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Role of infection and bleeding in multiple organ involvement and failure

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Abstract. Whole body exposure to high dose radiation causes combined injury; multiple organs are involved, depending on their sensitivity to radiation. The general current concept of multiple organ failure (MOF) includes the gradual and sequential failure of virtually all organs after external insults. MOF develops not as a consequence of the external insult itself, but rather owing to the host's response to the insult, and is closely tied to the phenomenon recognised clinically as "inflammation". This inflammation is caused by trauma, thermal or chemical burns, pancreatitis, infection, etc. Despite the development of modern intensive care, the mortality of patients with MOF remains high. Moreover, the exact mechanisms of MOF remain unknown. This review will focus on the possible roles of infection and bleeding in multi-organ involvement and failure.

Introduction

The development of monitoring and support systems for patients in critical care has allowed physicians to recognise that the major cause of death was not always an underlying illness, but rather a process of physiological failure of several interdependent organ systems [1]. From this observation, a concept of multiple organ failure (MOF), or multiple organ dysfunction syndrome (MODS), was developed. The current concept of MOF includes the gradual and sequential failure of virtually all organs following a wide spectrum of noxious stimuli, from infection to trauma [2]. Recent studies have revealed that 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 external insults [3]. Indeed, evidence has accumulated to show that systemic inflammation contributes to the development of multiple organ dysfunction, which is the major cause of mortality in patients with septic shock [4, 5]. Although infection is the most frequent trigger of systemic inflammation, it may also be caused by a variety of non-infectious insults such as bleeding, acute pancreatitis and autoimmune disorders.

In 1999, a criticality accident occurred in Japan [6]. The experience of treating the heavily exposed patients told us that MOF was the leading cause of death in these patients [7]. To our knowledge, however, there are few reports regarding long clinical courses of heavily exposed victims. In this review, I have tried to focus on the possible roles of infection and bleeding in multi-organ involvement and failure.

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Inflammation cascade following major stress leading to the development of MOF

Systemic inflammation is a consequence of activation of the innate immune system. Whole body trauma, burns, severe blood loss and infection are the most frequent triggers of systemic inflammation. The pathophysiology of inflammation is characterised by intravascular release of pro-inflammatory cytokines and vasoactive mediators (Figure 1). Cytokines and chemokines are produced at the early phase when cells or tissues are exposed to external insults [3, 4]. Upon external insult, pro-inflammatory cytokines such as tumour necrosis factor (TNF), interleukin-1 (IL-1), IL-6 and IL-8 are produced initially. Endothelial and epithelial cells as well as neutrophils, macrophages and lymphocytes produce pro-inflammatory mediators. Neutrophils and macrophages also release granular enzymes and reactive oxygen species (ROS). ROS cause tissue damage, leading to increased vascular permeability. These factors can cause circulatory collapse and vascular pan-endothelial injury, leading to increased microvascular permeability. The severity of systemic inflammation is affected by various factors, which in turn govern the patient's immune inflammatory response to invading microorganisms.

Of course, this response then triggers an anti-inflammatory response. Anti-inflammatory cytokines such as IL-12, IL-10 and transforming growth factor-β (TGF-β) are also produced, and these then attenuate the production of pro-inflammatory mediators. However, the imbalance in the production of pro- and anti-inflammatory cytokines results in a hyperreactive or hyporeactive response. Currently, it is thought that excessive levels of both cytokines are involved in the development of MOF. The overproduction of these inflammatory cytokines causes systemic inflammatory response syndrome (SIRS) (Figure 2) [2]. On the other hand, the excessive anti-inflammatory response leads to a state of immunosuppression; impaired adaptive immune function leads to immunoparalysis. This state is called compensatory anti-inflammatory response syndrome (CARS). A dramatic paralysis of cell-mediated immunity

