

Initial Symptoms of Acute Radiation Syndrome in the JCO Criticality Accident in Tokai-mura

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A criticality accident occurred on September 30, 1999, at the uranium conversion plant in Tokai-mura (Tokai-village), Ibaraki Prefecture, Japan. When the criticality occurred, three workers saw a “blue-white glow,” and a radiation monitor alarm was sounded. They were severely exposed to neutron and γ -ray irradiation, and subsequently developed acute radiation syndrome (ARS). One worker reported vomiting within minutes and loss of consciousness for 10–20 seconds. This worker also had diarrhea an hour after the exposure. The other worker started to vomit almost an hour after the exposure. The three workers, including their supervisor, who had no symptoms at the time, were brought to the National Mito Hospital by ambulance. Because of the detection of γ -rays from their body surface by preliminary surveys and decreased numbers of lymphocytes in peripheral blood, they were transferred to the National Institute of Radiological Sciences (NIRS), which has been designated as a hospital responsible for radiation emergencies. Dose estimations for the three workers were performed by prodromal symptoms, serial changes of lymphocyte numbers, chromosomal analysis, and ²⁴Na activity. The results obtained from these methods were fairly consistent. Most of the data, such as the dose rate of radiation, its distribution, and the quality needed to evaluate the average dose, were not available when the decision for hematopoietic stem cell transplantation had to be made. Therefore, prodromal symptoms may be important in making decisions for therapeutic strategies, such as stem-cell transplantation in heavily exposed victims.

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INTRODUCTION

Early in the morning of March 1, 1954, twenty-three Japanese fishermen saw a huge red light and heard a detonation sound while on board a fishing boat, the 5th "Fukuryu-maru" (Lucky Dragon). They had been exposed to a thermo-nuclear test explosion at Bikini Atoll of the Pacific Ocean, and suffered from acute radiation injuries^{1,2)}. To our knowledge, this was the first accidental whole-body exposure to radiation that required medical care in Japan. In September, 1971, a radiological accident occurred at an industrial radiation facility in Ichihara-city, Chiba Prefecture, 50 km southeast of Tokyo³⁻⁹⁾. In this accident, six construction workers were accidentally exposed to γ -rays from an ^{192}Ir source, and developed acute radiation syndrome. Twenty-two years after the accident, one of them developed angiopathy, which caused necrosis and atrophy of bones in his right hand¹⁰⁾. Since 1963, however, when the first nuclear reactor started operation in Japan, we have fortunately not had any nuclear accidents that required medical care for the people involved.

Criticality occurs when a sufficient quantity of fissionable material is accumulated, resulting in the liberation of nuclear energy; slightly enriched uranium systems require much larger quantities of material to achieve criticality. Historically, nuclear criticality accidents have occurred in facilities where factors that influence the criticality are studied, or where scrap is processed to recover valuable fissionable material. On the other hand, nuclear criticality accidents rarely occur. There have been 14 fatalities reported (personal communication with Dr. Mettler F, University of New Mexico). However, a fatal criticality accident did occur on September 30, 1999, at a uranium conversion facility in Tokai-mura, Ibaraki Prefecture, Japan. This article focuses on the initial dose assessment based on the initial symptoms of the workers involved in the JCO Criticality Accident in Tokai-mura.

OUTLINE OF THE ACCIDENT

Tokai-mura is located about 130 km Northeast of Tokyo and faces the Pacific Ocean. This "Nuclear Village" has a population of 34,000, and many nuclear facilities, such as The Japan Atomic Energy Research Institute and The Japan Nuclear Cycle Development Institute, are based there. There are also several companies related to these institutes. In this village, the criticality event occurred. The criticality was unexpectedly initiated when a worker (B) on a platform was leaning over a precipitation tank and pouring a nitrate solution of enriched ^{235}U in a stainless-steel bucket into the tank through a funnel. Another worker (A) was standing besides the tank holding the funnel. At the time of the accident, the three workers, including their supervisor (C), saw a "blue flash," and heard an alarm of the γ -radiation monitor sound. These three workers developed acute radiation syndrome (ARS) and were brought to the National Mito Hospital by ambulance. The initial Geiger-Muller (G-M)-counter readings from the body surface at the National Mito Hospital showed a much higher radioactivity than the background level. These results led doctors at the National Mito Hospital to consider that the patients had been contami-

