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The pathology of multi-organ involvement: two autopsy cases from the Tokai-mura criticality accident

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Abstract. We briefly report the pathological findings of two victims of the Tokai-mura criticality accident. Patients A and B were exposed to 17–24 Gy Eq and 8–12 Gy Eq, respectively. They received initial and intensive treatments, including blood transplantation and skin grafting, but both died, on day 82 and day 210, respectively. In Patient A the skin showed wide ulcerations on the anterior side of the whole body. The alimentary tract showed almost total loss of the epithelium. Other findings included hypocellular bone marrow with donor chimerism, oedema and congestion of the lungs without fibrosis, and markedly degenerated skeletal muscles. The skin of Patient B showed fibrosis and atrophy on the anterior side. His small intestine had segmental erosions caused by thrombotic microangiopathy (TMA). The bone marrow showed autologous recovery but remained hypocellular. His muscles showed degeneration, especially in the anterior sections. Pneumonia made it difficult to determine the radiation injury. These cases had relatively long survival times for the high absorbed doses, owing to the initial and intensive treatments. Patient A showed the early phase of radiation injury and Patient B showed early to chronic phase of the injury. Our cases displayed some notable findings, including the absence of lung fibrosis in both patients and TMA in the small intestine of patient B. It is still uncertain whether these findings were due to the quality and quantity of irradiation or to the therapies.

Introduction

A criticality accident occurred at a uranium processing facility in Tokai-mura, Ibaraki Prefecture, Japan, on 30 September 1999 [1]. Three workers were severely exposed to γ-ray and neutron irradiation when Workers A and B prepared excess uranyl nitrate in a precipitation tank, in which the critical reaction occurred. Worker A was standing by the precipitation tank holding a funnel. Worker B was pouring uranyl nitrate from a bucket into the tank from above. Estimated average doses were 17–24 Gy Eq (Gray equivalent of γ-rays) for Worker A and 8–12 Gy Eq for Worker B, based on their initial symptoms and duration, serial changes of lymphocyte numbers in the peripheral blood, chromosomal analysis of peripheral blood lymphocytes, and ^{24}Na activity in their bodies [2]. They received intensive care, but died on day 82 and day 210, respectively.

Patient A

Clinical course

Patient A received 17–24 Gy Eq of γ-ray and neutron irradiation. His clinical course has been previously described in detail [3]. In this article we refer to biopsies and related findings.

Bone marrow

The bone marrow was markedly hypoplastic on day 3. Peripheral blood stem cell transplantation (PBSCT) from his human leukocyte antigen (HLA) identical sister was performed on days 6 and 7. After PBSCT, haematopoiesis initially recovered with complete donor chimerism, but decreased thereafter. There was an increase of macrophages on day 56, which corresponded to the clinical haemophagocytic syndrome [3].

Skin

On day 2, the anterior surface of the body showed redness comparable with 1st degree burn. After day 4, blisters appeared on the right elbow and waist, which spread to the anterior surface of the body. Serial biopsies were taken from the right anterior chest wall near the axilla, which served to monitor the radiation injury.