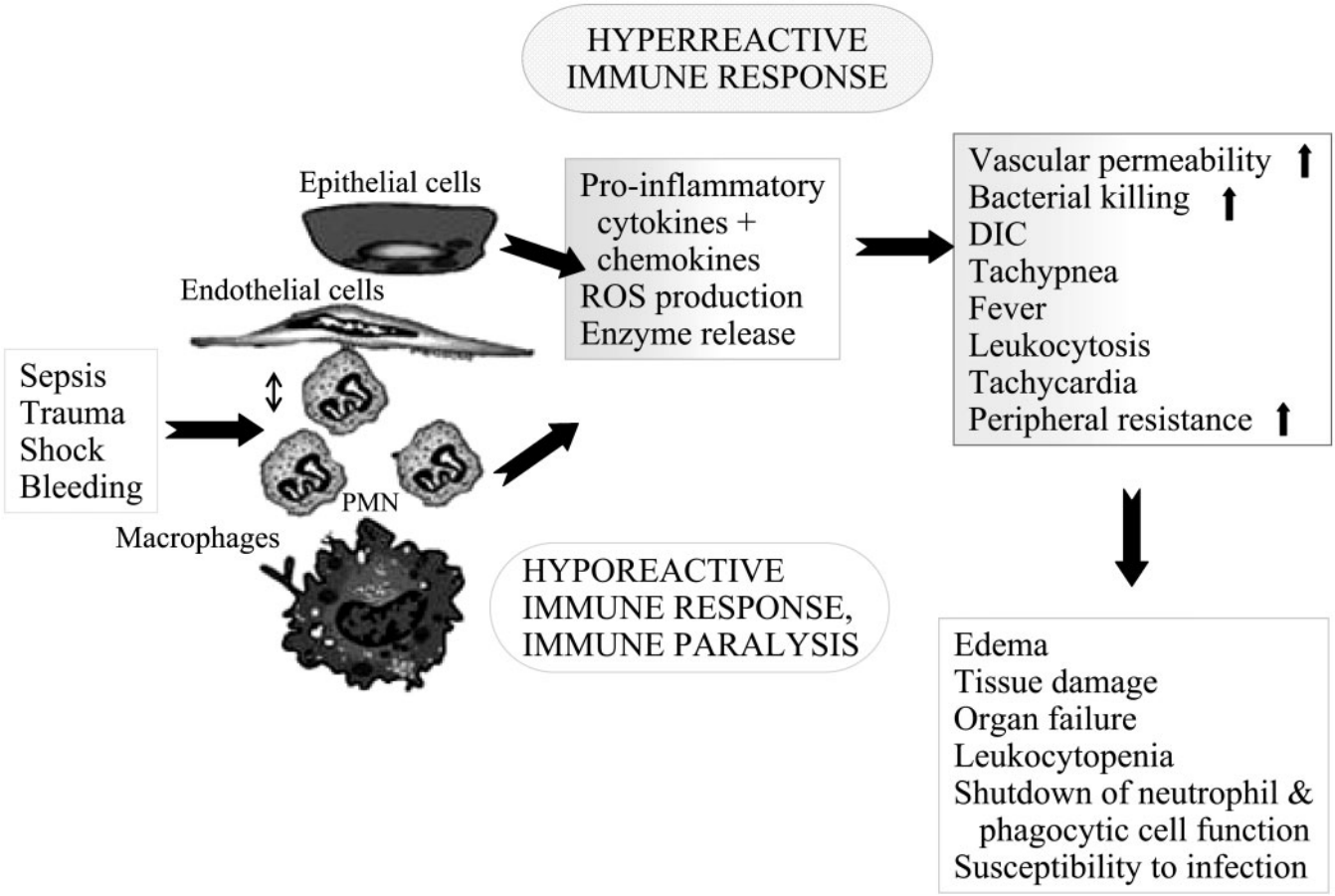

Figure 1. Inflammation cascade following major stress leading to multiple organ failure. ROS, reactive oxygen species; PMN, polymorphonuclear neutrophils; DIC, disseminated intravascular coagulation. Adopted and modified from Riedemann et al [8].

following major stress appears to be responsible for the increased susceptibility to MOF. CARS may also increase susceptibility to secondary infections. Thus, the balance of inflammation and anti-inflammation is extremely important.

Role of infection in MOF

Under normal circumstances, various bacteria live in coexistence with humans. The skin, gastrointestinal (GI) tract, upper respiratory tract and conjunctiva all contain bacteria. In particular, the GI tract contains billions of bacteria such as *Escherichia coli* that contribute to the function of the intestine. The presence of bacteria on these organs itself is not a threat to the body. However, if these microorganisms pass the barrier between the external and internal environment, an immune response is evoked; the individual host response to infection varies, depending on the patient's immune response.

