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Multi-organ involvement in the patient who survived the Tokai-mura criticality accident

T HIRAMA, MD, PhD and M AKASHI, MD, PhD

Department of Radiation Emergency Medicine, Research Center for Radiation Emergency Medicine, National Institute of Radiological Sciences, Chiba, Japan

Abstract. The clinical course of the only survivor among the three victims of the Tokai-mura criticality accident in 1999 is presented. The patient was exposed to more than 2 Gy in total of neutrons and γ-rays and consequently exhibited severe bone marrow failure during the first month after the exposure, for which granulocyte colony-stimulating factor was administered and measures to prevent infection were taken. Hypoxemia, interstitial oedema of the lungs, epilation and gingival lesion were also noted but were not clinically serious. The patient recovered from the disease and as of December 2003 remains well. In the chronic phase, the patient exhibited cataract and transient subclinical hypothyroidism.

Introduction

Exposure of a large part of the body to a high dose of ionising radiation results in severe damage to multiple organs in the body such as the bone marrow, gastrointestinal tract and cardiovascular system. This has been referred to collectively as acute radiation syndrome (ARS). Unwanted nuclear chain reactions, or nuclear criticality accidents, are often the cause of the syndrome. If in the immediate vicinity of the chain reaction, victims typically survive less than 10 days [1–4].

In the Tokai-mura criticality accident in 1999, three victims were exposed to mixed flux of neutrons and γ-rays, all of whom consequently developed ARS [5]. Patients A and B were very close to the source of radiation, whereas Patient C was several metres away. The three patients were initially admitted to the National Institute of Radiological Sciences (NIRS), where their symptoms and clinical signs were carefully observed to evaluate the severity of the damage caused by irradiation [5, 6]. At the same time, physical and biological methods were employed to estimate the irradiated dose to the patients [7, 8]. For example, based on the amount of ^{24}Na in the blood and the predicted neutron/γ-ray ratio, the estimated doses were 5.4 Gy of neutrons and 8.5 Gy of γ-rays for Patient A, 2.9 Gy of neutrons and 4.5 Gy of γ-rays for Patient B, and 0.81 Gy of neutrons and 1.3 Gy of γ-rays for Patient C [7]. Patient A, whose severity of the disease might be comparable with a historic patient who survived 9 days based on the dynamics of haematological parameters [5], received peripheral blood stem cell transplantation and survived 82 days [9]. Likewise, Patient B, who might be comparable with another historic patient who survived 1 month [5], received cord blood stem cell transplantation and survived 210 days [10]. In addition to the haematopoietic stem cell transplantation, state of the art therapy including the management of respiratory and circulatory conditions and the prevention and early treatment of infection must have significantly contributed to their unprecedented long survival. Survival of the patients well beyond the period of bone marrow suppression demonstrated that bone marrow failure per se was no longer the cause of death in ARS, but instead, for the first time, a spectrum of multiple organ involvement and failure was observed. In this regard, the clinical picture of Patient C, who was less severely irradiated than Patients A and B and who consequently survived the accident, would surely serve as the standing point from which to look at the other two patients. This report describes the clinical course of Patient C up to 2003, complementing recently published literature that largely covered the acute period of the disease [5].

Address correspondence to Toshiyasu Hirama, MD, PhD, Department of Radiation Emergency Medicine, Research Center for Radiation Emergency Medicine, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. E-mail: hirama@nirs.go.jp.

Patient data

Patient C was a 54-year-old male with a previous history of elevated blood pressure for 5 years, hyperuricaemia for unknown duration, positive urine sugar for 2 years, and right bundle branch block on electrocardiogram for at least 1 year. However, the patient had never been diagnosed with hypertension or diabetes mellitus. Among his family, his father was diagnosed with hypertension. Patient C experienced slight nausea several hours after exposure while he was aboard a helicopter on the way to the NIRS. On admission, he had slight but diffuse skin erythema. Mild infection of the conjunctiva bulbi was noted. After admission he complaint of thirst, but was otherwise asymptomatic. His blood pressure was 120–80 mmHg and his pulse rate was 90 min^{-1}. The day was rather a hot one, so it could not be certain whether the erythema and blood pressure, which was rather low, were associated with irradiation.

