelet function of these patients: Bleeding time (BT) (Duke's method), whole blood clotting time (CT) (Lee-White method), clot retraction (CR) (Macfarlane's method), capillary resistance (Cap-R) (positive pressure method), kaolin partial thromboplastin time (K-PTT) (Langdell's method), one stage prothrombin time (PT) (Quick's method), fibrinogen content (Fbg) (thrombin time method), fibrin and fibrinogen degradation product (FDP) (latex particle agglutination method), platelet count (Plt-C) (direct method), clotting factor activity (factor II through XII) (one stage method), platelet retention rate (Plt-ret) (Salzman's method),

platelet factor 3 availability (PF-3) (Weiss's method). The platelet aggregation rate (Plt-aggre) was determined by means of an aggregation meter (Evans, Ltd., London) using ADP (at a final concentration of 1×10^{-6}M), collagen (at a final concentration of 5 μg/ml) and Ristocetin (at a final concentration of 1.3 mg/ml) as inducers, and the highest platelet aggregation rate was taken as representative.

Using the above methods, an investigation was made of the changes in coagulability in these patients on referring to the criteria of functional increases and decreases given in Table 2.

TABLE 2. *Methods and determination of hyper- or hypoactivity*

	BT (min)	CT (min)	CR (%)	Cap-R	K-PTT (sec)	PT (%)	TT (%)	HT (%)	Fbg (mg/100 ml)
Hypofunction	>7.0	>15.0	>70	>10	>40.0	< 70	< 70	< 70	<150
Hyperfunction	<1.5	< 5.0	<40		<30.0	>100	>100	>100	>300

	FDP (μg/ml)	STT-30 (sec)	Platelet counts ($\times10^4$/mm^3)	Coagulation factor activity II~XII (%)	Platelet aggregation rate (%)	Platelet retension rate (%)	PF-3
Hypofunction			<15.0	<70	<30	<25	>CT of control
Hyperfunction	10	>20.0	>30.0	>120	>70	>40	<CT of control

BT, bleeding time; CT, clotting time; CR, clot retraction; Cap-R, capillary resistance; K-PTT, kaolin partial thromboplastin time; PT, 1 stage prothrombin time; TT, thrombotest; HT, hepaplastin test; Fbg, fibrinogen content; STT-30, serial thrombin time- 30 min; FDP, fibrin and fibrinogen degradation product; II–XII, factor II–XII activity; PF-3 ,platelet factor 3 availability.

RESULTS

Screening tests (Table 3) showed that BT and CT of the 14 ulcerative colitis patients were within a normal range, with neither marked prolongation nor shortening. If the anemia of the 5 cases of excessive CR is corrected for, it is thought that all 5 showed CR within a normal range. With regard to Cap-R, countless petechiae were found in one case, but in 2 other cases Cap-R returned to within normal limits. Kaolin PTT was not markedly reduced in any patient, but 3 (21%) showed prolongation to more than 40 sec. PT activity was within a normal range (79–100 %) in all patients. Five patients (36%) showed TT activity below 70%, whereas 2 (14%) showed increased TT activity. One case had decreased and 7 cases (50%) had increased HT activity greater than 150%. Fibrinogen content was below 150 mg/100 ml or above 300 mg/100 ml in 2 cases (14%) each and mild increases in FDP (to 20 μg/ml) were found in 4 cases (29%). STT showed increased fibrinolysis in 6 of the 14 patients (43%). Except for one case of disseminated intravascular coagulation (DIC), there were no cases of platelet count less than 200,000, but fully 7 cases (50%) had platelet counts greater than 300,000, indicating a definite tendency for platelet increases in ulcerative colitis.

By making an arbitrary classification of coagulation factor activity into two

groups – hypoactivity at less than 70% and hyperactivity at greater than 100% – hypercoagulability was found in 32%, which was slightly higher than the value found for hypocoagulability (27%) (Table 4). It is known that each factor has a certain degree of specificity, but further investigation is needed to determine the significance of that specificity.

