Pathological Changes in the Gastrointestinal Tract of a Heavily Radiation-exposed Worker at the Tokai-mura Criticality Accident

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Gastrointestinal syndrome after high-dose acute radiation whole body exposure is difficult to treat, although it is a well-known complication. In this report, we describe the clinical and pathological features of a patient who died after the criticality accident which occurred in Japan on 30 September 1999. The patient was estimated to have been exposed to 16–25 Gy equivalent of gamma ray, and died of multiple organ failure after acute radiation syndrome, especially gastrointestinal syndrome, on day 82. The stomach and small intestine contained a large amount of blood clots and the gastrointestinal epithelial cells were almost totally depleted at autopsy. In addition, the degree of the mucosal damage was dependent on the segment of the gastrointestinal tract; the mucosa of stomach, ileum and ascending colon was entirely depleted, but the esophagus, descending and sigmoid colon and rectum retained a small portion of the epithelial cells. From the posture of the patient at the time of exposure, the absorbed dose was presumed to be highest in the right-anterior abdomen. This agreed with the pathological differences in the mucosal damage by the position in the abdomen, which depended presumably on the radiation dose. This is the first report documenting the relationship between the absorbed dose and the severity of gastrointestinal damages in vivo.

INTRODUCTION

Patients suffering from accidental acute radiation exposure are often difficult to treat for several reasons: the difficulty and uncertainty of estimating the exposure dose, the heterogeneity of the absorbed dose in the body, the scarcity of medical staff who are well acquainted and experienced with the treatment of radiation damage to the organs, and the lack of sufficient human data on acute radiation damage to the organs after a single high-dose radiation exposure.¹)

Recent studies have revealed the close relationship between acute radiation syndrome and multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF).²,³) Moreover, the gastrointestinal tract plays an important role in developing MODS by the collapse of the intestinal barrier function from enteric bacterium after radiation exposure as well as after severe burns or other trauma.³,⁴)

The criticality accident occurred at the uranium fuel processing facility of JCO Co. Ltd. in Tokai-mura, Ibaraki, Japan in 1999. Two workers were pouring uranyl nitrate solution manually from a bucket into a precipitation tank, when the tank reached the critical state. Three workers received mixed gamma ray and neutron beam. Two of the victims died due to radiation damage. In this report, we focused on the gastrointestinal syndrome of the patient who was exposed most heavily and was treated at our hospital. We present the clinical course and pathological findings related to the irradiation damage in the patient’s gastrointestinal tract.

MATERIALS AND METHODS

Clinical course of the patient

The patient was 35-year-old male. The patient’s exposure was estimated to be a systemic mean dose of 16–25 Gy equivalent of gamma ray by the criticality accident at JCO
Co., Ltd., an uranium fuel processing plant in Tokai-mura, Ibaraki, Japan, on 30 September 1999. He was transferred from the National Institute of Radiological Sciences to the University of Tokyo Hospital on day 2. After his admission at our hospital, continuous intravenous administration of L-alanyl-L-glutamine was started expecting promotion of the epithelial regeneration of the gastrointestinal tract after radiation exposure. He received peripheral blood stem cell transplantation on days 6 and 7. Endotracheal intubation under sedation was introduced on day 10 because of gradual worsening in the patient’s respiratory status and in preparation for the future deterioration in the patient’s general condition. Despite the intensive care for his symptoms, exudation from the skin and diarrhea had got worse day by day. He had died on day 82. Details of the clinical course were documented previously.

Daily volumes of fluid discharge are shown in Fig. 1. Clinical course related to gastrointestinal injuries is summarized below. Mild diarrhea was observed for the first two days after the accident as a symptom of prodromal syndrome and, on day 26, severe diarrhea with bilious watery stool started as a symptom of radiation-induced gastrointestinal syndrome. The volume of watery stool increased to 3500 mL per day on day 39. Bloody stool was observed starting on day 45. The volume of bloody stool increased day by day. Continuous arterial infusion of vasopressin was started from

![Fig. 1. Daily change in the volume of fluid loss from lower gastrointestinal tract. Light gray bars represent watery diarrhea. Bloody stool, shown by dark gray bars, started on day 45. Major treatments and events are indicated. Abbreviation: PBSCT = peripheral blood stem cell transplantation.](image1)

![Fig. 2. The appearance of the ileum and colon by colonoscopy. The mucosa appeared almost normal on day 15, but the spots were observed on day 26. After day 35, no mucosa was observed in either the ileum or the colon. The number of bleeding sites thereafter increased.](image2)
an indwelling catheter in the superior mesenteric artery on day 55. The volume of bloody stool decreased from 4000 mL to 2000 mL per day by continuous vasopressin infusion. Vasopressin infusion, however, was discontinued on day 58, when there was a cardiac arrest of undetermined etiology. The patient was successfully resuscitated at that time. The volume of melena suddenly decreased on day 67, implying a blood clot-induced intestinal obstruction. A series of high-pressure enemas was tried thereafter but failed to relieve the obstruction. After the episode of cardiac arrest, multiple organ hypoperfusion developed, and finally the patient died of MOF on day 82.

