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Case review of severe acute radiation syndrome from whole body exposure: concepts of radiation-induced multi-organ dysfunction and failure

Koichi Tanigawa*

Futaba Medical Center, Fukushima Prefecture
*Corresponding author. Futaba Medical Center, Fukushima Prefecture, 817-1 Otsuka, Moto-oka, Tomioka-machi, Futaba-gun, Fukushima 979-1151, Japan. Tel: +81-240-23-5090; Fax; +81-240-23-5091; Email; tanigawa@futaba-med.jp
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ABSTRACT

Acute radiation syndrome (ARS) due to whole body exposure (WBE) presents various clinical pictures, occasionally leading to fatal consequences. In this report, the literature providing details of the clinical course of severe ARS owing to WBE is reviewed and the lessons learned from recent accidents are discussed, to better prepare for another radiological event. Studies investigating radiological accidents that provided details of medical care for severe ARS were searched in official reports from the International Atomic Energy Agency and through the databases of PubMed, Medline, CiNii and Google Scholar and reviewed. Four fatal cases of severe ARS due to WBE in Soreq 1990 and Nesvizh 1992, and two cases in JCO Tokaimura 1999 were reviewed. A common set of medical interventions was carried out, that put a focus on medical management assuming the occurrence of hematopoietic disorders. However, clinicians were faced with a mixture of chronic hematological and non-hematological events including persistent gastrointestinal disorders, gradual and progressive skin disorders, liver and renal dysfunction and respiratory failure. Clinical pictures following high-dose WBE have become more complicated as treatment modalities improve. To address these issues, a concept of severe ARS due to WBE has been proposed with respect to radiation-induced multi-organ dysfunction syndrome (RI-MODS) and failure (RI-MOF). These patients need to be managed at institutions where multidisciplinary, resource-intensive therapy can be provided.

Keywords: acute radiation syndrome; whole body exposure; multi-organ dysfunction syndrome; multi-organ failure; critical care

INTRODUCTION

Radiation damage has complex properties at the molecular, cell, tissue and organ system levels, and many of the related problems remain unresolved. Clinical experiences from accidents at the nuclear research institute in Los Alamos, NM, in the USA [1–3] in 1945, 1946 and 1958, and at the Boris Kidric Institute in Yugoslavia in 1958 [4] have led to elucidation of the pathology of acute radiation syndrome (ARS). Attempts have been made to develop therapeutic methods in ARS, such as hematopoietic transplantation. The Chernobyl nuclear accident in 1986 resulted in 237 cases of confirmed or unconfirmed ARS [5, 6]. Among these, 28 people died within 3 months of exposure. Of 27 patients with an exposure dose of >5–6 Gy, 11 of 13 patients treated with bone marrow transplantation (BMT) died; among 14 patients not treated with BMT, 11 died owing to different reasons such as burns, interstitial pneumonitis, graft-vs-host disease (GVHD), renal failure and acute respiratory distress syndrome (ARDS). In Goiania, Brazil in 1987, improper management of radioactive materials resulted in eight cases of severe hematopoietic syndrome. These individuals were treated with cytokine therapy [recombinant human granulocyte macrophage colony stimulating factor (GMCSF)], with four deaths owing to hemorrhage and sepsis [7]. Since the 1990s, the focus of treatment for severe ARS following whole body exposure (WBE) has shifted from pathology and prevention of bone marrow disorders to non-hematopoietic effects in important organs such as the gastrointestinal (GI) tract, skin, kidney, liver and lungs [8, 9].

Although uncommon events, clinical experiences of accidental WBE have been recorded and detailed descriptions of the clinical picture of severe ARS with progressive and sequential impairments in critical organs and tissues have become available [10, 11]. Despite modern medical efforts, however, delayed lethality often results.

This condition has been defined as radiation-induced multi-organ dysfunction syndrome (RI-MODS) and failure (RI-MOF) [12, 13].

In this report, the literature providing details of the clinical course of severe ARS owing to WBE is reviewed. This is followed by discussion on the lessons learned from recent accidents, to better prepare for another radiological event.