With regard to the correlation between platelet function and the above categories, it was found that BT, CR and Cap-R were normal, but, except for one patient with a platelet count of less than 115,000 with DIC, none had decreased platelet function and 7 patients had increases in platelet number to more than 300,000. The platelet aggregation rate was investigated using ADP, collagen, and Ristocetin. By considering a fall of the platelet aggregation rate to less than 30% as hypoactivity and an increase to more than 70% as hyperactivity, marked increases in platelet aggregation rate were observed. Measuring the platelet retention rate using a modification of Salzman's method, it was seen that 10 to 12 cases had increased retention, but none showed a decrease.

Determination of the activity of platelet factor 3 (PF-3) using Weiss's method in 2 cases indicated a marked shortening of coagulation time (that is,

TABLE 3. *Coagulation screening test*

	BT	CT	CR	Cap-R	K-PTT	PT	TT	HT	Fbg	FDP	STT-30	Plt-C
Ulcerative colitis												
Hypofunction	1/12 (8)	0/12 (0)	0/12 (0)	3/10 (30)	3/14 (21)	0/14 (0)	5/14 (36)	1/14 (7)	2/14 (14)	0/14 (0)	0/14 (0)	1/14 (7)
Hyperfunction	0/12 (0)	1/12 (8)	5/12 (42)	0/10 (0)	0/14 (0)	0/14 (0)	2/14 (14)	13/14 (93)	2/14 (14)	4/14 (29)	6/14 (43)	7/14 (50)
Crohn's disease												
Hypofunction	1/5 (20)	0/5 (0)	0/5 (0)	0/5 (0)	2/5 (40)	0/5 (0)	1/5 (20)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)
Hyperfunction	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	2/5 (40)	2/5 (40)	3/5 (60)	0/5 (0)	3/5 (60)	4/5 (80)

Number of cases/total cases examined. Percentages are given in parentheses.

TABLE 4. *Clotting factor activity*

	II	V	VII	VIII	IX	X	XI	XII
Ulcerative colitis								
Hypofunction	1/14 (7)	3/14 (21)	7/14 (50)	2/14 (14)	1/14 (7)	1/14 (7)	12/14 (86)	3/14 (21)
Hyperfunction	5/14 (36)	3/14 (21)	1/14 (7)	10/14 (71)	11/14 (79)	1/14 (7)	0/14 (0)	5/14 (36)
Crohn's disease								
Hypofunction	0/5 (0)	0/5 (0)	1/5 (20)	1/5 (20)	1/5 (20)	0/5 (0)	4/5 (80)	0/5 (0)
Hyperfunction	2/5 (40)	2/5 (40)	2/5 (40)	3/5 (60)	4/5 (80)	3/5 (60)	0/5 (0)	2/5 (40)

Number of cases/total cases examined. Percentages are given in parentheses.

increased activity) in 1 case as compared to controls. In summary, with regard to platelet function, a general increase in platelet count, aggregation rate, retention rate and PF-3 activity was apparent.

Similar investigations were made in 5 cases of typical Crohn's disease. Screening tests showed BT, CT, CR and Cap-R values to be within a normal range (Table 3). Other tests showed slight variations, but the most notable finding was a marked increase in platelet count, similar to that seen in the cases of ulcerative colitis. Clotting factor activity varied widely among the cases of Crohn's disease (Table 4), but the overall picture showed a definite tendency for hypercoagulability (45%), as opposed to hypocoagulability (18%).

With regard to the correlation with platelet function (Table 5), no major changes in BT, Cap-R or CR nor decreases of platelet count to below 200,000 were seen, but 4 of the 5 patients showed an increase of platelet count. Particularly in Case 1, in which platelet count was measured three times, marked increases of 620,000, 580,000 and 790,000 were seen. No decrease in platelet aggregation rate was seen with ADP, collagen or Ristocetin; rather, increased rates were seen in all cases. Similar results were found concerning platelet retention rates. Decreased PF-3 activity was apparent in 1 of the 2 cases measured.

