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# Multiple organ involvement and failure: selected Russian radiation accident cases re-visited

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**Abstract.** In this paper we analyse the role of multi-organ failure (MOF) syndrome in the cause of death of victims with severe and very severe (>10 Gy) forms of accidental acute radiation syndrome (ARS). From 1958–1997 we have followed and managed 11 patients with $\gamma$-neutron (criticalities), $\gamma$-$\beta$ (Chernobyl) and pure $\gamma$ whole body irradiation. We describe three types of MOF following high dose irradiation: an early syndrome, when the total dose is more than 20 Gy, related to damage to the microcirculation and leakage syndrome; MOF as a consequence of severe radiation burns, followed by kidney failure and encephalopathy; and late MOF (2–3 months after 10 Gy or more total dose) due to the irradiation itself, to infection and to iatrogenic problems. All three types of MOF are potentially fatal and play an essential role in the pathogenesis of severe ARS.

## Introduction

At the end of the 1960s, on the basis of clinical observations of the victims of radiation nuclear accidents, Guskova, Baysogolov, Kraevsky and Lemberg defined a toxaemic form of acute radiation disease (ARD) in humans intermediate between intestinal and central nervous system (CNS) syndrome following 20–50 Gy of $\gamma$-neutron irradiation [1–3]. At the same time, Fanger and Lushbaugh described a cardiovascular form, which was obviously established by a level of irradiation between the toxaemic and CNS syndrome level [4]. For both ARD forms, early decreasing blood pressure and the occurrence of renal failure and generalised capillary leakage were typical before distinct clinical signs and symptoms of intestinal and bone marrow radiation damage evolved. Thus, both clinical patterns are closely related to the development of early multiple organ failure (MOF).

Consequent clinical observations provided the basis for defining three additional pathogenic forms of ARD with predominant lung, skin and local radiation injuries. For all these forms of ARD, the toxic MOF is typically due to acute total or subtotal superficial $\beta$ skin burns (Chernobyl), or to extensive deep radiation dermatitis and severe lesions of the underlying tissues and organs following highly non-uniform $\gamma$ and $\gamma$-neutron irradiation.

This is broadly confirmed by the latest accident in Japan when, for the first time ever, a successful attempt was made to partially overcome the complications of this syndrome [5].

## Clinical course of MOF in selected Russian radiation accident cases

MOF syndrome basically consists of the development of a severe hepatorenal failure accompanied by nitrogenemia and cardiopulmonary failure, and very often results in brain oedema or toxaemic encephalopathy.

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In certain cases, it is combined with, or results in, acute respiratory distress syndrome (ARDS). Then, death is determined by pulmonary damage and hypoxaemia. It is important to point out that in all cases autopsy and morphology data indicate that MOF represents specifically a functional failure rather than a result of direct radiation damage to those organs. It appears to be a natural consequence of the toxaemic syndrome.

One may assume, with a reasonable degree of certainty, that MOF was one of the leading causes of death following irradiation either in the absence of fatal manifestations of the bone marrow syndrome (BMS) or after it has already been overcome (blood cell recovery), and there are no critical consequences of the gastro-intestinal syndrome (GIS) in the form of hydroelectrolytic and metabolic disorders or haemorrhage.

In its most spectacular form, MOF is observed in patients with large radiation skin burns (more than 50% of the body surface) and in the cohort of the victims with very high local doses resulting in irradiation of not only the skin but also the underlying tissues and internal organs (local radiation injury (LRI) syndrome).

To characterise MOF further, Table 1 contains a description of the causes of death in acute radiation sickness (ARS), which we will discuss in this paper.