Sepsis is defined as a systemic response to infection as well as evidence of organ system dysfunction [9]. Originally, the diagnosis of sepsis required confirmation of bacterial growth in blood cultures as well as the presence of two or more symptoms such as hypothermia or hyperthermia, tachycardia, tachypnoea and leukocytosis [8]. Sepsis is now the leading cause of death in critically ill patients, despite the development of modern intensive care and new antimicrobial agents. Circulatory shock is the major epidemiological predictor for mortality among patients with sepsis. The inflammatory system becomes hyperactive during the onset of sepsis, and both cellular and humoral defence systems are involved. The poor outcome of sepsis is thought to be a consequence of an overactive inflammatory response elicited by invading microorganisms. Indeed, accumulating evidence has implicated systemic inflammation as contributing to the development of MOF, and recent therapies have focused on modulating the immune response in accordance with the characteristics of the specific pathogen, the genetic profile of the patient and the duration of the disease. Furthermore, there is no single marker that would reliably identify at an early stage of sepsis that MOF is bound to develop. In later stages of sepsis, on the other hand, anti-inflammatory mediators are inadequately produced, and CARS is induced.

Roles of bleeding in susceptibility to immune dysfunction

Adequate oxygen delivery and metabolism are essential for the maintenance of cellular energy stores; failure of adequate oxygen delivery and utilisation can lead to organ dysfunction and death. Experimental animal models have suggested that haemorrhagic shock and global ischaemia trigger strong systemic inflammation [10]. Furthermore, the inability to increase oxygen consumption