MATERIALS AND METHODS

Studies investigating radiological accidents that provided details of medical care for severe ARS were searched and reviewed. First, official reports on radiological accidents from the International Atomic Energy Agency (IAEA) were reviewed. The general search strategy and selection criteria of published studies included a search of the databases PubMed, Medline, CiNii and Google Scholar using the search terms 'acute radiation syndrome' and 'fatality' or 'death', 96 items, 6 matched; and 'acute radiation syndrome, radiological accident', 64 items, 7 matched; 'acute radiation syndrome, medical management' hit 287 items, 25 items matched to review. Of 411 and 475 ('acute radiation syndrome' and 'critical care', or 'intensive care'), 184 and 268 articles ('acute radiation sickness', and 'critical care', or 'intensive care') matched; duplicate or irrelevant reports were excluded and reviewed. We also searched the databases using the terms 'Soreq', 'Nesvizh', 'JCO Tokaimura' and 'critical care', or 'intensive care' likewise and 26, 5 and 3 articles were matched; duplicate or irrelevant reports were excluded and reviewed.

RESULTS

Four fatal cases of severe ARS due to WBE in Soreq 1990 and Nesvizh 1992, and two cases in JCO Tokaimura 1999 were reviewed.

Radiological accident in Soreq

On 21 June 1990, a fatal radiological accident occurred at an industrial irradiation facility in Soreq, Israel [8]. Prepackaged medical products and spices were sterilized at the facility by irradiation by means of an intensely radioactive ^{60}Co source in a movable source rack. The accident occurred after the source rack became stuck in the irradiation position owing to obstruction by cartons on the internal conveyor. An operator, having misinterpreted two conflicting warning signals, entered the irradiation room by circumventing the safety systems and was acutely exposed, with an estimated whole body dose of 10–20 Gy.

The 32-year-old male patient demonstrated isolated facial and palmar erythema, diffuse abdominal tenderness and slight corneal injection with mild swelling of the lower eyelids ~2 h after exposure. Blood gas analysis showed hypoxemia (arterial partial pressure of oxygen, 54.1 mmHg) and his lymphocytes had dropped to 2% within 5 h after exposure. Over the next few days (days 1–3), the patient's general condition did not change. Vomiting occurred on the evening of day 3, and on day 4, his white blood cell count dropped and no lymphocytes were observed in the peripheral blood. He vomited twice or three times per day and had watery stools twice daily. A BMT was performed on day 4. On days 5–12, the patient's condition did not improve and he gradually developed renal insufficiency. His liver function began to deteriorate, with elevation of total bilirubin. On days 13–21, the patient continued to have nausea, vomiting and severe watery diarrhea. High body temperature persisted despite the empiric antibiotic regimen, and overt jaundice developed. Erythema on the hands, head and thorax became more marked. Hypoalbuminemia became evident, necessitating albumin administration. Chest X-rays revealed infiltrates in the right lower lobe. On days 22–34, his fever persisted (up to 40°C) but all blood cultures remained negative. Superficial and deep partial-thickness burn injuries were observed, jaundice persisted and liver function continued to deteriorate. On days 35 and 36, the patient became markedly confused and disoriented. He developed severe hypoxia and metabolic acidosis with massive bilateral interstitial infiltrates on chest X-ray. The patient died on day 36, 5 weeks after the accident.

Radiological accident at the irradiation facility in Nesvizh

On 26 October 1991, a fatal radiological accident occurred at an industrial sterilization facility in Nesvizh, Belarus [9]. Following a jam in the internal product transport system, the operator, a 34-year-old man, entered the irradiation chamber to clear the obstruction and was severely exposed to a lethal dose of radiation. It is estimated that he received a whole-body dose of 11 Gy, with localized areas of up to 20 Gy. He experienced nausea 5–6 min later and vomiting, which recurred frequently over the next few hours. Twenty minutes later, he was admitted to the hospital in Nesvizh.