**Table 1.** All Russian radiation deaths followed by the Institute of Biophysics, with selected non-Russian cases (60 victims)

| BMS | GIS | LRI | Number of patients | Time of death (range) (days) | Median WB irradiation dose (range) (Gy) |
|---|---|---|---|---|---|
| – | – | + | 5 | 2 (1.37–2.67) | 50 (43–80) |
| ± | – | + | 4 | 5 (4–8) | 30 (14–38) |
| + | + | + | 25 | 17 (7–136) | 10 (3–14) |
| + | – | + | 14 | 18 (18–696) | 6 (2–11) |
| + | + | ± | 7 | 36 (21–113) | 8 (5–14) |
| + | – | ± | 4 | 62 (24–96) | 6 (4–10) |
| + | + | – | 1 | 33 | 7 |

BMS, bone marrow syndrome; GIS, gastrointestinal syndrome; LRI, local radiation injury; WB, whole body.

**Table 2.** General data for four cases of $\gamma$-neutron ($\gamma$:n) irradiation after a SCR dose of 20–50 Gy

| Patient | Year | Dose (Gy) | Type | BMS/GIS | Cause of death | Area of skin burns (2nd degree) (%) | Time of death (day/h) |
|---|---|---|---|---|---|---|---|
| Los. | 1958 | 37 | SCR $\gamma$:n=1:1.5 | No | LRI | 67 | 5 |
| Mic. | 1958 | 38 | SCR $\gamma$:n=1:1.5 | No | LRI | 60 | 6 |
| Bor. | 1958 | 14 | SCR $\gamma$:n=1:1.5 | Yes, day 7 | LRI | 54 | 9 |
| Zah. | 1997 | 50 | SCR $\gamma$:n=1:10 | No | CVS+LRI | 40 | 2.67/64 |

BMS, bone marrow syndrome; GIS, gastrointestinal syndrome; LRI, local radiation injury; CVS, cardiovascular syndrome (cardiac arrest).

**Table 3.** Some clinical and autopsy data of $\gamma$-neutron SCR accident in 1958

| Patient | Blood pressure on the day of death (mmHg) | Protein/ albumin (g $l^{-1}$) | Nitrogenemia (urea) (mmol $l^{-1}$) | Autopsy data |
|---|---|---|---|---|
| Mic. | 80/40 | 63/22 | 45 (5 N) | Kidneys: plasma absorption of small vessels with necrosis |
| Los. | 65/35 | 60/19 | 34 (4 N) | Kidneys and lungs: plasma absorption of small vessels |
| Bor. | 90/30 | 60/25 | 18 (2 N) | Lungs: plasma absorption of small vessels<br>Kidneys: necrosis of glomerules. Signs of GIS |

GIS, gastrointestinal syndrome.

In Table 1, only 7 non-Russian cases (such as Los Alamos, Sorvan, etc.) are included; the remaining 53 are Russian, among which one-half (27) are Chernobyl cases.

MOF syndrome or its elements were generally observed in the 2nd, 3rd and 4th groups of patients (4, 25 and 14 patients, respectively), where the time of death was between 5 days and 18 days, with a whole body dose between 6 Gy and 30 Gy. Here, the most frequent cause of death was burns and LRI, with no lethality resulting directly from BMS or GIS.

Very definite signs of MOF syndrome were observed in the 2nd group (Table 1) comprising cases with uniform $\gamma$-neutron irradiation with doses ranging from 14 Gy to 38 Gy (see Table 2). Here, the first three observations from 1958 are almost identical to the Tokai-mura accident.

The incident in 1958 occurred as a result of the situation where the two workers were pouring a radioactive liquid from one receptacle to another, while the third worker was standing by. In violation of the rules of safe handling of radioactive substances, they accelerated the process, thus provoking a criticality accident resulting in a mixed $\gamma$-neutron whole body radiation exposure spontaneous chain reaction (SCR).

The fourth patient in this group is the well-known Sarov case of 1997 [6]. All the victims suffered a very severe, although not total, LRI with marked early oedema and damage to underlying organs. None of them lived to develop full BMS or GIS. The cause of death was dominated by LRIs with the development of fatal leakage syndrome. Only in the Sarov case could one assume the presence of signs of a cardiovascular death.

