RADIATION DAMAGE IN THE HUMAN BODY ACUTE RADIATION SYNDROME AND MULTIPLE ORGAN FAILURE

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Whole-body exposure to high-dose radiation causes injury involving multiple organs that depends on their sensitivity to radiation. This acute radiation syndrome (ARS) is caused by a brief exposure of a major part of the body to radiation at a relatively high dose rate. ARS is characterized by an initial prodromal stage, a latent symptom-free period, a critical or manifestation phase that usually takes one of four forms (three forms): hematologic, gastrointestinal, or cardiovascular and neurological (neurovascular), depending upon the exposure dose, and a recovery phase or death. One of the most important factors in treating victims exposed to radiation is the estimation of the exposure dose. When high-dose exposure is considered, initial dose estimation must be performed in order to make strategy decisions for treatment as soon as possible. Dose estimation can be based on onset and severity of prodromal symptoms, decline in absolute lymphocyte count post exposure, and chromosomal analysis of peripheral blood lymphocytes. Moreover, dose assessment on the basis of calculation from reconstruction of the radiation event may be required. Experience of a criticality accident occurring in 1999 at Tokai-mura, Japan, showed that ARS led to multiple organ failure (MOF). This article will review ARS and discuss the possible mechanisms of MOF developing from ARS.

KEYWORDS : Acute Radiation Syndrome (ARS), Dose Estimation, Multiple Organ Failure (MOF)

1. INTRODUCTION

A radiation accident is an unintentional exposure to ionizing radiation or radioactive contamination, resulting in possible deleterious effects on the exposed individuals [1,2]. Since the discovery of X-rays in 1895 and radioactivity in 1896, there have been accidents caused by radiation exposure, although radiological accidents requiring medical care rarely occurred [3]. As early as 1897, Becquerel observed an erythema on his abdomen, ascribing it to radioactive materials [2]. Today, on the other hand, devices or locations from which an individual could be exposed to radioactive materials are not rare [4]. These potential sources of exposure accidents include industrial radiography causes, therapeutic devices, sterilizers, transportation accidents, and nuclear power plants; devices used for industrial radiography and accelerators are frequent sources of accidents for external exposure, since radiation such as X- or γ-rays and neutrons is characteristically able to penetrate human bodies or other materials. Among them, ^{192}Ir, ^{60}Co, and ^{137}Cs sources which emit γ-rays are frequently employed for non-destructive testing or sterilizers and there are many reports of ARS caused by these sources.

Accidents of external exposure are different from those of contamination with radionuclides; exposed patients do not carry radioactive materials after these radionuclides have been removed [5]. However, the radiation in criticality accidents is a complex combination of neutrons and γ-rays of different energies, and neutrons are known to induce radionuclides in human body or other materials. Thus, exposure to neurons may not only cause acute radiation syndrome (ARS) but also be the subject of a great deal of work and discussion for dose assessment. In 1999, a criticality accident occurred at Tokai-mura, Japan, and two victims with ARS died of multiple organ failure (MOF) [6,7]. This review outlines

ARS and discusses MOF on the basis of our experience of the Tokai-mura criticality accident.

2. ACUTE RADIATION SYNDROME (ARS)

ARS is a combination of clinical syndromes occurring in stages during a period of weeks immediately after radiation exposure, and multiple organs are involved. ARS is caused by brief exposure of a major part of the body to more than approximately 1 GyEq (photon-equivalent, effective whole body dose) at a high dose rate, and usually occurs following exposure to external sources of penetrating radiation such as X- or γ-rays and neutrons [8]. Radiation at low dose rates or fractionated doses is less effective in terms of inducing ARS than a single dose of the same magnitude. Only in extremely rare cases, radionuclides deposited in the body may produce some ARS effects. In the past, few fatal accidents of internal exposure with radionuclides have occurred; there is a report of a fatal overdose accident by ^{198}Au from a diagnostic nuclear medicine liver/spleen scan [9]*. The ARS pathogenesis is based on a disturbance of the physiological recovery of various cellular damaged by radiation exposure.