nated with radionuclides, since no information about the accident was provided to them from the facility. They, therefore, organized to transfer these patients by helicopter to the National Institute of Radiological Sciences (NIRS) in Chiba City, which is located 120 km south, and directed the ambulance to the heliport in Mito-city. When the ambulance arrived at NIRS 5 hours after the exposure, radiation safety officers and health physicists checked the body surfaces of the patients by a survey meter. B- γ survey meters detected significantly higher levels of radioactivity than those of the background. However, α survey readings detected only the background level. Radiation safety officers also checked the blankets that covered the patients. In contrast, only a low level of radioactivity was detected. During the trip from the heliport in Chiba-city to NIRS, Worker A suffered from episodes of nausea, vomiting, and diarrhea in the ambulance. The staff of the ambulance kept his vomitus in plastic bags. Physicists detected ^{24}Na clearly in the vomitus in the evening, which led us to assume that a criticality accident had occurred and that neutrons had been emitted.

INITIAL SYMPTOMS

A flash was visible to Worker C, the supervisor of Workers A and B, who was located a few meters away from the tank and shielded by the wall of another room. Worker C correctly interpreted the meaning of the blue flash and γ -ray alarms sounded when he saw the flash. He asked the other two workers to get out of the room immediately. Upon criticality, Worker B complained of feeling a tingling in his neck, chest, arms, and hands and numbness in his fingers. These two workers went through the exit of the building and ran to a decontamination room located in the other building. He also asked a man who heard the γ -alarm to call an ambulance. Upon reaching the room, Worker A went to the bathroom, and then developed nausea and vomiting in the decontamination room five to eight minutes after the accident. At about the same time, he lost consciousness and had cramping for 10 to 20 seconds. Worker B put his hand into the mouth of Worker A to force it open. He soon regained consciousness, but had amnesia for a while. About ten minutes after the accident had occurred, an ambulance arrived. Worker A was placed in the ambulance on a stretcher, and the other two workers walked into the ambulance 50 minutes after the exposure. During the next ten minutes, Worker A had diarrheal stools and Worker B also developed nausea and vomiting. The ambulance left the facility for the National Mito Hospital, a large general hospital in the region, and arrived there 90 minutes after the accident. At this hospital, primary radiological surveys detected γ -rays from the body surfaces of these workers. Since their hematologic data 2–3 hours after the accident showed markedly reduced numbers of lymphocytes, suggesting high-dose exposure to radiation and suspected contamination with radionuclides, they were transferred to (NIRS). Since these patients had prodromal symptoms suggesting high-dose irradiation (described later in this article) and detected levels of radiation from the body surface were not so high as to affect the health of the medical staff, these patients were moved from a triage room to inverse isolating rooms.

HEMATOLOGY

Lymphocytes belong to one of the most sensitive groups of cells to radiation. The peripheral blood lymphocyte count and its serial change at an early phase of ARS also allowed us to estimate the radiation doses¹¹⁾. The total white blood cell, granulocyte and lymphocyte counts at an early phase are given in Table 1. This data showed the prominent leukocytosis and lymphocytopenia typical of heavily irradiated victims. Moreover, the numbers of lymphocytes of Workers A and B reached zero on Day 3 and 7, respectively (data not shown). The early disappearance of lymphocytes observed in Workers A and B suggested an ominous prognostic sign of high-dose irradiation. Furthermore, an increase in the hematocrit and hemoglobin levels was observed, as compared to those 6 months before the accident; these workers showed a post-exposure hemoconcentration. These two workers vomited and sweated heavily on the day of the accident. In spite of more than 5 liters of fluid administration to these workers, however, signs of hemodilution were not seen. Moreover, Worker A had erythema and swelling on the forearms, hands, face, trunk, and feet. Worker B also had mild erythema and swelling on the face. Thus, progressive leakage into extravascular spaces was particularly obvious clinically.

