Clinical and Pathologic Studies of Gastrointestinal Hemorrhage in Acute Leukemia

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KAWAMURA, S., SAWADA, Y., FUJIWARA, S., KAWATSU, S., CHIBA, Y. and YOSHIDA, Y. *Clinical and Pathologic Studies of Gastrointestinal Hemorrhage in Acute Leukemia*. Tohoku J. exp. Med., 1979, 127 (4), 345-352 — One hundred and sixty cases of acute leukemia observed at our Department between 1953 and 1977 were reviewed as to the presence and nature of the accompanying gastrointestinal hemorrhage. A massive gastrointestinal hemorrhage requiring blood transfusions occurred in 29 cases (18%). The most common lesion was hemorrhagic necrosis of the small intestines. There were three forms of hemorrhage: Type I: thrombocytopenia, hemorrhagic diathesis, diffuse hemorrhage of mucosa and submucosa, but no erosion nor ulceration. Type II: no specific pathologic findings. Diffuse hemorrhage, superficial erosions, bacterial and fungal invasions were observed. Type III: single and/or multiple ulcerations, necrosis and perforation of the small intestines and colon. Thrombocytosis was almost always present at the prebleeding phase in these cases. Intravascular microthrombi at the basis of ulceration were seen. Usually, more than one process were seen in each case. An appropriate approach to the severe gastrointestinal hemorrhage with a combination of anti-leukemic chemotherapy, anti-coagulant therapy, platelet transfusion, etc. would further add to the number of long-term survivors in acute leukemia. ——— gastrointestinal hemorrhage; acute leukemia; histopathologic study; ulceration; microthrombi

The progress in management of acute leukemia in adults by the current chemotherapeutic schedules has brought about a higher rate of complete remission and a longer survival duration. On the other hand, various kinds of complications in the course of leukemia have attracted much attention of clinicians. It is a common knowledge of hematologists that gastrointestinal (GI) hemorrhage in acute leukemia is one of the most fulminating and fatal complications. But, there have been only a few papers on GI hemorrhage in acute leukemia, and most of them (Prolla and Kirsner 1964; Amromin 1968) reported that GI hemorrhage occurred due to marked thrombocytopenia or leukemic infiltration in the digestive tracts. Although hemorrhage from gastrointestinal tracts has been clinically seen in the absence of thrombocytopenia, its pathologic mechanism has not been well elucidated. The present authors reviewed the clinical and pathologic aspects of GI hemorrhage in acute leukemia and offered their opinions as to its cause and treatment.

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MATERIALS AND METHODS

One hundred and sixty cases of acute leukemia, observed at our Department between 1953 and 1977, were reviewed with respect to the presence and nature of the accompanying GI hemorrhage. The cases consisted of 114 cases of acute myelogenous leukemia (AML), 25 of acute lymphocytic leukemia (ALL), 13 of acute monocytic leukemia (AMoL), and 8 of erythroleukemia. The diagnosis of massive GI hemorrhage was made by the episodes of fresh bleeding, tarry stool, or continuously prominent occult blood. Histopathologic studies were performed in post-mortem materials to evaluate the distribution and extension of the gastrointestinal lesions, in particular the presence or absence of leukemic infiltration, fungal infection and necrosis.

RESULTS

The incidence of GI hemorrhage in acute leukemia

A massive GI hemorrhage occurred in 22 out of 114 cases of AML, 3 of 25 cases of ALL, 2 of 13 cases of AMoL, and 2 of 8 cases of erythroleukemia (Table. 1).

TABLE 1. *The incidence of GI hemorrhage in acute leukemia*

	Number of cases	Bleeding	%
AML	114	22	19.3
ALL	25	3	12.0
AMoL	13	2	15.4
EryL	8	2	25.0
Total	160	29	18.1

The chronological incidence of massive GI hemorrhage

Massive GI hemorrhage occurred only in 2 cases in the years from 1953 to 1962. Since 1968, however, there have been 2 or 3 cases every year. Statistically, the yearly trend was not significant in these ten years (Fig. 1).

The relation to the induction schedules

GI hemorrhage was found in 52% of cases on 6MP-prednisolone combination therapy, in 29% on VEMP schedule and in 26% on DCMP schedule. Statistically, the differences were not significant among these three schedules (Table. 2).

Survival of patients with GI hemorrhage

Fourteen of 29 cases had severe GI hemorrhage from the beginning of the schedules and died within one month. An average survival of the other cases was 8.5 months (3-30 months). Only one out of 29 cases of severe hemorrhage had complete remission after hemorrhage. Surgical operation was performed in one case of AML because of the perforation in the small intestine.