ARS consists of a sequence of phased symptoms. Symptoms vary with individual radiation sensitivity, type of radiation, and absorbed dose. With increasing radiation dose, the extent of symptoms heightens and the duration of each phase shortens. ARS is characterized by an initial prodromal stage of malaise, nausea, vomiting, and diarrhea; a latent, symptom-free period; a critical or manifestation phase that usually takes one of four forms (three forms) — hematologic, gastrointestinal, or cardiovascular, and neurological (neurovascular) — depending on the exposure dose; and a recovery phase or death [10]. The prodromal stage lasts 1-2 days, with the severity of the symptoms being related to the exposure dose. The latent stage is a period of apparent wellness that is variable in length (hours to weeks), and is shorter with greater exposure. The stage of manifest illness is characterized by infection due to a decreased number of granulocytes and bleeding due to an insufficient number of platelets. Severe diarrhea and a resultant loss of body fluid and electrolytes may follow. If the victim can survive this stage, the next phase is recovery.

* The victim was intravenously administered colloidal ^{198}Au; the intended dose was 7.4 MBq, but he received 1000 times the dose, 7.4 G Bq. The estimated dose was 70 to 90 Gy for the liver and 4 to 5 Gy for bone marrow.

3. DIAGNOSIS

The diagnosis of ARS is usually made by obtaining an accurate history, with a thorough medical history being the first step (Table 1) [11]. The value of the history, of course, will depend on the ability to elicit relevant information. Laboratory findings including complete blood count (CBC) are helpful for the diagnosis for ARS. Victims with ARS may have some skin damage characterized by epilation or loss of epidermis. Attention should be paid to the presence of symptoms such as nausea, vomiting, diarrhea, abdominal cramping, and erythema or bullous formation.

Persons presenting with nausea, vomiting, or other signs such as acute developing parotitis that would lead to a suspicion of radiation exposure, should be transported to well-equipped hospitals. When suspected of having been exposed to a high dose of radiation, CBC analysis should be performed, paying special attention to lymphocyte count, every 4 to 6 hours following exposure, and CBC repeated for 24 to 48 hours.

4. PROGNOSIS

Initial fever, bloody diarrhea, headache, hypotension, and disorientation during the prodromal stage are signs for poor prognosis. However, radiation exposure alone does not cause immediate death. Combination injuries involving trauma and chemical or thermal burns are worse than radiation exposure alone. The mean lethal dose of radiation required to kill 50% of humans at 60 days ($LD_{50/60}$) of whole-body radiation is between 3.25 and 4 GyEq in victims managed without supportive care and 6 to 7 GyEq when supportive care is provided [12,13,14]. Children (<12 years) and seniors (> 60 years) may be more susceptible to radiation exposure, as $LD_{50/60}$ is lower [14]. There is only one case of survival for longer than 80 days after radiation exposure with a dose more than 20 GyEq, this one at the Tokai-mura accident [6,7]. There has been no reported case of survival longer than this following even a lower-dose radiation exposure of over 12 GyEq.

5. DOSE ASSESMENT

Dose assessment for exposed victims is essential for predicting prognosis and making treatment-related decisions. For the requisite multi-parametrical dose assessment, the estimate of absorbed dose can be obtained by several methods.