Therapeutic strategy

Unlike Patients A and B, who received peripheral blood stem cell transplantation at the University of Tokyo Hospital and cord blood stem cell transplantation at the

Hospital of the Institute of Medical Science, the University of Tokyo, respectively [9, 10], Patient C remained at the NIRS and was treated without haematopoietic stem cell transplantation. Measures to help bone marrow recovery and to prevent infection were taken, including administration of granulocyte colony-stimulating factor (G-CSF), selective gastrointestinal tract sterilisation until stool culture was negative, prophylactic administration of antifungal and antiviral reagents, and reverse isolation while necessary. Until the severity of his disease was evaluated, his body fluid balance was maintained as in the other two patients, by infusing electrolytes and plasma under central venous pressure monitoring. Laboratory tests revealed that he had diabetes mellitus, which was controlled with rapid-type insulin and diet therapy. His blood pressure remained normal in the hospitalised situation. Pentoxyfyllin was also administered to improve microcirculation, as well as glutamine to facilitate epithelial recovery in the gut.

Damage to the organ systems

Clinical findings in Patient C for each organ system are described below. Information regarding damage to the haematopoietic and respiratory systems has been published elsewhere [5] and is therefore only briefly reviewed here.

Haematopoietic system

On admission (day 0), 5½ h after exposure, the neutrophil count was $13.7 \times 10^9\ l^{-1}$. It decreased to $6.7 \times 10^9\ l^{-1}$ on the next day, then increased in response to G-CSF (4.4–7.4 $\mu g\ kg^{-1}\ day^{-1}$), which was started on the evening of day 2. Neutrophils then decreased and reached a nadir of $1.09 \times 10^9\ l^{-1}$ on day 20. The patient was kept under reverse isolation while the neutrophil count was at its lowest. Following recovery of the neutrophil count, administration of G-CSF was reduced and was eventually discontinued on day 28. The decrease of platelets in this patient was slower than that in the other two patients, but necessitated platelet transfusion on days 17, 20 and 23. Thereafter platelets made a gradual recovery. The number of lymphocytes was lowest on day 2 and also made a slow recovery. This is in sharp contrast to Patients A and B, in whom lymphocytes disappeared from the peripheral blood on day 3 and day 7, respectively. Serum immunoglobulins were normal throughout the course. Haemoglobin concentration was $175\ g\ l^{-1}$ on admission, which was not significantly altered from his previous values (data not shown), and slowly decreased to $102\ g\ l^{-1}$ on day 26 without any evidence of bleeding. Reticulocytes comprised 2% of red cells on admission, decreased during the first week to 0.8%, underwent two transient rises before increasing to 4.2% on day 31, and stayed high for about a month. Bone marrow taps on day 1 showed hypocellular marrow with decreased erythroid series and some morphologically abnormal megakaryocytes. The myeloid series was described well preserved. Patient C recovered from haematological nadir without major complications, despite a transient rise of serum C-reactive protein, which was judged to be due to gingivitis.

Respiratory system

The three patients exhibited transient hypoxemia starting on the day of exposure, for which oxygen was given via nasal prongs. In Patient C, partial pressure of oxygen in arterial blood (PaO_2) was 62.6 mmHg on admission, with 94% oxygen saturation. CT of the chest taken on day 1 was suggestive of interstitial oedema of the lungs [5]. The CT findings, together with the PaO_2, improved remarkably by day 6, leaving only minimal reticular shadows.