TABLE 5. *Platelet function test*

	BT (min)	CR (%)	Cap-R	Plt-C (10^4/mm^3)	Platelet aggregation rate (%)			Platelet retention rate (%)	PF-3 (sec)
					ADP (10^{-6}M)	Collagen (5 μg/ml)	Ristocetin (1.3 mg/ml)		
Ulcerative colitis									
Hypofunction	1/12 (8)	0/12 (0)	3/10 (30)	1/14 (7)	1/13 (8)	1/12 (8)	0/12 (0)	0/12 (0)	0/2 (0)
Hyperfunction	0/12 (0)	5/12 (42)	0/10 (0)	7/14 (50)	5/13 (39)	7/12 (58)	2/12 (17)	10/12 (83)	1/2 (50)
Crohn's disease									
Hypofunction	1/5 (20)	0/5 (0)	0/5 (0)	0/5 (0)	0/4 (0)	0/2 (0)	0/4 (0)	1/5 (20)	1/2 (50)
Hyperfunction	0/5 (0)	0/5 (0)	0/5 (0)	4/5 (80)	3/5 (60)	2/2 (100)	4/4 (100)	3/5 (60)	0/2 (0)

Number of cases / total cases examined. Percentages are given in parentheses.

DISCUSSION

Incidence of thromboembolism. From the above coagulation studies on 14 patients with ulcerative colitis, 5 with Crohn's disease, and 3 with related diseases, a significantly large number of patients were found to be in a hypercoagulable state. The first report of ulcerative colitis accompanied with thromboembolism was that of Bargen and Barker (1936). They found an incidence of thromboembolism to be only 1.2% in 1500 clinical cases of ulcerative colitis, but the incidence in 43 autopsy cases was fully 31%. Subsequently, the incidence in clinical studies has gradually risen. Dennis and Karlson (1952) reported an incidence of 7.1% in 261

cases and Edwards and Truelove (1964) reported an incidence of 6.4% in 647 cases. In autopsy studies, Graef et al. (1966) found an incidence of 39% in 100 cases. The incidence was particularly high in young patients with severe ulcerative colitis (Edwards and Truelove 1964). In Japan, the nation-wide collective study of 278 cases by Yoshida et al. (1974) and the study of 159 cases by Watanabe et al. (1977) revealed no cases associated with pulmonary embolism or pulmonary thrombosis.

Although reasons for the differences in incidence between Japan and the Western countries are not known, racial differences, living conditions, etc. must be taken into consideration. And yet, in the light of the increases in incidence of such complications found in various Western countries, it is possible that changes in the nature of the lesion have occurred with time, or that the degree of understanding by clinicians and pathologists of thromboembolism is greatly different in the two worlds.

Site. Other than the pulmonary embolism reported by Lam et al. (1975) in a case of Crohn's disease, sites at which thromboembolism is said to occur include cerebral veins, the thoracoepigastric veins, the iliofemoral vein, the femoral artery, portal vein, and pulmonary vein. Our patient died of pulmonary arterial thrombosis (Kawamura et al. 1978).

Causes of thromboembolism and coagulation abnormalities. It is generally considered that the cause of thrombosis is a state of hypercoagulability. Barker (1958) argued that if coagulation abnormalities are indeed the cause, then thromboembolism should occur in the first stage of coagulation and should be related to platelet function or thromboplastin generation. Spittel et al. (1964) found that all 12 of their cases of ulcerative colitis had increased thromboplastin generation, 6 of which also had thromboembolic complications. They maintained that there is in fact a tendency for hypercoagulability among ulcerative colitis

TABLE 6. *Means and standard*

	BT (min)	CT (min)	CR (%)	Cap-R	K-PTT (sec)
Ulcerative colitis (♂6, ♀8)	4.9±1.1 (N=12)	6.3±0.9 (N=12)	44.0±7.9 (N=12)	Normal 7 Abnormal 3 (N=10)	36.1±4.4 (N=14)
Crohn's disease (♂5)	5.2±1.5 (N=5)	7.4±1.0 (N=5)	47.6±7.5 (N=5)	Normal 5 (N=5)	37.1±5.9 (N=5)