For victims heavily exposed, a quick dose estimation is vital for prompt medical decision-making. Prodromal symptoms, lymphocyte depletion kinetics, and whole-body count of neutron exposure provide the earliest indicators of exposure in the initial assessment. Determining the type,

Table 1. History of Radiation Exposure

1. Known or possible radiation exposure
2. Entering a radiation chamber when the source is unshielded
3. Proximity to an unknown (usually metallic) object, and a history of nausea and vomiting, especially if nausea and vomiting are unexplained by other causes
4. A tendency to bleed and/or respiratory infection with neutropenia, lymphopenia, and thrombocytopenia, with a previous history of nausea and vomiting
5. Epilation, with a history of nausea and vomiting two to three weeks previously

time of onset, severity and frequency of these symptoms is important for a quick dose assessment in case of high-dose exposure [6,7]. It stands to reason that these symptoms must be monitored throughout the clinical course after the exposure. Circulating lymphocytes are one of the most radiosensitive cells, and the best and most useful laboratory test is to determine the decline in their absolute number, which will provide a rough dose estimation of the radiation exposure at the early phase if victims do not have significant conventional injuries such as thermal burn. This means that performing blood cell counts as soon as possible post exposure as well as regular repetitions thereafter is of the utmost importance. Thus, lymphocyte depletion kinetics will provide a quick guide for the first two or three days and allow a dose assessment with an acceptable level of uncertainty (usually between 1 and 10 GyEq). Careful observation and repeated laboratory studies are the only measures of evaluation until further information becomes available.

Chromosome aberrations are induced by radiation in circulating lymphocytes and constitute a reliable dosimeter. A peripheral blood sample, heparinized, should be obtained within 24 hours after exposure. The types of aberrations considered to be most representative of radiation exposure are dicentrics, rings and fragments. In addition, they are quasi-specific; only one dicentric can be detected in 2000 lymphocytes in the unexposed, irrespective of sex and age. It takes about 3 days to obtain results of the analysis, since lymphocytes need to be cultured for at least 48 hours to obtain sufficient metaphases for evaluating the frequency of chromosomal aberrations. Moreover, the scoring requires considerable expertise. The sensitivity of the technique depends on the dose and radiation quality. The limit of detection, which depends on the number of cells examined, is approximately 0.2 GyEq.

In the past, dose assessment from reconstruction of the accident was used as the key parameter for medical decision-making and determining a patient's prognosis. However, performing reconstruction of the accident (physical dose reconstruction) or mathematical dose calculation is a time-consuming procedure.

6. TREATMENT OF ARS

6.1 Initial Treatment

Radiation does not cause immediate death, and clinical manifestations except prodromal symptoms do not become apparent immediately after exposure. Burns apparent immediately after exposure have to be considered as thermal or chemical burns. Of course, management of life-threatening injuries takes precedence over radiological surveys. Initial treatment should be based on actual symptoms, and the results of routine laboratory tests, and the initial symptoms for radiation exposure are non-specific. However, as mentioned above, they are important for primary dose estimation in heavily exposed patients. On the first day, treatment of whole-body exposure will be directed at these symptoms and an attempt should be made to estimate the order of magnitude of the exposure and its distribution within the body, since these two parameters will condition prognosis and consequently the nature of the most appropriate treat-

ment. Meanwhile, in certain cases, all efforts should be primarily directed toward providing appropriate substitutes, such as blood typing for stem cell transplantation.

Although prodromal symptoms are usually self-limited, sedatives and anti-emetics may be used. For vomiting, selective serotonin receptor antagonists may be effective, and emesis usually abates within 48-72 hours. Since nausea, vomiting, and diarrhea lead to a marked imbalance of body fluids and electrolytes, fluid and electrolyte replacement should be considered. It must also be kept in mind that exposure to high-dose radiation results in the increased permeability of vessels. In addition, for bone marrow suppression, management of the patient should focus on the treatment of infection and hemorrhage.

6.2 Current Therapeutic Measures

Treatment is not indicated for patients exposed to less than 1 GyEq. Early initiation of treatment should be emphasized for patients with exposure of more than 3 GyEq. Treatment of ARS includes cytokine therapy, blood component transfusion, even stem-cell transplantation, and of course supportive care. The experiences of the Chernobyl accident in 1986 and the Toaki-mura criticality accident in 1999 suggest that comfort care is indicated for people with an exposure dose greater than 12 GyEq because of their poor prognosis [1,15]. Timely consultation with radiation and hematology experts is required for dose assessment and prediction of prognosis. Treatment-related decisions should be made after consultation with specialists and the primarily dose assessment.