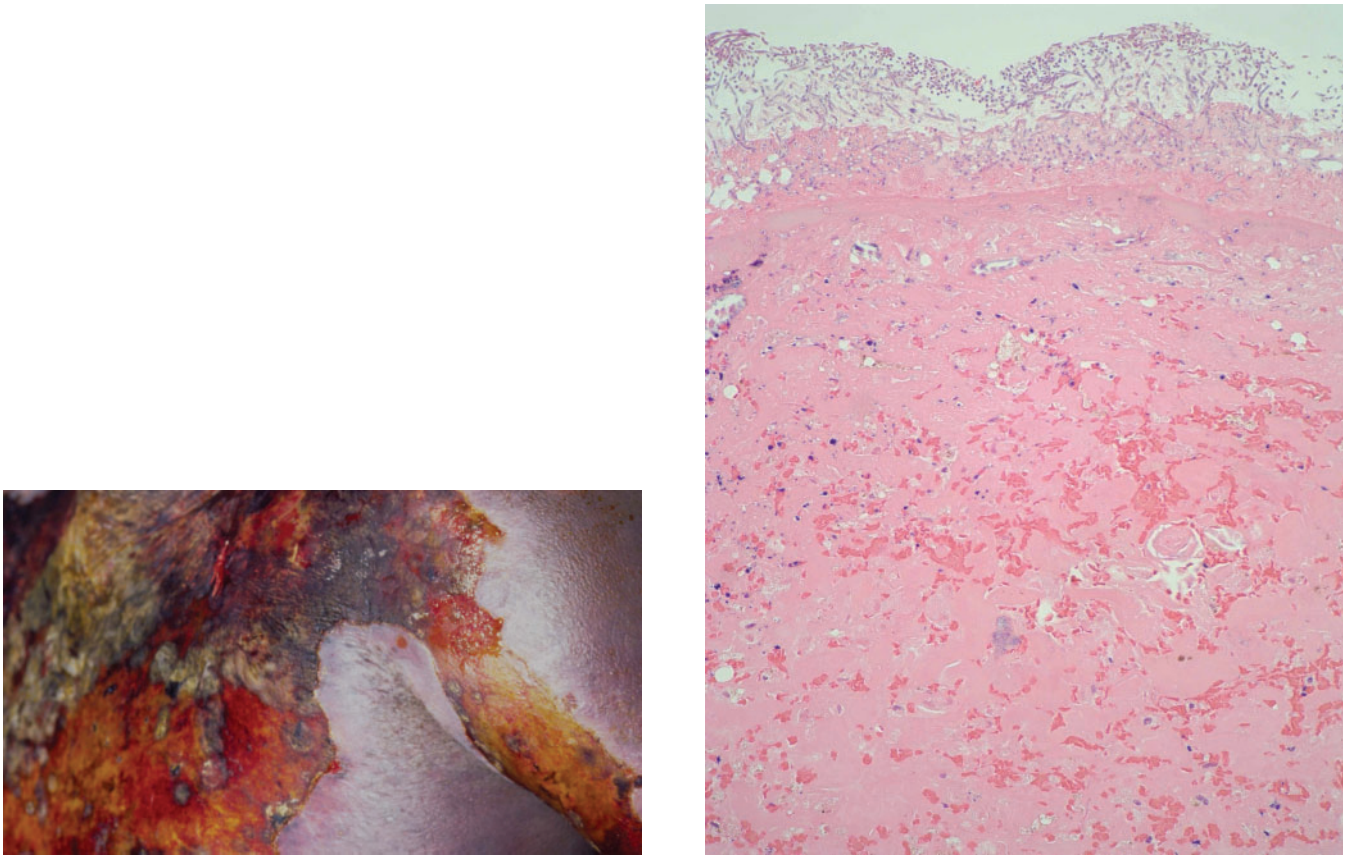
On day 13, when blisters appeared on the chest wall, the skin showed intraepidermal single cell necrosis, mild oedema in the basal layer, and increase of melanin in the epidermis. On day 31, the blisters became significant and the histology showed a gap in the basal layer. On day 46, the epidermis was lost completely and necrotic hair follicles and granulation were observed in the dermis. During these days, leakage of body fluid increased to reach 3–4 l day^{-1}.

Digestive tract

Diarrhoea started on day 26, and bloody stools and haemorrhage continued after day 49. The patient died of multiple organ failure 82 days after the accident.