	Coagulation factor activity					
	II (%)	V (%)	VII (%)	VIII (%)	IX (%)	X (%)
Ulcerative colitis	110.7±13.8 (N=14)	57.4±36.8 (N=14)	77.4±20.1 (N=14)	182.6±156.6 (N=14)	201.6±112.3 (N=14)	95.8±17.3 (N=14)
Crohn's disease	123.2±37.3 (N=5)	132.0±38.2 (N=5)	109.4±35.9 (N=5)	143.0± 62.4 (N=5)	295.6±323.1 (N=5)	131.0±28.8 (N=5)

patients. However, it has also been reported that in ulcerative colitis there are prolonged PT (Page and Borcovitz 1942) and PT consumption abnormalities (Rinaldo et al. 1964) and both of which would facilitate hemorrhage rather than thrombus formation. Lee et al. (1968) undertook a study of 16 ulcerative colitis patients dividing them into 3 groups according to coagulability as judged by factor VIII activity, thromboplastin generation and fibrinogen content. They found that in all colitis patients there was hyperfunction of all three indicators during the active stage of the disease, whereas in the same patients there was a return to normal activity due to therapy during stages of remission. Furthermore, Lam et al. (1975) found that, in a coagulation study of 12 ulcerative colitis patients, 12 Crohn's disease patients, 19 patients with other diseases and 15 normal controls, there were marked increases in platelet count and fibrinogen in both ulcerative colitis and Crohn's disease, as well as decreased antithrombin III activity in both. Although factor VIII activity was normal in the ulcerative colitis cases, it was roughly twice that of the normal controls in the Crohn's disease cases, indicating a marked increase in coagulability. In our screening test for coagulability in 14 cases of ulcerative colitis, a large variation was not seen, but increased HT activity (greater than 150% in 7 cases), prolonged STT (in 6 cases or 42.9%), increased platelet counts and increased retention rates were found. There were also marked increases in the activity of factors VIII and IX.

Similar results were obtained in the Crohn's disease cases. That is, screening tests showed increased fibrinogen content, increased activity of factors VIII and IX, as well as platelet hyperactivity, including marked increases in platelet count and increased platelet aggregation and retention rates (Table 6).

Nevertheless, no definite findings of causal factors giving rise to such hypercoagulability were obtained. Bed rest, toxemia, immunological mechanisms, surgical intervention, etc. must all be considered as possible causes, but regardless

deviations of hemostatic tests

PT (%)	TT (%)	HT (%)	Fbg (mg/100 ml)	STT-30 (sec)	FDP (μg/ml)
93.3±7.5 (N=14)	82.1±20.1 (N=14)	149.4±35.2 (N=14)	227.4±71.3 (N=14)	19.8±4.9 (N=14)	10.7±10.7 (N=14)
90.0±7.8 (N=5)	90.0±20.2 (N=5)	155.4±22.8 (N=5)	304.0±41.6 (N=5)	19.3±5.1 (N=5)	7.0± 2.7 (N=5)

		Plt-C	Plt aggregation rate (%)			Plt-ret
XI (%)	XII (%)	(10^4/mm^3)	ADP (10^{-6}M)	Collagen (5 μg/ml)	Ristocetin (1.3 mg/ml)	(%)
45.1±20.6 (N=14)	115.7±58.7 (N=14)	30.3± 9.3 (N=14)	61.5±16.7 (N=13)	70.2±10.3 (N=11)	51.2±13.2 (N=12)	47.9± 8.6 (N=12)
51.0±30.7 (N=5)	115.4±55.9 (N=5)	37.6±14.6 (N=5)	82.7±12.3 (N=4)	87.7± 0.9 (N=2)	78.4± 3.7 (N=4)	39.4±15.0 (N=5)

of the cause it is apparent that there is a close relationship between the hypercoagulable state and the onset of ulcerative colitis and Crohn's disease.

Correlation with therapy. Although the effects of steroid hormones and Salazopyrin administration must be considered, we believe that hypercoagulability is not brought about by these drugs in the light of our present findings.

Conclusion

From the above results, the following conclusions have been reached:

1) Despite differences in degree according to the type, severity, and stage (active or remittent) of the disease, most cases of ulcerative colitis or Crohn's disease showed definite signs of hypercoagulability. Due to such hypercoagulability, there is a danger of thromboembolism in such patients.

2) Considering that hypercoagulability is one aspect of these diseases, it offers important information concerning severity, prognosis and surgical indication.

3) When marked hypercoagulability and intravascular coagulation syndrome are present, the therapeutic program for ulcerative colitis and Crohn's disease must include anticoagulant therapy (oral anticoagulants, heparin and/or suppressants of platelet function), which should lead to a favorable effect.

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