6.2.1 Cytokine Therapy

Cytokine therapy with such as granulocyte colony-stimulating factor (G-CSF) should be initiated as early as possible for those who are judged to have been exposed to over 3 GyEq, and for those <12 and > 60 years old, CSF therapy should be initiated at a lower exposure dose (1-2 GyEq) [17]. Moreover, CSFs must be given to radiation victims with combination injuries in excess of 2 GyEq [17]. Experimental animal studies have demonstrated that CSFs may not only be effective for bone marrow suppression but also offer a survival advantage if administered early [7,16].

6.2.2 Transfusion

Specific indications concern red blood cells and platelets but not neutrophils. Transfusion of cellular components is required for patients with severe bone marrow damage, a complication that does not typically occur until 2 to 4 weeks after the exposure unless the dose was over 5 GyEq [7]. All cellular products must be irradiated with 25 GyEq or more to prevent transfusion-associated graft-versus-host disease (GVHD) in victims with immunosuppression. It may be difficult to distinguish transfusion-associated GVHD from radiation-induced organ damage, which may include fever, pancytopenia, skin rash, desquamation, severe diarrhea, and liver dysfunction.

6.2.3 Stem Cell Transplantation

Experience from past radiation accidents suggests that the role of stem cell transplantation, and especially bone marrow transplantation, is limited. This experience has shown that the outcome of stem cell transplantation is poor, despite a transient engraftment with partial chimerism. This poor result is largely because of the impact of multi-organ involvement including radiation burns and gastrointestinal or lung injuries, and suggests that serious radiation injury to other organs is of greater consequence than bone marrow injury. The radiation level needed to cause irreversible failure of bone marrow is not clear, although there are reports of the auto-recovery of bone marrow in patients exceeding 12 GyEq [18].

The European Cooperative Group for Blood and Bone Marrow Transplantation (EBMT) reached a consensus concerning hemopoietic stem cell transplantation (HSCT), concluding that it should not be performed in any radiation accident victim possessing the potential of any degree of endogenous hemopoietic recovery because of the non-uniform exposure in most accidents (personal communication, February 2006). Nevertheless, the experience of the Tokai-mura accident has shown that stem cell transplantation from umbilical cord blood transiently rescued bone marrow suppression until autologous recovery. If resources allow, stem cell transplantation may be considered in patients with an exposure dose of 10±2 Gy and without other major complications. Because of the possibility of GVHD, the use of stem cells from peripheral blood or cord blood is recommended.

6.3 Supportive Care

Supportive care includes prevention of infection, fluid and electrolyte replacement, anti-metric or -diarrhea therapy, prophylaxis against ulceration of the gastro-intestinal tract, and others. Indeed, increased permeability of blood vessels has been observed shortly after exposure to radiation in patients in the Sarov, Russia [19] and the Tokai-mura accidents [7]. Careful attention must be given to early fluid resuscitation of patients with significant skin injury, hypovolemia, and hypotension. Resources permitting, routine critical care therapy should be provided to patients who develop MOF several days to weeks after exposure, as their dose will have been in the high range.

6.3.1 Infections

Controlling infection during the critical neutropenic

phase is a major limiting factor for prognosis. For prophylaxis in neutropenic patients, broad-spectrum antimicrobial agents should be given during the potentially prolonged neutropenia period, including antibiotics, antiviral drugs, and antifungal agents. Herpes simplex is a frequent cause of morbidity, and medicines prophylactic to Vazicella zoster virus and cytomegalovirus should also be administered.

6.3.2 Gastrointestinal Injury

Supportive measures include fluid replacement, antibiotic therapy, and prophylaxis against ulceration of the gastrointestinal tract. Instrumentation of the gastrointestinal tract should be performed judiciously if at all, since the intestinal mucosa is friable and prone to sloughing and bleeding after mechanical manipulation. For prophylaxis for gastrointestinal tract injury, the goal of antibiotics has ranged from "total decontamination" of the alimentary tract with oral non-absorbable antibiotics to "selective decontamination," the aim of which is to eliminate potentially pathogenic aerobic flora (enteric gram-negative bacteria).