![Abdominal radiographs](image1)

**Fig. 3.** Abdominal radiographs (A) and abdominal CT images (B). (A) The radiograph on day 2 appeared almost normal. Ileac gas was prominent on day 11, but Kerckring’s folds were observed. On day 45, the small intestine was swollen without Kerckring’s folds. The abdominal opacity decreased and the small intestine was more swollen with intestinal gas on day 68, when melena suddenly stopped. The decreased opacity of the abdomen represented the increased ascites and intestinal bleeding. On day 74, the decrease in the abdominal opacity was more prominent, and the ileac gas decreased. (B) Only the wall of the ascending colon was thickened, but the small intestine and the transverse and descending colon appeared normal on day 1. Thickening of the entire intestinal wall with the contents of fluids and air was observed on day 29. The wall thickening and the fluid collection were more prominent on day 37. The arrowhead indicates thickening of the colon wall and mesentery with intestinal fluid collection. Ascites appeared on day 47. The intestinal wall thickening was generally decreased, but the wall of the ascending colon remained thickened.

![Autopsy images](image2)

**Fig. 4.** The macroscopic findings at autopsy. (A) The macroscopic appearance of the small intestine and the colon, which was swollen and contained a large number of blood clots *in situ*. Erosive lesions were observed in the mucosa of the entire intestine. (B) Magnified view of the ileum. Segmental intestinal bleeding is present.
RESULTS

Endoscopic findings

Figure 2 illustrates representative serial endoscopic findings in the ileum and colon from days 15 to 65. The patient had his first colonoscopy on day 15, revealing bilious intestinal contents with no signs of mucosal injection or loss. The second colonoscopy was performed on day 26, since the volume of watery stool increased suddenly to 1433 mL a day. There were brown spottings on the sigmoid and descending colon, and the surface was covered with a pseudo-membranous white coat on the transverse and ascending colon. The mucosa was generally injected, but the edematous appearance was slightly relieved compared with the findings of the previous colonoscopy. The ileal mucosa was totally lost and presented a so-called lead-pipe appearance on day 35. Colonoscopy performed on day 52 revealed that the ileal mucosal spots had increased in number. On day 65, the colon contained a large number of blood clots, which occupied the majority of the intraluminal space of the colon. Areas of patchy bleeding were observed on the ileal wall.

Radiological findings

Representative abdominal radiographs and CT images were shown in Fig. 3. CT images revealed that the wall of...
the ascending colon was swollen and edematous as early as day 1, but there were no specific findings in other sites of the gastrointestinal tract (Fig. 3). An abdominal radiograph on day 2 was almost normal. On day 11, the dilated small bowel with prominent ileac gas was observed. The wall thickening of the entire gastrointestinal tract increased thereafter, suggesting the presence of inflammation such as infectious enteritis and radiation-induced enteritis. The volume of ascites was estimated to be 2500 mL by abdominal ultrasonography on day 42. The ileum was partly dilated with gas on day 45 on the abdominal radiograph. The attenuation level was increased in the whole abdomen, which suggested an increased volume of ascites. On day 68, dilatation of the ileum filled with gas was more remarkable. But on day 74, bowel gas decreased and the attenuation level was more prominent in the whole abdomen, which was a so-called gasless abdomen.

Postmortem examination findings

Postmortem examination was performed 4 hours after the patient’s death. The stomach, jejunum, and ileum were filled with coagulated bloody content and were prominently congested at autopsy (Fig. 4). The stomach and small intestine contained 2040 g and 2680 g of clots, respectively. Throughout the gastrointestinal tract, the mucosal epithelial cells were ablated, mucosal congestion was seen, and bleeding occurred in many places (Fig. 4). Dyskaryotic cells proliferated in the stroma, and fibrotic changes in the submucosa and smooth muscle degeneration were also observed (Fig. 5 and 6).