Autopsy findings

The anterior side of the body showed broad ulcerations (Figure 1a). Yellowish lesions were due to *Candida* infection, which occurred just before the patient's death. The epidermis was lost on the chest wall, with necrosis and haemorrhage in the dermis. *Candida albicans* fungi were growing on the surface (Figure 1b). The epidermis on his posterior side was preserved, but the skin was coloured dark purple. The dose of irradiation to the back was



(a) (b)

Figure 1. Skin of Patient A. (a) Broad ulceration with yellowish lesions observed on the anterior chest wall. (b) Histology of the anterior chest wall showed *Candida* infection on the surface, and dermal necrosis and haemorrhage.

one-eighth that at the anterior side. Histologically, the epidermis and sweat glands were preserved.

The gastrointestinal tract showed diffuse erosions and haemorrhages from the oesophagus to the rectum. The contents were haemorrhagic, 2040 g in the stomach and 2680 g in the intestine. The stomach was dilated and its whole mucosa showed erosions. The mucosa of the small intestine and colon was also diffusely haemorrhagic and erosive. Histologically, there was almost total loss of epithelial cells from the stomach to the descending colon, although the epithelium remained sparsely preserved in the sigmoid colon and rectum.

The left lung weighed 700 g and the right lung 900 g. Both lungs were heavy due to oedema and congestion. Haemorrhage was also seen on the posterior side. The anterior segment of the middle lobe of the right lung (segment 5) showed more severe congestion and oedema compared with the left S1+2. Lung fibrosis was not observed.

The bone marrow was severely hypoplastic.

The skeletal muscles of the whole body showed marked degeneration and atrophy.

The testes were severely atrophic.

The liver weighed 1920 g and showed necrosis in the left lobe and centrilobular necrosis in the right lobe.

The spleen weighed 120 g and showed geographic necrosis.

The brain (1450 g) was so-called respirator brain.

The kidneys were swollen, with the left weighing 230 g and the right 230 g. Glomerulosclerosis was not observed.

Patient B

Clinical course

Patient B was a 40-year-old male. His irradiated dose was estimated to be 8–12 Gy Eq. The irradiation was relatively homogeneous at the anterior side. His treatment and clinical course have been described in a previous article in this issue [4]. In brief, following his treatment, including umbilical cord blood transplantation and skin grafting, he died on day 210 owing to respiratory failure and gastrointestinal bleeding.

Bone marrow

Biopsy of the bone marrow showed no haematopoiesis on day 5. Umbilical cord blood transplantation was performed on day 9, when the bone marrow recovered with mixed chimerism. However, his autologous haematopoiesis gradually recovered up to day 60 when immunosuppressive drugs were reduced [5].

Skin

Blisters appeared on both his forearms since day 30, and spread to the anterior side of the whole body by day 50. Biopsies of the forearm skin on days 33 and 50 showed blistering in the basal layer. Both biopsies were taken after the cord blood transplantation, but there was no finding suggesting acute graft-versus-host disease (GVHD). Allogeneic skin grafting was performed on the hands, forearms, lower legs, left femur and face on days 81–123.

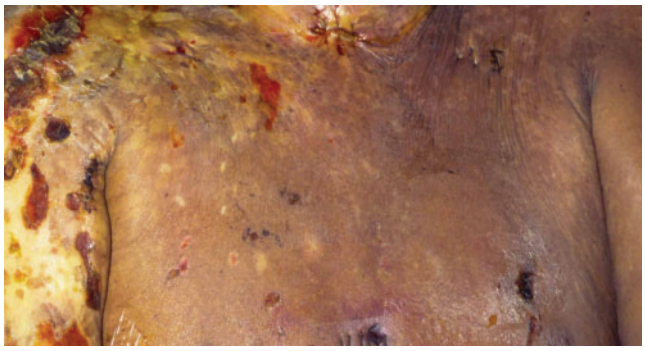


Figure 2. Anterior chest wall of Patient B showed brown pigmentation, sclerosis and atrophy.

More than 90% was engrafted. However, dermal sclerosis and fibrosis gradually manifested 5 months after the accident. Biopsy of the right upper arm on day 195 showed marked fibrosis of the dermis and marked atrophy of the skin appendages.