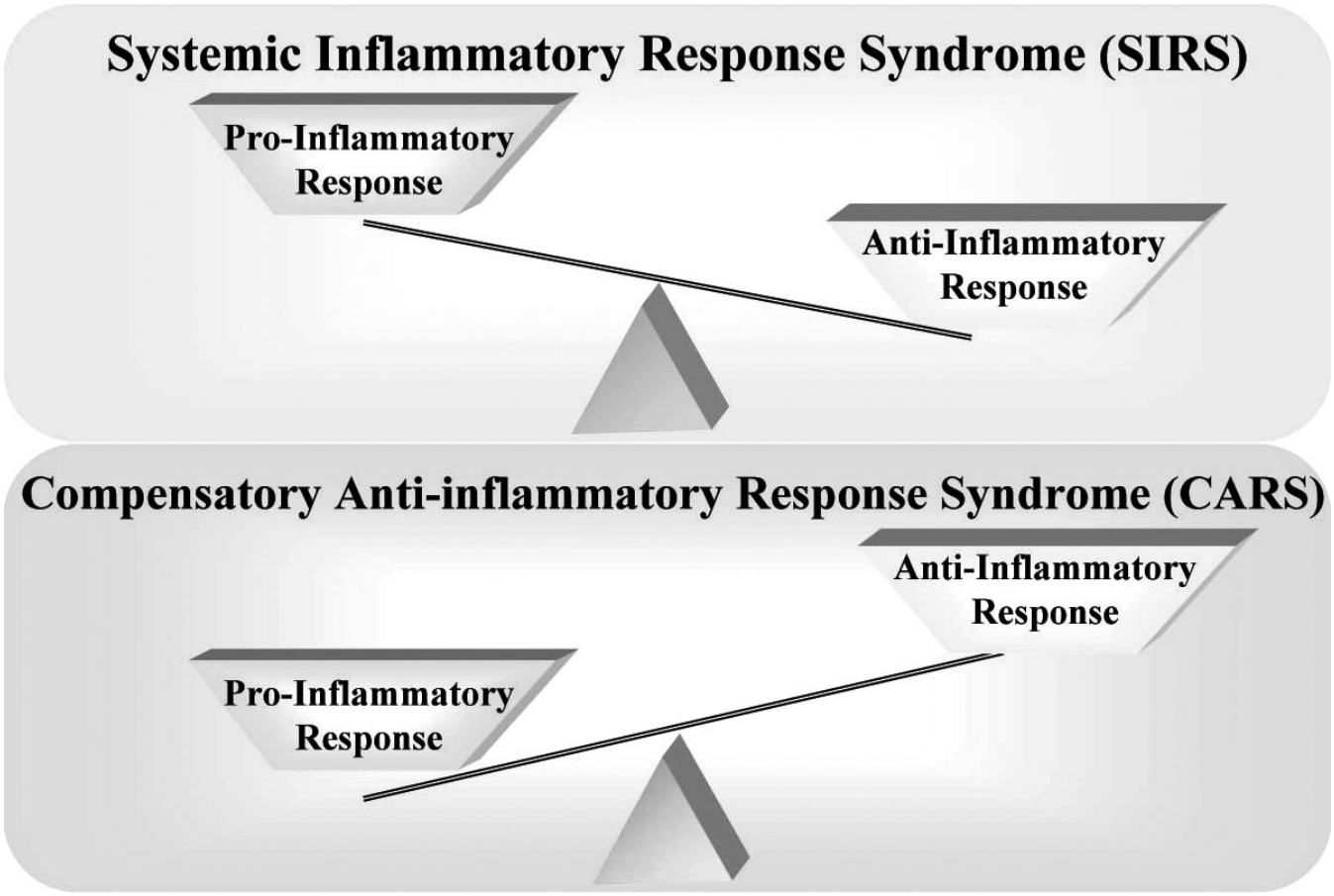

Figure 2. Balance of inflammation and anti-inflammation.

after severe injury, despite adequate oxygen delivery, has been associated with the development of MOF [11]. Thus, bleeding is also known to be one of the most important risk factors for the development of MOF [12]. Loss of blood results in inadequate blood flow to meet the metabolic demands of organs, leading to impairment of oxygen consumption [13, 14]. Over 90% of cellular oxygen is consumed by mitochondria in the process of oxidative phosphorylation [15]. Patients with severe trauma from injury who develop MOF specifically display evidence of mitochondrial oxidative dysfunction [16]. Severe blood loss results in inherent mitochondrial dysfunction as manifested by decoupling [14, 16].

The effects of haemorrhage on the lymphocyte response to T-cell mitogenesis and mixed lymphocyte reaction have also been shown [17]. In experimental and clinical studies, simple haemorrhage is known to impair the proliferative response capacity of splenocytes in response to the T-lymphocyte mitogen concanavalin A (Con A) [18]. Antigen presentation by macrophages is a process whereby cells express antigens on their surface in a form capable of being recognised by T-lymphocytes. These impaired functions are thought to be due to defects of antigen presentation by macrophages following haemorrhage, leading to MOF [17]. Thus, immune suppression following simple haemorrhage results in enhanced susceptibility to sepsis.

Evidence of severe inflammation following exposure to high dose radiation

Acute radiation syndrome has four stages of symptoms that appear after radiation exposure: prodromal, latent, manifest and death/recovery phases [6]. The stage immediately after exposure to a high dose of radiation for several hours, when nausea, vomiting, diarrhoea and high fever (prodromes) appear, is called the prodromal period. These prodromal symptoms are typical of systemic inflammation. Radiation also induces transient leukocytosis, the mechanisms for which are not clear. Increased numbers of neutrophils have been observed in many radiation accidents as well as in experimental animals [6, 19]. 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 [20, 21]. Thus, whole body exposure to radiation causes severe inflammation, and symptoms are probably induced through the generation of ROS and cytokines. In skin, signs resembling sunburn also appear. Studies have shown that irradiation induces the expression of pro-inflammatory cytokines in human cells [22, 23]. Following exposure to high dose irradiation, an anti-inflammatory response is transiently induced, the so-called latent phase. However, the anti-inflammatory response cannot fully compensate for the inflammatory response, since bone marrow suppression develops. Therefore, the hyperreactive

response becomes prolonged. Radiation also causes GI tract injury and loss of electrolytes, leading to circulatory and renal dysfunction and contributing to MOF.

Lessons learned from the Tokai-mura accident

In 1999, a criticality accident occurred at Tokai-mura, a village in Japan, and two workers died of MOF [6, 7]. One received a blood stem cell transplant from his human leukocyte antigen (HLA)-identical sister [24]. After the transplantation, bone marrow recovery with complete donor chimerism was observed in this patient. However, random chromatid breaks were observed in lymphocytes from the donor. The other worker received HLA-DRB1-mismatched unrelated umbilical cord blood transplantation, following which autologous haematopoietic recovery was observed [25]. However, mitogenic responses of T-lymphocytes and allogeneic mixed leukocyte reaction were severely suppressed [26]. Moreover, endogenous immunoglobulin production was also suppressed, although a cadaver-derived skin graft for radiation burns was quite successful. It remains unknown how the random chromatid breaks observed in the donor-derived lymphocytes is related to immunological dysfunction. However, the impaired immune responses might have contributed to the successful engraftment of the transplanted cadaver-derived skin graft. In any event, the patients exposed to high dose radiation displayed immunological dysfunction following treatment.