A few squamous cells were observed in the esophagus, and the esophageal glands were partly remnant. No epithelial cells were remnant from the stomach to the ascending colon, but a few epithelial cells were observed in the descending colon, sigmoid colon, and rectum (Fig. 5 and 6). In the colon, fibrotic change was seen in the lamina propria, which was covered partially with regenerating epithelial cells. The proliferative status of the epithelial cells in the descending and sigmoid colon were examined by anti-Ki-67 immunostaining (Fig. 6). In the descending and sigmoid colon, 71% and 35% of the epithelial cells were positive for Ki-67 immunostaining, respectively. In addition, the activity of the apoptotic cascade in these epithelia was also examined by TdT-mediated dUTP-biotin nick end labeling (TUNEL) and anti-p53 and anti-p21 immunostaining (Figs. 6 and 7B). Apoptotic cells were not observed in these epi-

![Fig. 7.](A) Magnified view of hematoxylin and eosin staining of the descending and sigmoid colon. Dyskaryosis was more severe in the descending colon than in the sigmoid colon. (B) Anti-p53 and anti-p21 immunostaining of the descending colon. Staining of the epithelial cells was negative for both.)
thelia, because the epithelial cells were negative for TUNEL as well as for both p53 and p21 immunostaining. On the ileal mucosa, neither mitotic cells nor apoptotic cells were seen. Comparing the epithelial appearance of the descending colon and the sigmoid colon, the dyskaryosis was more severe in the epithelial cells of the former (Fig. 7A). The absorbed dose of each segment of the gastrointestinal tract was estimated from the phantom model of the dose distribution and CT images, as shown in Table 1. Although the methods of estimating these absorbed doses have uncertainties, pathological changes of the radiation-induced tissue injuries in each segment of the gastrointestinal tract appeared to be dose-dependent in general.

Major findings other than those for the gastrointestinal systems were previously reported elsewhere.

**DISCUSSION**

We report the clinical course and the pathological features of the gastrointestinal tract in a severely radiation-exposed victim of the 1999 Tokai-mura criticality accident. At 82 days after the accident, the patient died of MOF caused by acute radiation syndrome, especially by gastrointestinal syndrome due to radiation exposure.

Abdominal radiograph revealed enlargement of the small intestine on day 11. Since then, the small intestine was consistently swollen, and Kerckring’s folds were not observed on the abdominal radiograph. This suggested peristaltic dysfunction, although no clinical signs of such abnormalities were seen. The mucosa of the colon, however, appeared almost normal during the colonoscopy on day 15. These observations together indicate that functional disruption of the gastrointestinal tract preceded the morphological changes. Watery diarrhea started on day 26, and on the same day the second colonoscopy revealed multiple spotty bleeding on the mucosa of the colon. Thereafter, the symptom of watery diarrhea deteriorated and bloody diarrhea also developed. These observations can be interpreted as a collapse in the absorptive function of the gastrointestinal systems due to radiation exposure, with no obvious recovery process. Total depletion of the mucosa, which was observed both during the colonoscopy and at autopsy, appeared to cause these gastrointestinal malfunctions.

There are some previous reports on autopsy results after acute radiation exposure accidents. In the Los Alamos criticality accident of 1946 and in the Norwegian case of Co gamma ray exposure in 1982, victims were exposed to doses similar to that received by the patient we present here, and they died on the 9th day and 13th day after exposure, respectively (estimated approximate systemic dose of 21 Gy for the Los Alamos case and 10–30 Gy for the Norwegian case). At autopsy, the gastrointestinal epithelium was entirely depleted in those two cases. In general, the patient experiences radiation-induced gastrointestinal syndrome 4–10 days after exposure to a dose in the range of 5–12 Gy. The Los Alamos and Norwegian cases appeared to present typical clinical courses.

On the other hand, the mucosa of the colon looked almost normal in the patient we treated by the colonoscopy even on day 15. In addition, this patient did not suffer from apparent symptoms of MODS before day 18, when a deep burn developed in the right forearm and was presumed to be the onset of MODS. The reason for this difference is unknown, but the early start of intensive care for this patient might have had a good clinical effect; such care included blood stem cell transfusion on days 6 and 7, prophylactic administration of anti-bacterial, anti-fungal, and anti-viral drugs started on day 2, selective digestive tract decontamination, and intravenous administration of high-dose L-glutamine. Ziegler et al. suggested that infection might alter gut barrier function to facilitate translocation of bacteria and absorption of endotoxin. Inflammation cascade following such major stress contributes to a patient’s susceptibility to MODS.

Many other radiation accident victims who received a systemic dose of greater than 10 Gy are reported to experience similar clinical courses of gastrointestinal malfunctions.