Skin and mucosa

Despite the diffuse erythema of the skin on the day of admission, the patient did not subsequently exhibit desquamation of the skin that is characteristic of high dose exposure. However, approximately 1 month after exposure the patient claimed that his beard had hardly grown since the accident. At that time spotty epilation on his scalp was also noted (Figure 1a). He had moderate but diffuse gingivitis, for which weekly hygienic care by a dentist was arranged, with very little effect. The dentist described the gingivitis as being unusually poorly responding, and tended to ascribe it to irradiation. On day 33, when the patient had regained neutrophils, his left lower gum became purulent and painful. On day 19, a localised painless defect on the oral mucosa was found on the upper left gum (Figure 1b). Although it resembled squamous cell carcinoma because it lacked surrounding inflammatory manifestations, it spontaneously healed within a week. We reasoned that the phenomenon was due to the fragility of the mucosa and lack of inflammation, both associated with irradiation.

Other laboratory findings

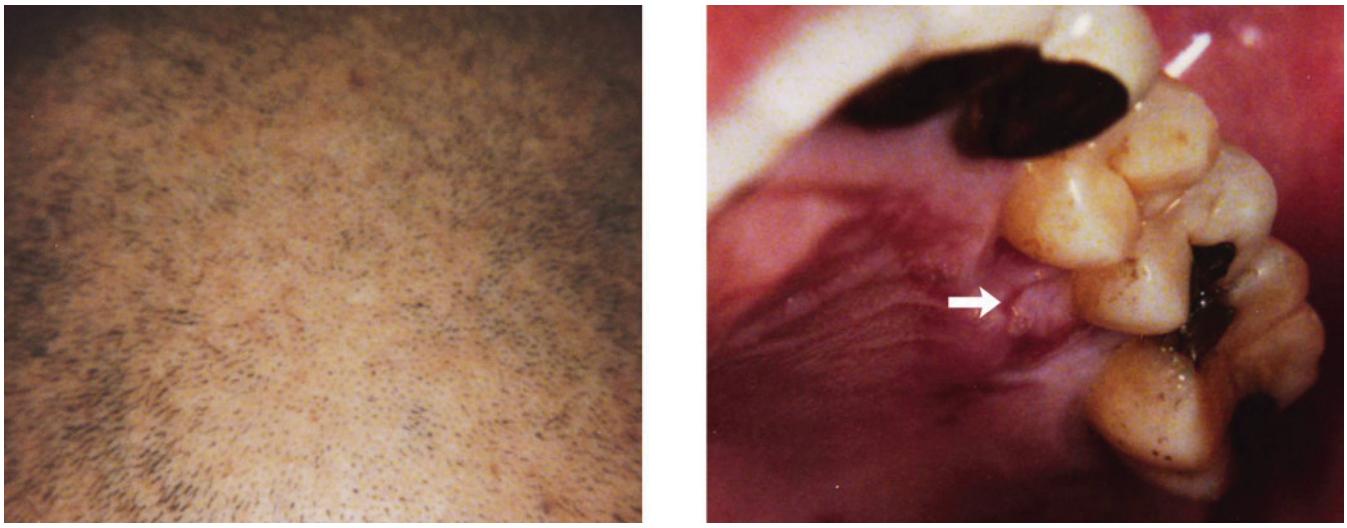
Serum amylase of salivary gland origin increased during the first 24 h, then returned to normal in a few days. Uric acid decreased during the first week of admission, which was in sharp contrast to Patients A and B in whom uric acid level markedly increased initially (Table 1). The patient declined a proposal to examine his sperm. However, serum follicle-stimulating hormone increased transiently after the accident, suggesting damage to spermatogenesis (Figure 2a). It then apparently returned to his baseline level, which appeared to be higher than the normal range. Serum luteinising hormone has been normal.

