Blood Coagulation Studies of Various Hematological Disorders

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We have carried out blood coagulation studies of various hematological disorders encountered routinely, in which hemorrhagic diathesis is the cardinal symptom and also it has important influence upon the prognosis of the diseases. Those which we studied are mainly acute leukemia, idiopathic thrombocytopenic purpura (ITP) and aplastic anemia, and hemophilia, iron deficiency anemia and purpura simplex are also studied in parallel to the said three diseases.

A) General aspects of blood coagulation studies

The results of blood coagulation studies in various blood diseases are illustrated in Fig. 1. Hemorrhagic diathesis of acute leukemia, aplastic anemia and ITP are similar in nature, characterized by abnormality of platelet, i.e., prolongation of bleeding time, depletion of clot retraction, decrease of platelet count, depletion of aggregation, adhesiveness and factor 3 of platelet, associated with impairment of prothrombin consumption were those of common findings as shown in Fig. 1.

In addition, marked increases of vascular fragility were found in both ITP and aplastic anemia, and these data may be related with some aspect of etiology of the diseases. Likewise in acute leukemia, increase of vascular fragility was present, yet its degree was not as much as in ITP or aplastic anemia. In aplastic anemia, increase of heparin-like substance was found and also we experienced two cases in which increase of anti-blood thromboplastin was significant.
Fig. 1. Results of hemostatic tests in various hematological disorders (mean value).
Fig. 2. Results of hemostatic tests in various hematological disorders in relation to hemorrhagic manifestations.
B) In hemorrhagic and non-hemorrhagic stage

We studied factors related with hemorrhagic diathesis in both hemorrhagic and non-hemorrhagic stages of the diseases, and the results are illustrated in Fig. 2. In ITP, aplastic anemia and acute leukemia, hemorrhagic cases showed more significant prolongation of bleeding time, decrease of platelet count, depletion of clot retraction and factor 3 as compared with non-hemorrhagic cases. Depletion of aggregation of platelet was observed in hemorrhagic cases in ITP.

Factor VIII was decreased in hemorrhagic cases in all three diseases, associated with impairment of prothrombin consumption and weakened vascular resistance. In chronic leukemia, not much difference was found between hemorrhagic and non-hemorrhagic cases, except for decrease of factor V and factor VII plus X in the former cases. In hemophilia A, factor VIII was found to be decreased generally but not so much in hemorrhagic cases.

C) Platelet

1) Platelet count

Correlation between platelet count and hemorrhage was carefully analyzed in acute leukemia, ITP and aplastic anemia. Thus, three groups were classified as listed below;

(1) Below 20,000 or 30,000/cu.mm. of platelet count associated with high frequency of bleeding.

(2) Above 60,000 or 70,000/cu.mm. of platelet count associated with low frequency of bleeding.

(3) 30,000 to 60,000/cu.mm. of platelet count associated with moderate frequency of bleeding.

From these results, platelet count ranging from 30,000 to 60,000/cu.mm. can be a critical zone for hemorrhagic manifestations.

2) Function of platelet

Function of platelet in each case of the diseases was plotted in Fig. 3.

Although each value of the platelet function was scattered in considerably wide range, adhesiveness, aggregation, clot retraction and factor 3 tended to diminish in acute leukemia, aplastic anemia
and ITP. However, no definite correlation between diminished value and bleeding was observed. Meanwhile, in the other diseases, platelet function tended toward normal level showing less variation. In other words, hemorrhagic diathesis of acute leukemia, ITP and aplastic anemia depends mainly upon abnormality of platelet function.

3) Life span of platelet

Life span of platelet in various hematological disorders by means of $\text{Na}_2\text{Cr}^{15}$O labeling are illustrated in Fig. 4. The survival time of platelet in ITP, aplastic anemia and leukemia was shortened, especially in the former two diseases.
D) Interdependence between various factors constituting hemorrhage

Interdependence among platelet count, clot retraction, platelet aggregation, platelet adhesiveness, bleeding time, platelet factors was evaluated and the following coefficients of correlation were obtained.

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\begin{align*}
\text{Platelet count and bleeding time} &= -0.518 \\
\text{Platelet count and clot retraction} &= +0.527 \\
\text{Platelet count and vascular fragility} &= -0.385 \\
\text{Platelet factor 1 and 3} &= +0.346
\end{align*}
\]

Interdependent coefficients between the other factors were generally lower than those listed above.

E) Fibrinolysis

Data of fibrinolysis in each case of the various diseases varied a great deal, yet antiplasmin tended toward normal level in almost all cases and free plasmin, euglobulin fraction, plasminogen and plasminogen activator were found to be increased in some cases.

No correlation was observed between hemorrhagic manifestation
and increases of such factors. But these results suggest that some of cases with those diseases can develop bleeding by fibrinolysis.

F) Discussion

Elements constituting bleeding can be grossly divided into defect of blood vessel, decrease of platelet count, deficiency of clotting factors, excess of anticoagulants and excess of fibrinolysis. Regardless of hemorrhagic manifestations, in those diseases, disturbance of such elements was present in either single or complex form.

Based on the data obtained from well examined 50 cases, we have made comparative studies on complex of defective elements between hemorrhagic and non-hemorrhagic cases (Fig. 5).

Fig. 5. Number of elements constituting bleeding, in relation to hemorrhagic manifestations.

In hemorrhagic cases, only 3.8% of cases showed bleeding associated with disturbance of a single element, whereas 30.8% of cases developed bleeding with two ill elements and 64.5% with disturbance of more than three elements.

Meanwhile, in non-hemorrhagic cases, 29.2% of cases showed disturbance of single element, 37.5% two elements and 25% more than three elements respectively.
It is noteworthy that disturbance of more than three elements was more frequent in hemorrhagic cases than in non-hemorrhagic cases. Namely, in hemorrhagic state number of factors are disturbed in complex form, meanwhile in non-hemorrhagic state it was found that ill element in either single or complex form is present.

Moreover, when analyzing degree of relation between hemorrhage and the said 5 elements, 85% of all hemorrhagic cases had platelet count less than 30,000/cu. mm., 79% weakened vascular fragility, 59% diminished coagulation factors, 57% increase of anticoagulants, 65% increase of fibrinolysis, respectively.

These data imply that disturbance of platelet and vascular resistance have to be regarded as of great importance to development of bleeding.

Disturbance of etiological factors of hemorrhage per se does not mean manifestation of bleeding. However, condition of complex of ill elements or both quantitative and qualitative measurements of factors especially those of platelet and blood vessel are to be always watched carefully.

In each blood disease, there are characteristic pattern of disturbed hemorrhagic factors in a sense of its degree and composition.