At the time of admission, the patient complained of fatigue, headache, an ache in the abdomen, and pains in the hands and feet. His lymphocyte percentage was 7% at 2 h after exposure. Treatment with GMCSF and interleukin-3 were started on days 1 and 6, respectively. The erythema evident on day 1 began to diminish on day 2 and had completely disappeared by day 6. The patient's granulocyte and thrombocyte counts rapidly decreased. Mucositis in the mouth, diarrhea with watery stools and moderate fever were observed.

On day 8, deep pancytopenia and severe diarrhea developed. Skin lesions appeared on day 11 with a form of epilation, secondary erythema, blisters, small erosions and dry desquamation successively on various parts of the body. By the end of the first month, skin lesions were extended to near total-body erythema, with localized wet desquamation. On day 36, intestinal bleeding was observed. On day 38, a solid shadow could be seen in the middle lobe of the right lung and some infiltrates in both lungs. Transaminase and creatine phosphokinase were elevated, with significantly progressed hypoalbuminemia. During this period, neutrophil and lymphocyte counts increased but then remained stable at a lower level. Bone marrow examinations performed on day 44 demonstrated an increase in cellularity.

On day 54, chest computed tomography showed increased infiltration in the left lung, and on day 58, clinical signs of bilateral pneumonia with no known etiology appeared. Hepatic dysfunction had become more evident by the end of the second month. The skin of the left leg was hyperemic with edema of the underlying tissues and superficial erosions; pain was exacerbated during this period.

The patient continued to lose weight despite continuous parenteral nutrition. Biochemical findings showed a persistent cholestatic pattern, which became particularly evident around day 80, indicating a toxic effect of the antibiotic on the liver. Three months after exposure, signs of renal failure appeared. On day 100, considerable infiltration in the lower left pulmonary lobe was revealed on X-ray. On day 102, an

open biopsy of the left lung was carried out, which showed no sign of infection. Two days later (day 104), the patient's respiratory condition suddenly worsened, resulting in typical acute adult respiratory distress syndrome complicated by a pneumothorax. Hypoxemia increased rapidly and he died on day 113.

JCO Tokaimura accident

The Tokaimura nuclear accident occurred on 30 September 1999 at a nuclear fuel-processing facility run by JCO, an affiliate of Sumitomo Metal Mining, in Tokaimura, Japan. The accident occurred as a result of an attempted shortcut in the protocol for processing nuclear fuel. Three workers were manually dissolving a high concentration of triuranium octoxide and pouring nitrate solution into a vessel when a criticality occurred, and the workers were exposed to a massive dose of radiation [10, 11]. They were transported to a nearby hospital, then to the National Institute of Radiological Sciences, and two workers who required intensive care and peripheral blood stem cell transplantation (PBSCT) were transferred to the University of Tokyo.

The most critically exposed patient was a 35-year-old man whose exposure dose was initially estimated to be 16–20 Gy. This worker experienced a brief convulsion immediately after exposure and he vomited 10 min later. After 2 h, his lymphocytes had decreased to 3%. Five hours later, erythema, facial edema, swelling and tenderness of the submandibular glands were noted. On day 2, oliguria and hypoxemia appeared, and blood tests showed zero lymphocytes. Similar to severe burns, a marked increase in vascular permeability occurred soon after radiation exposure, which made fluid management very difficult. Heavy fluid loading exceeding 4000 mL/day was required to maintain blood pressure; however, pulmonary edema developed on day 3, and marked pleural effusion was observed on day 6. The patient was intubated on day 10 for mechanical ventilation. PBSCT from an Human Leukocyte Antigen (HLA)-identical sister was performed on days 6 and 7. Severe diarrhea had begun within the first hour after exposure and continued for 4 days, and then restarted as massive hemorrhagic diarrhea (>1000 mL/day) on day 26. On day 49, gross bloody stool was observed and upper GI hemorrhage was diagnosed. Skin lesions changed from edema and erythema to blistering and desquamation in the order of the right forearm, precordium, face, upper left arm and right lower leg at intervals of a few days to 10 days; the skin of the right forearm with a high exposure dose developed dry necrosis. On day 42, the amount of exudate from the wound that had lost the epidermis exceeded 2000 mL per day, so a skin graft was performed on day 49. On day 56, the patient developed sudden cardiac arrest. Although he was revived after 1 h of cardiopulmonary resuscitation, he developed anuria and was started on continuous hemodiafiltration. Following this event, his liver function deteriorated rapidly, hemophagocytic syndrome developed and he became extremely hemodynamically unstable. The patient died of MOF on day 82.