Autopsy findings

The skin on the anterior side of the body showed brown pigmentation and marked sclerosis with scattered erosions (Figure 2). The histological findings of the forearms were similar to those of the biopsies on day 195. The dermis showed fibrosis and atrophy.

The content of the intestine was a blood clot, 1.6 l in total. The small intestine showed segmental erosions and mucosal atrophy. The other parts of the digestive tract were relatively preserved, but there was mild congestion and intramucosal haemorrhage. Histologically, the segmental erosions of the small intestine were accompanied by fibrin thrombi in the small vessels (Figure 3), which showed subendothelial oedema and exudation. The findings were consistent with thrombotic microangiopathy (TMA) [6].

The lungs (left 800 g, right 1280 g) showed pneumonia, including diffuse alveolar damage, organisation and haemorrhage.

The bone marrow was hypoplastic.

The muscles showed degeneration, especially on the anterior side.

The testes were severely atrophic.

The liver, spleen, and left and right kidneys were swollen, weighing 2370 g, 170 g, 240 g and 250 g, respectively.

The heart weighed 400 g and the brain weighed 1440 g.

Discussion

In criticality accidents, mixed radiation of γ-rays and neutrons occurs. Neutron radiation is different from γ-rays in the absorption and permeability to the body. Since neutron radiation delivers its energy to those tissues enriched with water and fat, its effect on the body is different from that of γ-rays [7]. Since there have been only a few cases of victims with high dose neutron radiation [8], the autopsy findings in the present cases are highly relevant for the evaluation of radiation injury *in vivo*. However, it is also true that caution is necessary for their interpretation, because initial treatment in the present

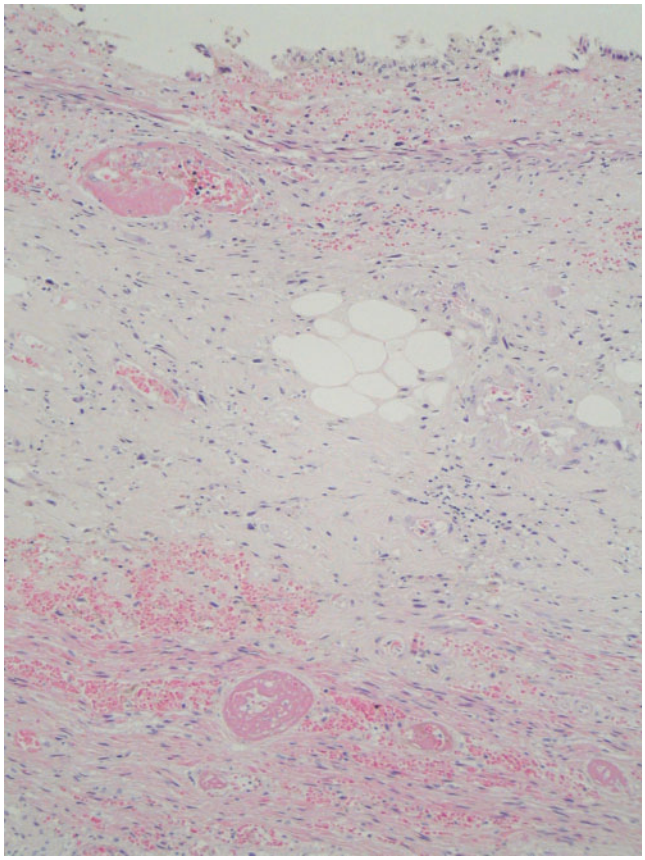


Figure 3. Segmental erosion of the small intestine of Patient B. Low power view of the histology showed many thrombi in the small vessels.

cases was more sophisticated and intensive than in those of previous radiation accidents.