Table 1. Numbers of blood cells 2–3 hrs after the accident.

Name	WBC ($\times 10^6$ cells /L)	RBC ($\times 10^{10}$ cells/L)	PLT ($\times 10^{10}$ cells/L)	Hb* (g / dl)	Granul ($\times 10^6$ cells /L)	Lymph ($\times 10^6$ cells /L)	Hct ** (%)
A	22,800	533	16.1	18.0	21,888 (97%)	684 (3%)	53.1
B	12,700	424	15.9	14.3	12,446 (98%)	127 (1%)	41.6
C	11,500	558	16.5	18.3	10,005 (85%)	1,495 (13%)	52.8

WBC; white blood cells, RBC; red blood cells, PLT; platelets, Hb; hemoglobin, Granul; granulocytes, Lymph; lymphocytes.

* Levels of hemoglobin of A, B, and C 6 months before the accident were 15.7 g/dl, 13.1, and 15.0, respectively.

** Hematocrit values of A, B, and C 6 months before the accident were 45.9 (%), 38.5 and 45.7, respectively.

OTHER INITIAL FINDINGS

Blood pressure

Worker A was hypotensive with a systolic pressure of 70-mmHg on admission to NIRS, which required anti-shock agents, such as steroid hormone, to improve the steady decline in their pressure. After his initial fluid losses in his attacks of vomiting and diarrhea, he was oliguric in spite of large amounts of intravenous fluid administration.

Amylase in serum

When these workers were transferred to NIRS, they developed a painful bilateral enlargement of the parotid glands (Fig. 1). An examination of serum amylase in the three workers showed

that its levels had increased in a time-dependent manner (Table 2). Worker A had a level of about 3-times more than the upper limit of the normal range in our hospital 9 hours after the exposure, and the level reached 9-times more the next day. Worker B had a higher level of amylase compared to the normal value when he came to NIRS; the level was approximately 10-times the upper limit of the normal range on Day 1. The amylase level of Worker C was within the normal range, whereas it started to increase gradually during the day of the accident, and was almost 5-times over the normal limit on Day 1.



Fig. 1. A painful enlargement of the parotid gland developed in a patient.

Table 2. Serum amylase levels upon admission.

Workers	Day 0 (16:00)	Day 0 (19:40)	Day 1 (7:00)
Normal	76 – 231 (IU / ml)		
A	176	781	2,143
B	421	1,593	2,454
C	104	187	1,094

INITIAL DOSE ASSESSMENT

One of the most important things for treating victims exposed to radiation is to estimate the exposure dose. When high-dose exposure is considered, an initial dose estimation must be performed in order to determine the treatment strategy as soon as possible. However, the radiation in criticality accidents is a complex combination of neutrons and γ -rays of different energies. Therefore, the radiation doses received by exposed persons are the subject of a great deal of work and discussion. For making strategy decisions for treatment, including the hematopoietic stem-

cell transplantation of heavily exposed victims, we tried a preliminary dose evaluation from the prodromal symptoms of those workers and doses corresponding to those in the literature on previous accidents^{12,13}. Since most of the results in the literature were derived from accidents of exposure to γ -rays and are presented as Gy, we evaluated the doses of these patients as Gy equivalent to γ -rays (GyEq).

Acute radiation syndrome (ARS) is caused by a brief exposure of a major part of the body to more than approximately 1 Sv¹³. ARS is characterized by 1) an initial prodromal stage of malaise, nausea, vomiting, and diarrhea, 2) a latent, symptom-free period, 3) a critical or manifestation phase that usually takes one of four forms: hematologic, gastrointestinal, cardiovascular, and neurological, depending upon the exposure dose, and 4) a recovery phase or death. The severity of the clinical symptoms at the prodromal phase of ARS from which these workers suffered is illustrated in Fig. 1. Worker A started to vomit within a few minutes of the exposure and developed diarrhea less than an hour after. At the time of admission to NIRS, his body temperature rose to 38.5°C without any evidence of infection. From these clinical symptoms, the estimated dose which he received was thought to be, at least, more than 8 GyEq. Furthermore, he lost consciousness upon criticality. From these symptoms, we estimated his dose to be at least 10 GyEq. Worker B started to vomit almost one hour after exposure. This episode suggests that his dose was around 6 and 8 GyEq. Worker C became nauseated about 5 hours after the exposure, but did not vomit. We estimated his exposure dose as having been less than 4 GyEq. Dose estimations for the three workers were also performed by chromosomal analysis and ²⁴Na activity (data not shown). The values obtained from these methods were fairly consistent. The average doses to the whole-body for Workers A, B, and C were 16–20 GyEq, 6–10 GyEq, and 1–4.5 GyEq, respectively. Moreover, there was other information available for a dosimetric evaluation. Hair was also analyzed for induced phosphorus-32 (³²P) (data not shown).