Platelet counts

The most common lesion in the autopsy cases was hemorrhagic ulceration of

Fig. 1. The chronological incidence of massive GI hemorrhage.

TABLE 2. *The relation to the induction schedules*

	Number of cases	Bleeding	%
6MP+PS	25	13	52.0
VEMP	17	5	29.4
DCMP	34	9	26.4
DcyMP	4	0	
Others	80	2	
Total	160	29	

PS: prednisolone.

VEMP: VCR+cyclophosphamide+6MP+prednisolone.

DCMP: Daunomycin+ara-C +6MP+prednisolone.

DycMP: Daunomycin+cyclocytidine+6MP+prednisolone.

the small intestine. The gastric mucosal hemorrhage was also seen frequently. Only 9 of 29 cases had marked thrombocytopenia below $30,000/\text{mm}^3$ at the time of GI hemorrhage. On the contrary, platelet counts in 16 of 29 cases were over $50,000/\text{mm}^3$ at the time of GI hemorrhage. It may show that the thrombocytopenia does not play an important role as the cause of GI hemorrhage in some of the cases of acute leukemia.

Histopathologic review

There were three histopathologic forms of hemorrhage (Fig. 2). Type I: diffuse hemorrhage of the mucosa and submucosa. Infiltration of leukemic cells was slight. Erosion or ulceration was not recognized. Almost all of these cases had severe thrombocytopenia. Type II: no specific pathologic findings. The

Fig. 2. Histopathological types.

Fig. 3. Clinical correlation.

leukemic cells infiltrated diffusely or solitarily into the mucosal and submucosal layers. Diffuse hemorrhage, superficial erosion, and bacterial and fungal invasions were observed. Type III: single and/or multiple ulceration, necrosis and perforation of the small intestine and colon. In these cases, thrombocytosis was almost always present at hemorrhage and prehemorrhage phases. Intravascular microthrombi at the base of ulcer were seen. Usually, each case had two types of

hemorrhage, but there was no case in which both Type I and Type III were observed.

Hematologic findings and clinical manifestations

In cases of Type I, the platelet counts averaged $3.3 \times 10^4/\text{mm}^3$ within a week before hemorrhage and $3.4 \times 10^4/\text{mm}^3$ at the time of hemorrhage (Fig. 3). There was marked thrombocytopenia in Type I at the hemorrhage and prehemorrhage phases. On the other hand, the platelet counts in cases of Type III averaged $6.6 \times 10^4/\text{mm}^3$ a week before hemorrhage and $26.1 \times 10^4/\text{mm}^3$ at hemorrhage. There was no severe thrombocytopenia even in severe GI hemorrhage. There were only 9 cases of Type III in all 160 cases of acute leukemia. Cases of Type III were rather rare. They had no sign of disseminated intravascular coagulation upon the examinations of fibrinogen, red cell sedimentation, FDP and TEG. Therefore, Type III was considered to be a special clinical type of GI hemorrhage in acute leukemia.

The average counts of WBC in all but two cases were 1×10^3 – $1 \times 10^4/\text{mm}^3$, and did not differ significantly among the three types mentioned above. Leukemic cell counts in the peripheral blood were more than 20% except in one case.

Most important clinical signs of GI hemorrhage were abdominal distension and abdominal pain before GI hemorrhage. Particularly, severe abdominal distension was more frequent in cases of Type III than in Type I or Type II, and the former had gas retention without fluid level on plain film of the abdomen. Sometimes the patients complained of acute abdominal pain, which was so severe that it was difficult to differentiate from other acute abdomens.

In many cases of acute leukemia examined, the platelets decreased while leukemic cells increased. However, it is interesting that in cases of Type III the platelets increased following the increase of leukemic cells. In autopsy cases, the leukemic cell infiltration was found in the liver, spleen, lung and heart in Type III.

A case of Type III

A 45-year-old woman was admitted to a hospital on March 27th, 1974, because of fever and bleeding from the gums. On April 10th, the patient was transferred to the 2nd Department of Internal Medicine of our University Hospital.

Laboratory data. White blood cell count, $102,000/\text{mm}^3$ with 80% leukemic cell; platelets, $2 \times 10^4/\text{mm}^3$; red blood cell, $358 \times 10^4/\text{mm}^3$. Hemoglobin value was 10.4 g/100 ml. Leukemic cells in the smear of peripheral blood were all negative for peroxidase reaction.