The second most critically exposed patient was a 40-year-old man whose exposure dose was initially estimated to be 6–9 Gy. Early erythema and swelling were noted on the face and right forearm at admission, but these disappeared a few days later. His lymphocytes were decreased to 1% at 5 days after exposure. Cord blood transplantation (CBT) was performed on day 9, and his hematopoietic function recovered quickly; engraftment was observed 9 days after transplantation. Pain appeared in his fingers and lower legs from the third week after exposure, and secondary erythema and blisters were observed on the face, palms and right forearm by the fourth week. At 7 weeks, 67% of the body surface had developed desquamation and ulceration. Skin grafts were performed on days 81 and 123, and 90% were engrafted, but skin fibrosis and sclerosis gradually progressed. Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected on the skin over the whole body and pharynx, and after 152 days, MRSA pneumonia due to aspiration developed and progressed to ARDS. Systemic skin fibrosis/sclerosis was prominent, and the patient developed renal insufficiency caused by abdominal compartment syndrome. Pathological findings of the skin lesion showed scattered single-cell necrosis in the basal layer, indicating possible involvement of GVHD. Respiratory distress due to decreased thoracic compliance became prominent, and he died of MOF on day 210.

DISCUSSION

In the four cases described above, a common set of medical interventions was carried out, including immediate and frequent blood analysis; reverse isolation; GI tract sterilization; fluid administration; cytokine treatment; BMT, CBT or PBSCT; continued platelet and erythrocyte transfusions; and long-term use of broad-spectrum antibiotics. In the case of Soreq, hypoxemia was observed soon after exposure. GI disorders started and persisted thereafter; renal and liver damage developed within 2 weeks; and abnormal skin lesions appeared followed by pulmonary edema as a lethal event within 5 weeks after exposure. In Nesvizh, recovery of bone marrow function was observed after cytokine therapy. However, subsequent GI disorders, gradual skin disorders, liver dysfunction with mainly jaundice, and renal disorders occurred. Complications from invasive testing for localized lung injury might accelerate fatal ARDS progression. In the first case of the JCO accident, hypoxemia and oliguria occurred rapidly, followed by an aggressive course of marked pulmonary edema due to a drastic increase in vascular permeability, GI disorders that persisted after the exposure, and systemic skin disorders. In the second case of the JCO accident, the skin disorder spread and progressed over the entire body; abdominal compartment syndrome and decreased thoracic compliance due to severe fibrotic/sclerotic change of the skin led to fatal consequences. One of the biggest challenges was that skin lesions, hepatic dysfunction and GI disorders observed in JCO cases were indistinguishable from those caused by pretreatment for transplantation or GVHD.

In these four cases, initial interventions were focused on medical management, assuming the occurrence of hematopoietic disorders. However, they involved a mixture of chronic hematological and non-hematological events. As attempted treatments for patients with higher-dose exposure, the pathophysiology of multi-organ injuries involving the GI tract, skin, liver, kidney and lung have been highlighted [12], and new challenges and limitations have been clarified. The development of medical care, e.g. stem cell transplantation, contributes, in part, to improved prognosis in ARS patients; however, this has also created new medical problems, further complicating the clinical picture of ARS [13].