6.3.3 Comfort Measures

There is almost no chance for long survival after radiation with a dose of more than 12 GyEq, and it may be appropriate for definitive care to be withheld from such individuals. Rather than being treated aggressively, these patients should be provided with comfort measures, which include attention to pain management and general comfort. In addition, psychological support and pastoral care are essential not only for the patient but also for family. As can be imagined, this approach is the subject of a great deal of discussion.

7. MEDICAL FOLLOW-UP OF ARS

The studies on atomic bomb survivors in Hiroshima and Nagasaki have shown that diseases other than cancer have occurred at significantly increased levels in patients who were exposed to radiation of more than 1 GyEq, although the dose-response relationship is not clear [20,21]. The objective of follow-up for patients who recovered from ARS is the maintenance of their state of health. For the health management of these patients, the radiation dose as well as the distribution of radiation exposure should be taken into account, since the dose received varies among parts of the body. Medical follow-up has to be based on medical and radiobiological knowledge — the threshold values for deterministic effects available on the past radiation exposure and the stochastic effects currently available from epidemiological data. Medical examinations for radiation exposure should be conducted in order to identify the early effects and also to detect the delayed effects that can arise after a long duration following exposure.

7.1 Identification of Deterministic Effects

Transient infertility appears in males exposed to about 0.15 GyEq. However, current medical knowledge indicates that a natural recovery can be expected. Permanent infertility occurs at doses of 3.5 GyEq or more for males and 2.5 GyEq or more for females. As for the lens of the eye, cataracts appear with exposure exceeding 0.5 GyEq, and visual impairment occurs at 5 GyEq. Thus, periodic ophthalmological examinations are recommended.

Hyper-parathyroidism and parathyroid tumors are often diagnosed from hypercalcemia, pointing to the importance of checking the levels of serum calcium. In addition, hyperparathyroidism may also be complicated by thyroid diseases [22]. In atomic bomb survivors, an increased prevalence of hypo-thyroidism has been found. This emphasizes the fact that follow-up for the thyroid including blood tests and ultrasound examinations should be started fairly soon after the exposure.

Myoma of the uterus may also develop [23], and a statistical increase in cardiovascular disease and digestive system disorders, such as liver dysfunction, has been observed among atomic bomb survivors.

7.2 Identification of Stochastic Effects

The medical follow-up for stochastic effects focuses on malignant tumors. Doses exceeding 0.05 - 0.2 GyEq are associated with significant incidences of leukemia as well as thyroid, breast, lung, stomach, colon and ovarian cancer [20]. Furthermore, there is an excess incidence of cancer of the esophagus, salivary gland tumors, urinary tract cancer, and skin cancer. The interval before the appearance of malignant tumors varies is organ-dependent. The peak of the onset of leukemia occurs 5 to 8 years after exposure. Increases in thyroid cancer appear about 10 years later, about 20 years later for breast and lung cancer, and about 30 years later for stomach and colon cancer.

The follow-up of stochastic effects should be directed toward early detection and treatment of malignant tumors. Tests for solid cancers such as breast, lung, and colon cancer should always be included in the follow-up examinations over the long term.

8. MULTIPLE ORGAN FAILURE (MOF) AND INFLAMMATION

The concept of MOF includes the gradual and sequential failure of virtually all organs following a wide spectrum of noxious stimuli [24]. MOF develops when biochemical mediators escape physiological control, and a poor outcome is considered to be a consequence of an overactive systemic

inflammatory response elicited by these external insults [25]. Although infection is the most frequent trigger of systemic inflammation, it may also be caused by a variety of non-infectious attacks.