Hospital course. A diagnosis of AML was made and she was given daunomycin, cytosine-arabioside, 6MP and prednisolone. Despite the antileukemic drugs, white blood cell counts increased from 1.5×10^4 to $5 \times 10^4/\text{mm}^3$, and platelet counts increased from 1×10^4 to $53 \times 10^4/\text{mm}^3$. Then, she complained of severe abdominal distension and colicky pain. Tarry stools were noted every day for 7 days. She died of severe GI hemorrhage on May 6th, 1974 (Fig. 4).

Fig. 4. H.Y. 45-year old F

Fig. 5. Multiple ulcerations in the colon.

Fig. 6. Ulcerations showed marked necrosis.

Fig. 7. Thrombi in the small vessels near the base of ulcers.

Autopsy findings. Multiple ulcerations of several centimeters in the diameter were seen in the colon (Fig. 5). There were marked edema and thrombi in the small vessels near the base of ulcers (Fig. 7). Ulcerations showed marked necrosis (Fig. 6).

DISCUSSION

Severe GI hemorrhage occurred in 29 (18%) out of 160 cases of acute leukemia, and it was the direct cause of death in almost all of them when it occurred in spite of the platelet transfusion. We reviewed the clinical and pathologic aspects of the GI hemorrhage to offer suggestions as to its cause, prophylaxis and treatments.

There were three forms of hemorrhage. Type I has thrombocytopenia, hemorrhagic diathesis and diffuse hemorrhage to the mucosa and submucosa without erosion or ulceration. Type II has no specific pathologic finding. Diffuse hemorrhage, superficial erosions, bacterial and fungal invasions were observed. Type III has single and/or multiple ulcerations, necrosis and perforation of the small intestines and colon; thrombocytosis was almost always present at the hemorrhage in this type. Intravascular microthrombi at the base of ulcer were seen. In this Type III, GI hemorrhage occurred when the platelet counts exceeded about $15 \times 10^4/\text{mm}^3$ at the hemorrhagic phase. Their fibrinogen and FDP were within normal limits. Thus, it seemed unlikely that there was any relation between the hemorrhage and the phenomena of DIC. The mechanism of Type III was considered as follows: This process is initiated by the stasis or microemboli with leukemic cells, and this leads to the dilatation of the vessels, hemostasis and necrosis of the mucosa and submucosa, followed by ulcer formation. Togawa et al. (1977) reported a patient who had leukemic cell infiltration in the submucosa and mucosa of gastrointestinal tracts at the beginning of therapy, and died of GI hemorrhage. In this specific case many leukemic cells were not observed in the

peripheral blood. Steinberg et al. (1973), in their review of 7 autopsied leukemia cases of necrotizing enterocolitis, pointed out some possible pathologic factors such as granulocytopenia, various chemotherapeutics, thrombocytopenia and infection. Amromin and Solomon (1962) classified the leukemic necrotizing enteropathy into four types: Type I, shock and/or ischemia; Type II, therapeutic necrosis of lymphoma or leukemic GI infiltrations; Type III, thrombocytopenia, hemorrhagic diathesis, and mucosal necrosis over hemorrhages; Type IV, stasis and traumatic, stercoral or decubital mucosal erosions. Steinberg et al. (1973) reported that 7 cases including 2 surgical cases were all unsuccessfully treated. But, in cases of children, Exelby et al. (1975) reported that a more aggressive surgical approach to the acute abdomen, combined with careful supportive measures, would increase the number of long-term survivors in childhood leukemia.

We succeeded in saving the patients with severe GI hemorrhage by combination therapy with parenteral hyperalimentation, blood transfusion and anticoagulant therapy. Abdominal distension and pain are important symptoms as the auras of hemorrhage in acute leukemia. In such cases, we must check the stool repeatedly for occult bleeding, peripheral blood counts, smear, TEG and red cell sedimentation rate. If the platelet counts decrease below $1-2 \times 10^4/\text{mm}^3$, platelet transfusion must be given immediately to keep the counts over $5-6 \times 10^4/\text{mm}^3$. Anticoagulant therapy with antileukemic agents may be more effective in cases of Type III.

Although the management of acute leukemia in adults is improving year by year, GI hemorrhage is still the fulminating and fatal complication of this disease. We must differentiate the mechanism of GI hemorrhage in each case to select the most effective and suitable therapy.

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