These observations suggest that ARS due to WBE may be considered as consequences of multiple organ involvement, rather than

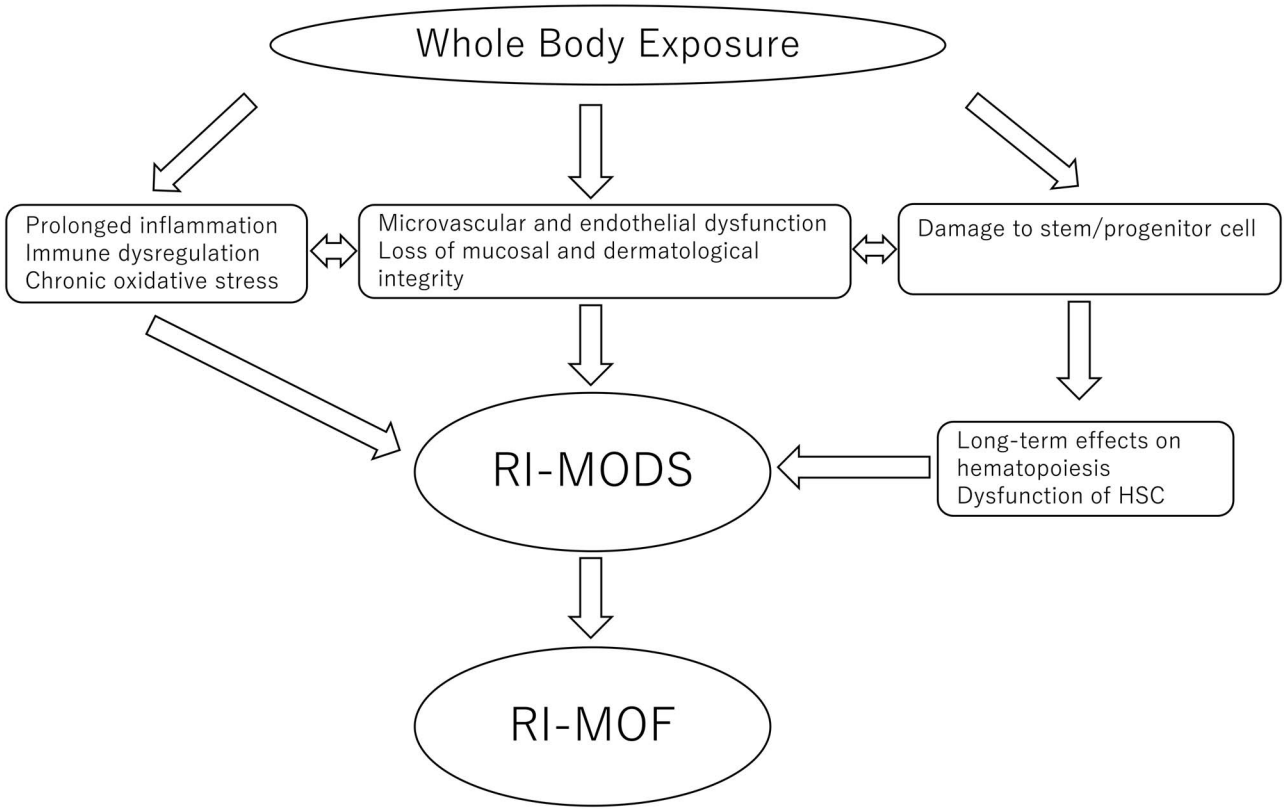

Fig. 1. Conceptual diagram of RI-MODS and RI-MOF. HSC = hematopoietic stem cell. This diagram was produced based on the hypothesis proposed by Williams and McBride [13].

individual events. The timing of onset and dose relationships following high-dose exposure may not be associated with classical concepts of ARS, a conglomerate of subsyndromes depending on the absorbed doses. Any tissue can contain cells with various radiosensitivities; therefore, the timing of a radiation response may not dictate which organs are failing. Furthermore, inflammatory responses, loss of vascular homeostasis, loss of mucosal and dermatological integrity, regenerative processes and medical interventions can make the clinical picture much more complicated. The JCO accident is a good example. Of the two affected workers who died, one had a successful initial bone marrow transplant but died 7 months later owing to MOF consisting of substantial fibrotic/sclerotic changes of the skin, refractory GI bleeding and lung damage [11].