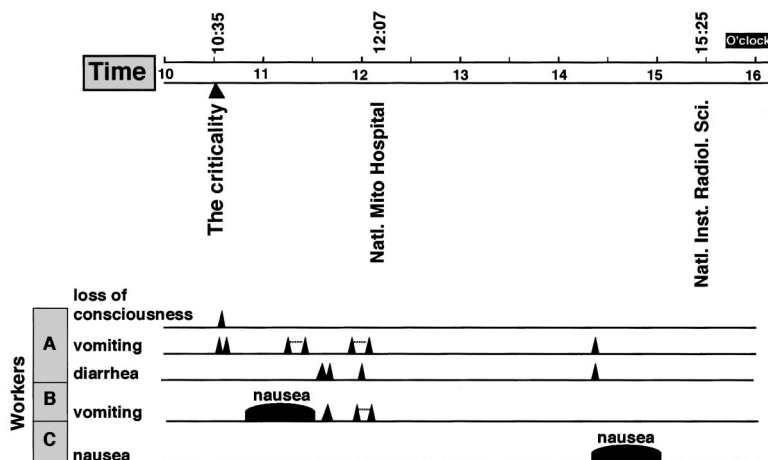


Fig. 2. Prodromal symptoms of acute radiation syndrome in the three workers.

DISCUSSION

The prodromal stage of acute radiation syndrome shows a variety of symptoms, such as malaise, nausea, vomiting, diarrhea, and consciousness disturbance^{12,13}. In the accident discussed here, one patient had consciousness disturbance; he lost consciousness within a few minutes of the exposure, but recovered soon. Previous reports of accidents have shown that consciousness disturbance, such as unconsciousness, coma, and convulsions, were observed in victims exposed to more than almost 50 Sv^{12,13}. In a criticality accident, unconsciousness within about 10 minutes of the exposure was reported in a patient who was exposed to 45 Gy of the average total body dose from neutrons and γ -rays¹⁴⁻¹⁶. This immediate incapacitation was followed by hypotension. In the Tokai-mura accident, Worker A was also hypotensive about 6 hours after the criticality, while his blood pressure was recovered by the administration of steroid hormone. Cardiovascular collapse can occur from more than 30 Gy of total body exposure before a massive loss of fluid and electrolytes¹⁷. Furthermore, studies using experimental animals have shown that irradiation of the head alone can induce hypotension^{18,19}. On the other hand, in a criticality accident which occurred in Sarov, Russia, a victim had hypotension, but no consciousness disturbance after having been exposed to estimated doses of 45 Gy from neutrons and 3.5 Gy from γ -rays (personal communication with Dr. Gusev I, Institute of Biophysics, Moscow, Russia). The nature of the radiation in criticality accidents is complex; a complex combination of neutrons and γ -rays, their energies, and the positions at exposure of the victims vary in each accident. Therefore, it is very difficult to compare each accident. However, these symptoms have been observed in many of the criticality accidents²⁰. The occurrence of transient consciousness disturbance and hypotension during the early phase, probably due to systemic vascular damage, may be characteristics of the instantaneous exposure to high-dose radiation, such as that in criticality accidents. Furthermore, one of the workers in the accident reported here had vomiting within minutes of the exposure. A sudden onset of vomiting may also be involved in a mechanism for immediate incapacitation.