Patient A showed the early effects of radiation and illustrated the importance of the position of the patient at the time of the accident. The discordant distribution of tissue injury was observed not only in the skin, but also in the intestine and lung. Regarding the intestine, the remaining epithelium was only sparsely preserved in the sigmoid colon and rectum. The distribution may reflect differences in the irradiation dose, *e.g.* greatest dose on the right side of the abdomen and lower dose on the left side. Regarding the lungs, oedema and congestion were most severe in the right S5, which may also reflect the uneven distribution of irradiation at the accident. It is also interesting to note that we could not observe lung fibrosis in Patient A. In radiation therapy, lung fibrosis may appear around 3 months, which is comparable with day 82, when patient A died. Radiation injury of high dose at one time may be different from injury owing to repetitive exposure to small doses. Alternatively, the patient's survival time of 82 days might simply be too short for lung fibrosis to develop.

Patient B showed subacute to chronic effects of radiation at autopsy. Gastrointestinal bleeding occurred after day 140, although endoscopic examination could not detect the origin of the haemorrhage. Autopsy revealed that patient B's small intestine had segmental erosions with TMA. TMA is occasionally observed in patients who received bone marrow transplantation and is usually also accompanied by severe GVHD. However, this patient

Table 1. Comparison of Patients A and B

	A	B
Estimated absorbed dose	17–24 Gy Eq	8–12 Gy Eq
Survival time	82 days	210 days
Major autopsy findings related to irradiation		
Skin	Wide ulcer on the anterior surface. Grafted skin was not engrafted	Sclerosis and atrophy on the anterior surface
Gastrointestinal tract	Erosions over entire length	Segmental erosions in the small intestine caused by thrombotic microangiopathy (TMA)
Bone marrow	Donor chimerism	Recipient chimerism
Lung	Oedema and congestion	(Pneumonia)
Muscle	Marked degeneration	Degeneration of the anterior muscles
Others	Centrilobular necrosis of the liver, geographical necrosis of the spleen	

showed no evidence of GVHD during his entire clinical course. The term TMA was first introduced by Symmers in 1952 [6], and includes several entities, such as haemolytic–uraemic syndrome, thrombotic thrombocytopenic purpura, microangiopathic haemolytic anaemia, bone marrow transplantation (BMT)-related TMA, etc. TMA is intimal injury of the microvasculature followed by microthrombi formation pathophysiologically. BMT-related TMA occurs in approximately 5% of transplanted patients within 100 days after BMT [9, 10]. The symptoms and distribution of TMA are similar to those of GVHD [11]. Taking into consideration the fact that possible aetiologies of intimal injury in BMT-related TMA are intensive therapy before transplantation (including anti-cancer drugs), radiation, GVHD, immunosuppressive drugs, infection, etc., there are three possible causes of TMA in the present case, namely radiation, immunosuppressive drugs and infection. Regarding immunosuppressive drugs, administration of cyclosporine A had been stopped 100 days before the gastrointestinal bleeding occurred. Only methylpredonisolone was administered at the beginning of bleeding. There was no evidence of infection in the intestine at the beginning of bleeding. Thus, we consider that TMA in this patient represented radiation injury to the vessels. The difference in conditions between the small intestine and the other organs might reflect the difference in sensitivity to irradiation.

Comparison of the two cases

The differences in the autopsy findings between Patients A and B are summarised in Table 1. Most of the differences are due to the quantity of absorbed dose and to their survival times. Both cases showed severe degeneration of skeletal muscles. The main cause of degeneration may be disuse atrophy and the patients' general condition. However, in Patient B, skeletal muscles on the anterior side were more severely atrophic than those on the posterior side. Since this degeneration of Patient B's muscles resembles the distribution of absorbed dose, the finding suggests that radiation may also damage the muscles directly.

Conclusion

In conclusion, we observed the early phase of radiation injury in Patient A and the early to chronic phase of radiation injury in Patient B. Autopsy findings in the present cases showed some notable findings, such as TMA in the small intestine of Patient B, and absence of lung fibrosis in both patients. It is still uncertain whether these findings are due only to the quality and quantity of the irradiation or were modified by the therapies.

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