**Table 1. The estimated absorbed dose by the gastrointestinal tract**

| Site            | Gamma ray (Gy) | Neutron beam (Gy) | Total dose (Gy) | Equivalent dose (GyEq) |
|-----------------|----------------|-------------------|----------------|------------------------|
| Esophagus       | 8.8–13.9       | 1.1–4.6           | 9.8–18.5       | 10.6–21.7              |
| Stomach         | 9.1–25.1       | 1.9–16.3          | 11.0–41.3      | 12.3–52.7              |
| Small intestine | 7.2–29.2       | 2.1–19.0          | 9.3–48.2       | 10.7–61.6              |
| Ascending colon | 20.9–33.8      | 15.1–24.5         | 36.0–58.4      | 46.6–75.5              |
| Descending colon| 8.4–13.7       | 1.0–7.6           | 9.5–21.2       | 10.2–26.5              |
| Sigmoid colon   | 10.3–12.5      | 3.3–6.7           | 13.7–19.2      | 16.0–24.0              |

Notes. The absorbed dose of each segment of the gastrointestinal tract was estimated by projecting CT images acquired after the patient’s hospitalization on the phantom model of the dose distribution. The equivalent doses were calculated assuming the relative biological effectiveness of the neutron beam as 1.7 according to the report by National Institute of Radiological Sciences.

10.6–21.7
These symptoms included nausea, vomiting, and mild diarrhea shortly after the exposure, with no obvious deterioration for several days. Thereafter, the symptoms deteriorated progressively to watery diarrhea and bloody stool, resulting in MODS. The diminished barrier function of the gastrointestinal tract is associated with systemic infection or MOF after acute radiation exposure, as is in the case of trauma or skinburns.\textsuperscript{3,12–15}

The systemic radiation dose was inhomogeneous. The dose to the ascending colon was assumed to be highest among segments of the gastrointestinal tract, because the patient was irradiated from the right-anterior direction from the detailed inquiry about the situations and the postures of each victims at the accident.\textsuperscript{16–18} The severity of the radiation damage to the gastrointestinal tract in the patient presented here depended on the absorbed dose (Figs. 5 and 6 and Table 1). Total depletion of the epithelial cells in the ileum and ascending colon indicates high-dose radiation, whereas the mucosa in the esophagus, descending colon, and sigmoid colon was less damaged because of the relatively lower radiation dose. At autopsy, the epithelial cells were positive for Ki-67 staining and negative for both p51 and p21 immunostaining in the descending and sigmoid colon, implying active proliferation of the epithelial cells without activation of the apoptotic cascade (Figs. 6 and 7B). This is interpreted as the process of tissue recovery of the colon epithelium from radiation injury. Pathologically, the absorbed dose in the descending colon was speculated to be higher than that in the sigmoid colon, because the rate of Ki-67-positive epithelial cells was higher and dyskaryosis of the epithelial cells was more severe in the descending colon (Fig. 7A). These observations did not appear to reflect the estimated absorbed dose shown in Table 1 (10.7–25.2 GyE in the descending colon vs. 16.0–24.0 GyE in the sigmoid colon). Possible explanations for this include: (a) the inherent uncertainties of absorbed-dose estimation;\textsuperscript{6,17} (b) the posture-related differences in the positions of the descending and sigmoid colon in the abdomen between the time of the accident and that of the CT examination used for calculation of the absorbed dose of each gastrointestinal segment; (c) the location on the colon of the tissue sample used for the pathological evaluations. However, pathological findings in terms of tissue injury caused by acute radiation exposure generally correlated well with the estimated absorbed dose of each segment of the gastrointestinal tract.

When a person is exposed to radiation exceeding the dose at which bone marrow death occurs, bone marrow or stem cell transplantation is generally considered.\textsuperscript{19} For many radiation victims, however, even successful bone marrow or stem cell transplantation would not have enabled them to survive acute radiation syndrome.\textsuperscript{7} Those patients died of MOF with severe gastrointestinal syndrome, as far as the dose was not sufficient to cause radiation-induced central nervous system or myocardial injuries. Moreover, radiation accidents themselves are rare. Accordingly, it is quite important to describe both the clinical course and the pathological confirmation and to confirm the pathology in order to assess the radiation effects on the gastrointestinal systems. In this respect, our report is unique in its focus on the clinical course and the pathological features of the gastrointestinal function.

In conclusion, the epithelial cells in the stomach, ileum, and ascending colon were totally depleted, but a small portion of the epithelial cells was remnant in the esophagus, descending colon, sigmoid colon, and rectum at autopsy. The degree of radiation injury of the gastrointestinal tract in this patient differed pathologically by the position in the abdomen, depending possibly on the radiation dose. These findings we presented here in this report have not been described \textit{in vivo} in the previous literature, although it is a well-known fact that the whole body radiation dose is inhomogeneous in the victim of an accident of high-dose radiation exposure. Detailed inquiry about the situations at the Tokai-mura criticality accident enabled us to specify the radiation dose absorbed in each segment of the gastrointestinal tract in this patient and to clarify the correlation between the absorbed dose and the severity in the gastrointestinal damages. In this point of view, detailed description of the patient’s course contributes to an understanding of the fundamentals of acute radiation injuries and to clinical decision-making for the treatment of such patient.

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Written informed consent to publish the patient’s data including descriptions, radiographs, and photographs was obtained from the patient’s family.

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