Granulocytosis is commonly observed in victims exposed to high-dose irradiation, and has been shown in experimental animals that have been irradiated²¹. However, the mechanisms are still unclear. Previously, we found that irradiation induces the production of cytokines, such as granulocyte-colony stimulation factor (GM-CSF) and interleukin-1 (IL-1) in human fibroblasts^{22,23}. Fibroblasts constitute a major element of bone-marrow stroma, and the administration of GM-CSF increases the number of granulocytes *in vivo*²⁴. An increase in temperature after exposure to irradiation is thought to be one of the reactions to circulating protein breakdown products and post-diarrheal loss of fluid²⁰. Inflammation also enhances the production of hematopoietic growth factors, including GM-CSF. The granulocytosis typically observed in heavy irradiation may be due to not only an outpouring of these cells from bone marrow and other tissue reserves in response to widespread tissue damage²⁰, but also an enhanced production of hematopoietic growth factors.

An increased level of amylase in serum commonly occurs when radiotherapy is given in the treatment of head- and neck-cancers. This radiation injury is also observed in patients with thyroid cancer treated with iodine 131 (¹³¹I)²⁵. One study has reported that increased levels of

amylase in serum were observed for doses to the parotid glands over 0.5 Gy and irradiation over 2 Gy to these glands induced higher levels of amylase, more than 2.5-times the upper normal value 24 hrs after irradiation in 91% of patients²⁶). Another study also demonstrated a close correlation between the peak rise in serum amylase and the amount of parotid tissue in the treatment volume²⁷). Moreover, it has been reported that early damage of rat salivary gland function was seen as early as one day after radiation^{28,29}). In the Tokai-mura accident, serum levels of amylase were also elevated in these three workers, and that magnitude was almost dose-dependent on the dose to the head and neck regions (data not shown); the elevation was particularly remarkable in Worker B. A further study of the isozyme confirmed that elevated levels of amylase had originated from the salivary glands. Taken together, these results suggest that the increased level of serum amylase may be a good biological dosimeter for dose assessment in accidentally irradiated patients, although further studies are required. On the other hand, the exact mechanisms behind the inherent radiosensitivity of salivary glands remain to be elucidated, since a salivary gland is not a proliferating tissue, and these cells are expected to be later responders to radiation. Apoptosis is a primary mechanism of radiation-induced damage in cells, including salivary glands³⁰). An *in vivo* study has shown that the irradiation of 2 Gy induced apoptosis in rat parotid and submandibular glands about 7.5 and 24 hrs after irradiation³¹). In this study, however, apoptosis was observed in at most 3% of the cells and plateaued at a dose of 5 Gy; no dose-effect relationship was found for doses of over 5 Gy. Therefore, a small amount of cell loss due to apoptosis cannot explain the markedly high levels of amylase in victims. An increased permeability of cell membranes in salivary gland cells may contribute to the higher levels of serum amylase, rather than apoptosis.

Clinical symptoms at the prodromal phase of ARS that appeared after the exposure in the Tokai-mura criticality accident in Japan and the initial dose assessment from these symptoms have been described in this article. However, there is an important point to be discussed. In the Tokai-mura accident, no information about the accident, such as the type of exposure and the possibility of contamination with radionuclides, was provided to staff of the Tokai Fire Department, the National Mito Hospital, or NIRS. Therefore, several problems arose. The staff of the Tokai Fire Department tried to find a hospital that would accept the patients. However, it took almost one hour to find a hospital, since contamination had not been ruled out. Moreover, the detection of γ -rays by the initial G-M-counter readings from the body surfaces led the hospital staff to believe that the patients were contaminated with γ -rays emitters. The reason why this information was not provided is not clear. In the latest accident, the company ignored the procedures approved by the government, which required dissolving the uranium powder with added nitric acid in a dissolution tank. Actually, the uranium powder was dissolved in a 10 liter stainless-steel container. They poured three batches (1 batch: 2.4 kgU) of uranyl nitrate solution into a precipitation tank which was designed to limit the mass to one batch. Therefore, the criticality was indeed an unexpected event in the facility. This probably made the company confused. Since radiation cannot be detected unless special devices or apparatus are used, information about the accident is extremely important.

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