The eyes

Because he had diabetes mellitus, periodical check-ups by an ophthalmologist were arranged shortly after his admission to the NIRS. On day 19, the ophthalmologist

Table 1. The dynamics of serum uric acid ($mg\ dl^{-1}$) in the three patients (normal range 3.0–7.5 $mg\ dl^{-1}$)

Patient	Day 0	Day 1
A	9.0	11.2
B	8.5	9.8
C	6.7	6.2



(a) (b)

Figure 1. Effect of ionising radiation on the skin and mucosa of Patient C. (a) Spotty epilation on the scalp on day 33. (b) Painless defect (arrow) on the oral mucosa found on day 19.

found no signs of cataract or retinopathy. On day 55, soft exudates were noted in both eyes. The soft exudates have so far been worsening, sometimes accompanied by retinal bleeding. On his visit 33 months after the accident, posterior subcapsular type cataract, which is typical following irradiation to the eyes, was diagnosed in both eyes. The patient underwent lens extraction the following month.

Chronic phase

As of December 2003, 4 years have passed since the accident. After the patient was discharged from the NIRS on 20 December 1999, he went back to his home near Tokai-mura and has been followed up by a nearby physician. So far, control of diabetes mellitus has been insufficient. He also takes antihypertensive reagents.

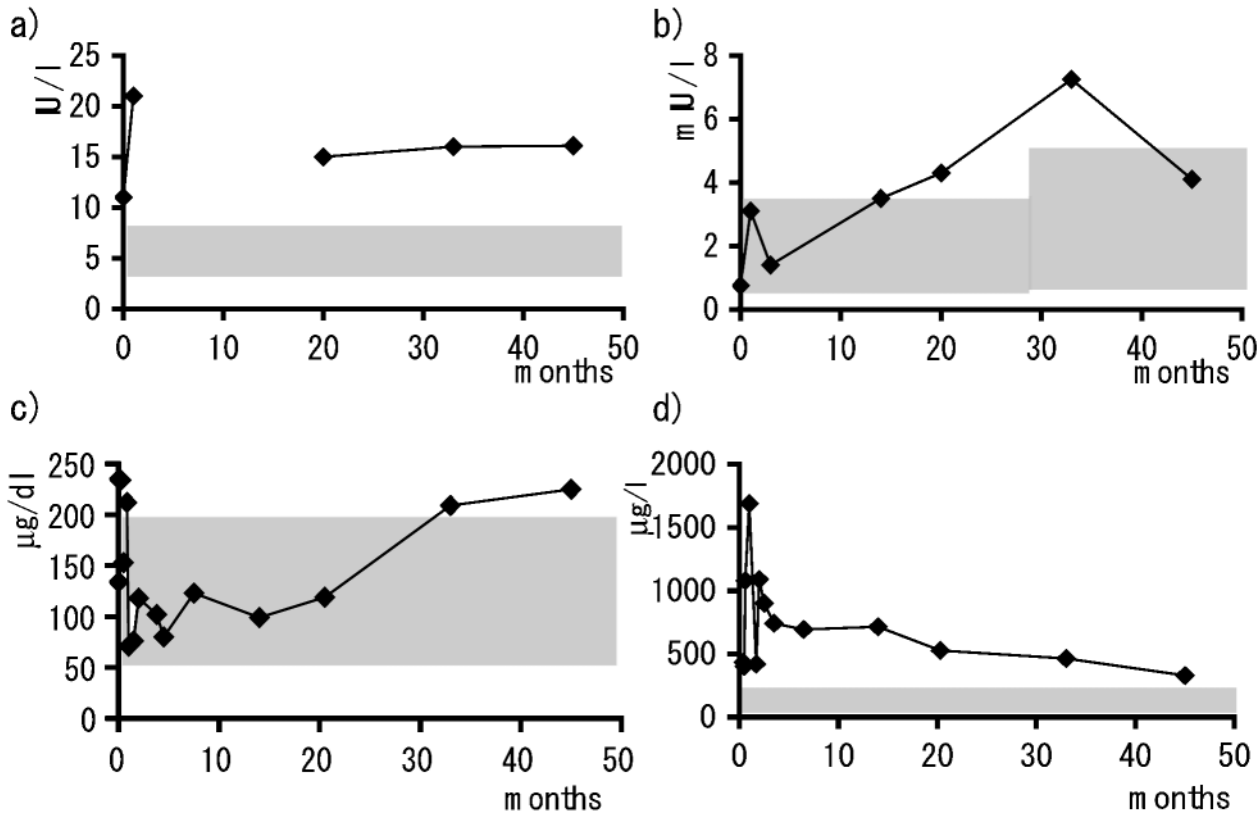


Figure 2. Selected laboratory findings in the serum of Patient C. (a) Follicle-stimulating hormone; (b) thyroid-stimulating hormone; (c) iron; and (d) ferritin. (Shaded areas depict normal range.)

Although the patient has been largely well except for the eyes, some potential problems that he has been facing are listed.

Although the serum level of thyroid hormones has been normal throughout his clinical course, the level of thyroid-stimulating hormone (TSH) was elevated on his visits 22 months and 34 months after the accident, suggesting subclinical hypothyroidism (Figure 2b). On his last visit 45 months after the accident, TSH had returned to normal.

Parameters of iron metabolism might represent another set of examples that illustrate the protracted effect of ionising radiation to the body. Serum iron increased during the first 24 h, presumably reflecting damaged erythropoiesis (Figure 2c). It then abruptly decreased after 1 month, when reticulocytes started to appear. Thereafter, it has been gradually increasing up to now, recently exceeding the normal range. Serum ferritin was beyond the normal range on admission, markedly increased thereafter, and has been gradually decreasing (Figure 2d). These findings suggest that his body needed to keep rebalancing iron in different compartments well after haematopoietic recovery from ARS was complete.

Discussion