Role of blood vessel injury in irradiation-related MOF

The early decrease in the number of endothelial cells has been postulated to be due to apoptosis of a part of the endothelial population after radiation therapy [27]. Early irradiation effects in the blood vessels occur predominantly in the microvasculature [28]. In this regard, it is known that disturbance in the microcirculation is involved in the development of organ dysfunction in sepsis [29]. This vascular injury could further accelerate radiation injury in parenchymal tissues (Figure 3). On the other hand, damaged endothelial cells overproduce plasminogen activator-1, leading to fibrinolysis-suppressive disseminated intravascular coagulation [30]. These changes characterise septic coagulopathy, which is often complicated by MOF. A coagulation abnormality is initiated by the expression of tissue factor (TF) on the surface of monocytes/macrophages and endothelial cells, which are induced by endotoxins and pro-inflammatory cytokines [30]. TF is also known to be released from endothelial cells upon major insults, and levels have been reported be higher in patients with severe sepsis with organ dysfunction [30]. These observations suggest that injuries of blood vessels may also be important for the development of MOF in radiation exposure, since vascular injury can presumably add to the severity of injuries in other organs.

Conclusions

The history of clinical studies has confirmed that even extremely successful results from animal models and *in vitro* studies cannot be readily translated into clinical settings. Therefore, detailed analyses of the clinical data of patients are of major importance, and great caution must be taken in the interpretation of results from experimental data. This is especially true for radiation exposure accidents, since they rarely occur, and studies or research on radiation exposure are not performed in many institutions. In this review, I have tried to determine the roles of infection and bleeding in MOF and involvement in high dose radiation exposure (Figure 4). Whole body exposure to high dose irradiation causes severe, probably

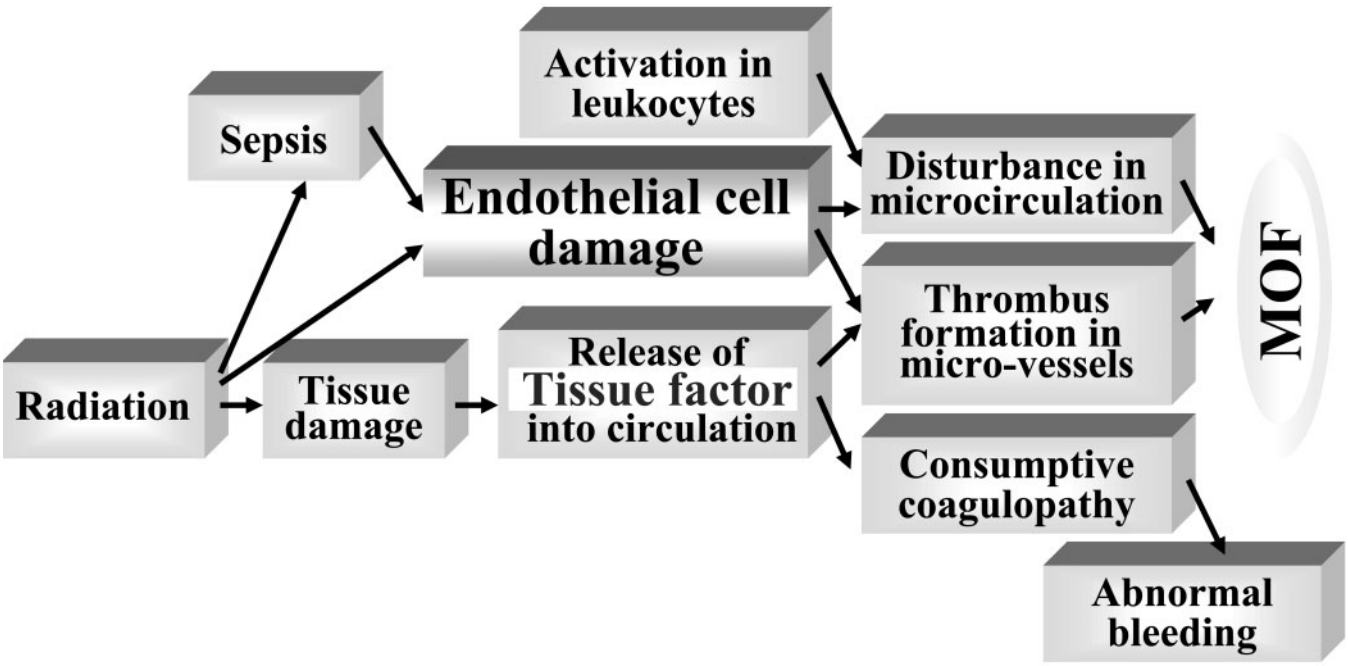

Figure 3. Role of blood vessel injury in multiple organ failure (MOF). The endothelial cell damage and release of tissue factor may be important in the development of MOF. Adopted and modified from Kidokoro et al [29].