Systemic inflammation is a consequence of activation of the innate immune system. Trauma, burns, severe blood loss and infection are the most frequent triggers of systemic inflammation. The patho-physiology of inflammation is characterized by intravascular release of pro-inflammatory cytokines and vasoactive mediators. Cytokines are produced at the early phase when cells or tissues are exposed to external insults [25,26]. Pro-inflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin-1 (IL-1) are initially produced. Endothelial and epithelial cells as well as neutrophils and macrophages produce proinflammatory mediators. Neutrophils and macrophages also release granular enzymes and reactive oxygen species (ROS), which in turn cause tissue damage, leading to increased vascular permeability. These factors can cause circulatory collapse and vascular pan-endothelial injury, leading to increased microvascular permeability. This response then, on the other hand, also triggers an anti-inflammatory response. Anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGFβ) are produced, and these then attenuate the production of pro-inflammatory mediators. The resulting imbalance in the production of pro- and anti-inflammatory cytokines, however, then leads to a hyper-reactive or hypo-reactive response. The overproduction of these inflammatory cytokines causes systemic inflammatory response syndrome (SIRS) [24]. In contrast, the excessive anti-inflammatory response leads to a state of immunosuppression, and impaired adaptive immune function leads to immunoparalysis. This state is called compensatory anti-inflammatory response syndrome (CARS). A dramatic paralysis of cell-mediated immunity following major stress appears to be responsible for the increased susceptibility to MOF. Thus, the balance of inflammation and anti-inflammation is extremely important.

8.1 Evidence of Severe Inflammation Following Exposure to High-dose Radiation

The prodromal symptoms such as nausea, vomiting, diarrhea and high fever are also typical symptoms of systemic inflammation. Radiation exposure also induces transient leukocytosis, the mechanisms for which are not clear; increased numbers of neutrophils have been observed in ARS [6,7,16]. Moreover, increased permeability of blood vessels has been observed shortly after exposure to radiation in patients in the Sarov, Russia and the Tokai-mura accidents [7,19]. Thus, whole-body exposure to radiation causes severe inflammation, and symptoms are probably induced through the generation of ROS and cytokines. Radiation induces the expression of pro-inflammatory cytokines in human cells [27,28]. Following exposure to high-dose radiation, the anti-inflammatory response transiently induced is probably the latent phase. However, as injuries of the immune system including bone marrow suppression develop, it is clear that the anti-inflammatory response cannot fully compensate for the inflammatory response. The hyper-reactive response thus becomes prolonged. Radiation also causes gastro-intestinal tract injury and loss of electrolytes, leading to circulatory and renal dysfunction and contributing to MOF.

9. CONCLUSIONS

In this review, we have tried to discuss ARS and MOF. Whole-body exposure to high-dose radiation causes severe, probably excessive, systemic inflammation, and anti-inflammatory compensation cannot be fully induced at the early phase [29]. Further, prolonged bone marrow suppression leads to a dramatic paralysis of cell-mediated immunity, resulting in bleeding. In the Tokai-mura criticality accident, two workers died of MOF [6,30]. One received a blood stem cell transplant from his human leukocyte antigen (HLA)-identical sister [31]. However, random chromatid breaks were observed in lymphocytes from the donor. The other received HLA-DRB1- mismatched unrelated umbilical cord blood transplantation, following which autologous hematopoietic recovery was observed [32]. However, mitogenic responses of T lymphocytes and allogeneic mixed leukocyte reaction were severely suppressed and endogenous immunoglobulin production was also suppressed, although the impaired immune responses might have contributed to the successful engraftment of a transplanted cadaver-derived skin graft [33]. Damage of endothelial cells by high-dose radiation is known to lead to disturbance of the microcirculation. Since radiation causes damage to parenchymal cells in each organ, blood vessel injuries are also an important factor in the increased susceptibility to MOF. Taken together, it is clear that the mechanisms of MOF in ARS are indeed complex and the details remain elusive, highlighting the urgent need for further intensive analyses of all accumulated medical data.

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