Based on the ^{24}Na content in the peripheral blood and the predicted neutron/γ-ray ratio, the dose to Patient C was calculated and has been published to be 0.81 Gy of neutron and 1.3 Gy of γ-rays [7]. The γ-ray dose has recently been refined to be 1.5 Gy [11]. On the other hand, chromosome analyses of peripheral blood lymphocytes predicted that the exposure was equivalent to 2.6–2.8 Gy of X-rays [11]. The partial epilation and fragile gum exhibited by Patient C are compatible with these estimated values. Looking at the dynamics of the platelet count during the first 7 days, the severity of damage to Patient C might be comparable with a victim of the accident at Los Alamos in 1945 who survived 24 days following exposure [2, 5].

Physicians at the NIRS decided to treat Patient C without haematopoietic stem cell transplantation and focused on preventing infection and supporting his general condition. He recovered from severe bone marrow failure caused by the irradiation without major complications. Although he suffered from cataract and retinopathy, and had subclinical hypothyroidism, which we believe were associated with the irradiation, he remains well as of December 2003. In his future, increased risk of cancer and leukaemia is a major concern. At the same time, because he has diabetes mellitus and hypertension, he is at risk of atherosclerotic diseases, which might be further augmented by the irradiation. It should be stressed that the patient's wellness in the future largely depends on how such ordinary diseases are treated, rather than the history of radiation exposure itself. The physicians at the NIRS have been communicating with the patient as well as the caring physician in his neighbourhood to serve this purpose.

Conclusion

Among the three victims of the Tokai-mura criticality accident, a 54-year-old male exposed to more than 2 Gy in total survived. Although the patient was virtually asymptomatic, clinical examinations revealed the consequences of acute cell damage in multiple organ systems, which included severe bone marrow suppression and subtle but obvious interstitial oedema of the lungs during the first month of exposure, and cataract and subclinical hypothyroidism in the following years. Thus, multiple organ involvement appears to be the rule in ARS even when the degree of exposure is such that the resultant physical symptoms are rather subtle. Accordingly, in following up a patient who has survived ARS, a physician should not only be aware of the rare evolution of leukaemia or cancer but also look carefully for clinical signs that reveal either the consequences of, or secondary reactions to, acute cell damage in organ systems.

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