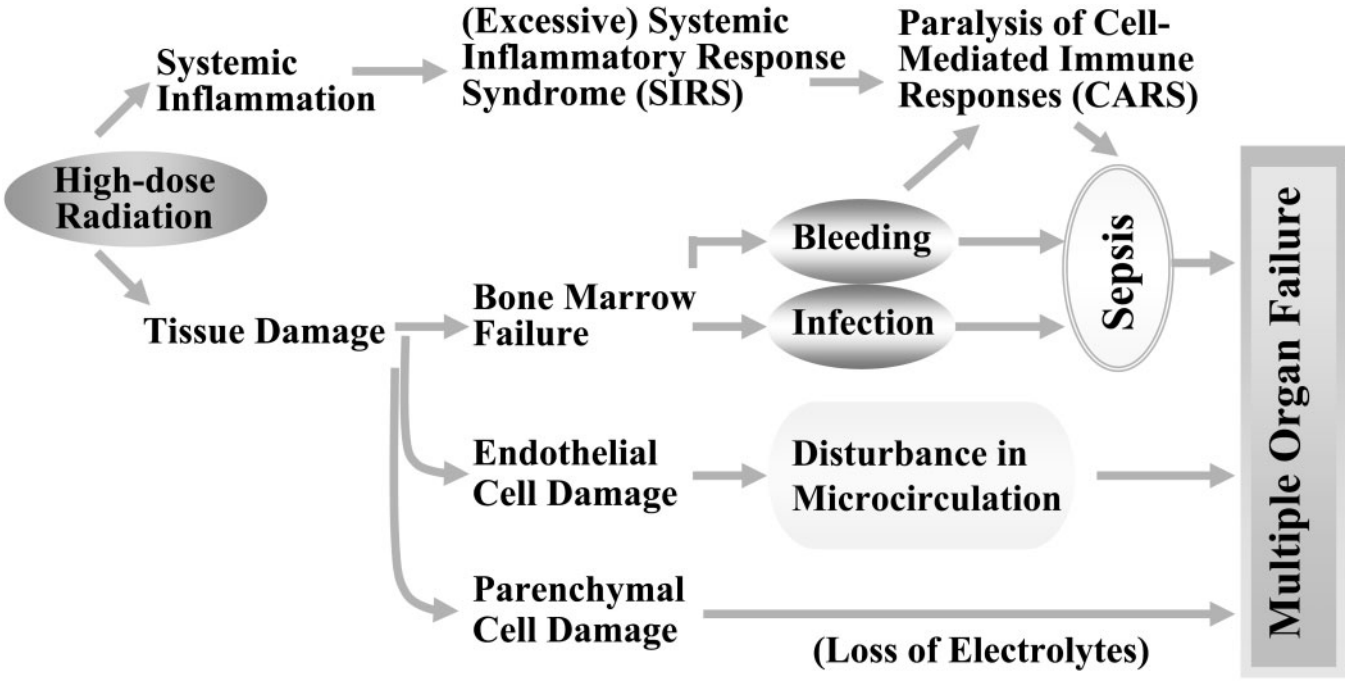

Figure 4. Possible mechanisms for multiple organ failure in radiation exposure. CARS, compensatory anti-inflammatory response syndrome.

excessive, systemic inflammation, and anti-inflammatory compensation cannot be fully induced at the early phase. Further, prolonged bone marrow suppression leads to a dramatic paralysis of cell-mediated immunity, and bone marrow failure leads to bleeding.

Studies of the Tokai-mura accident have shown impaired functions of lymphocytes recovered from bone marrow suppression by whole body exposure to radiation as well as damage to donor cells in a recipient. In addition, damage of endothelial cells by high dose radiation was seen to result in 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, the mechanisms of MOF in radiation exposure 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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