As isolated experiences in severe ARS are reported, the concept of ARS is evolving [14]. A new concept has been proposed regarding the medical consequences of radiation-induced multi-organ involvement (RI-MOI) and RI-MOF [12]. In this new paradigm, ARS is perceived as a continuum of events associated with uncontrolled inflammatory responses and loss of vascular homeostasis that may lead to RI-MODS(Fig. 1) [13]. Although the specific pathophysiological mechanisms involved in RI-MODS remain unknown, there is some similarity with MODS due to other pathophysiology in the critical care arena. Additionally, the care of patients requires the same approaches, e.g. multidisciplinary, resource-intensive therapy. These patients should be managed at institutions staffed by clinicians with experience in providing care to critically ill patients or those with severe immunodeficiency, or both.

MOF is associated with a high mortality regardless of the initial insult. MOF is responsible for >60% of deaths from severe trauma [15], 50% of deaths from pancreatitis [16] and 30% of deaths from burns [17]. The higher the number of failed organs, the higher the mortality [18]. Even in survivors, long-term quality of life is inversely affected by MOF [19]. Sepsis is one of the leading causes of death resulting from MOF in the intensive care unit. Much previous research has clarified this mechanism. In severe sepsis and septic shock, microvascular and endothelial dysfunction, autonomic failure and characteristic bioenergetic and metabolic responses at the cellular level have been observed in multiple studies [20]. Thus, many investigators have proposed targeting one or more of these mechanisms to reduce the development of sepsis-induced MODS. Various treatments such as use of nitric oxide inhibitors and cytokine modulation have been tried, but these have a history of failure [21]. Owing to advances in training, better surveillance and monitoring, and prompt initiation of therapy to treat the underlying infection and support failing organs, however, mortality from severe sepsis and septic shock has decreased from >80% ~30 years ago to closer to 20–30% in many reports [22].

The World Health Organization convened a panel of experts to rank the evidence for medical countermeasures in the management

of ARS [23, 24]. The goal of this panel was to achieve consensus on optimal management of ARS based upon evidence in the published literature. Medical management of severe ARS in hospitalized patients optimally involves critical care specialists, hematologists, radiologists, dermatologists, GI specialists, infectious disease specialists etc., as well as experts in dosimetry of radiation. A multidisciplinary team approach is a prerequisite in this scenario. The greatest challenge is a lack of reliable evidence. No randomized controlled trials (RCTs) of medical countermeasures have been completed among individuals with ARS. Recommendations for specific countermeasures rely heavily on the results of studies in experimental animals and published guidelines for therapy in non-irradiated individuals.

Radiation accidents are rare; therefore, few treatments are based on sufficient evidence, such as from RCTs. We need to carefully review each case of severe ARS to accumulate our knowledge and deepen understanding of the pathophysiology of RI-MODS and MOF. Cellular therapies using stem or blood progenitor cells, mesenchymal stromal cells or cells derived from other tissues have the potential to impact recovery and tissue/organ regeneration for ARS [25]. Also, efforts have been made to identify compounds with radiation mitigating properties, however most of these investigations remain experimental [26]. Meanwhile, evidence-based therapies for other pathologies must be maximally used based on consensus until specialized treatments for radiation injuries are developed. Finally, expert advice from national as well as international specialists is valuable from an early stage, such as in the Niasvizh and Tokaimura accidents, where international support became available soon after the accident.

CONCLUSION

Four fatal cases of severe radiation injury were reviewed based on IAEA reports and the available literature. Clinical pictures following high-dose WBE have become more complicated as treatment modalities improve. To address these issues, a concept of severe ARS due to WBE has been proposed with respect to RI-MODS and RI-MOF. A coordinated team approach is imperative in medical countermeasures for patients with severe ARS due to WBE.

CONFLICT OF INTEREST

None declared.

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