Table 3 shows certain clinical and autopsy data relating to the 1958 accident. In all cases there was terminal hypotension caused by hypovolaemia, nitrogenemia and marked plasmat absorption of the tissues revealed by autopsy.

Patient Z from the Sarov accident presented with an early and very severe LRI resulting virtually from pure neutron irradiation. Marked oedema of the upper part of the body and arms was observed on the second day, accompanied by a bilateral effusion into the pleural cavity and pneumonitis. As in previous observations, critical hypoalbuminaemia, nitrogenemia and hypovolaemia developed. It may be suspected that death was also caused by direct radiation injury to the myocardium, because the dose received by the front part of the thorax was very high.

In this case with high local doses, one may speak of a MOF that may develop because of direct radiation injury of the microcirculation (minor vessels) in the tissues accompanied by toxaemia. Most probably, this was a consequence of the leakage syndrome.

Repeated analyses of the Chernobyl materials from the perspective of studying the terminal clinical pattern and the sectional data in the group of victims with 4th degree ARS and severe burns led us to the necessity to single out two new forms of radiation-related death: $\beta$-radiation skin burn syndrome ($\beta$-RSBS) and a pulmonary form resulting in death from ARDS and hypoxemia.

Of course, when the dose of overall $\gamma$-irradiation is 6–12 Gy, and the time of death is 14–30 days, it is very difficult to identify one single main cause of death. In all such patients, BMS, GIS and burns are observed at the same time, with all the syndromes fully developed. However, for certain patients, we were able to do this.

**Table 4.** General data for six Chernobyl patients with severe $\beta$-radiation skin burn syndrome ($\beta$-RSBS)

| Patient | $\gamma$ dose (Gy) | $\beta$-RSBS (% of BS)[a] | Day of death | BMS (day 500 granulocytes)[b] | GIS (degree) |
|---|---|---|---|---|---|
| Sh. | 9.5 | 50 | 23 | 6 | 2 |
| Br. | 10.9 | 60 | 18 | 7.5 | 0 |
| Top. | 11.8 | 100 | 18 | 8 | 2 |
| Ak. | 8.9 | 96 | 15 | 8 | 2 |
| Kon. | 6.7 | 100 | 32 | 8 | 2 |
| Per. | 5.8 | 100 | 48 | 14 | 0 |

BS, body surface; BMS, bone marrow syndrome; GIS, gastrointestinal syndrome.

[a] $\beta$-RSBS is % of 2nd degree or more.

[b] Beginning of agranulocytosis (day at 500 cells $\mu l^{-1}$).

**Table 5.** Some clinical and autopsy data for six Chernobyl cases with severe $\beta$-radiation skin burn syndrome ($\beta$-RSBS)

| Patient | Nitrogenemia/day | Liver failure/day | ARDS | Coma/day | Restoration of blood | Microbial infection in tissues at autopsy |
|---|---|---|---|---|---|---|
| Sh. | +/15 | +/18 | + | +/23 | – | – |
| Br. | +/13 | +/13 | – | +/17 | – | – |
| Top. | +/14 | +/16 | – | – | – | – |
| Ak. | +/9 | – | + | – | – | $\pm$[b] |
| Kon. | +/21 | +/27 | + | +/30 | $\pm$[a] | – |
| Per. | +/41 | +/20 | – | +/36 | + | – |

ARDS, acute respiratory distress syndrome.
[a]Granulocytes >100 cells $\mu l^{-1}$ and <500 cells $\mu l^{-1}$.
[b]Only in the lungs.

Table 4 shows six Chernobyl victims with doses of 5.8–11.8 Gy, all with severe and early $\beta$-RSBS affecting either the entire skin surface or one-half of the body surface, and with a time of death of 15–48 days following irradiation. As one can see, two of the victims did not have GIS (at least in the clinical sense), while the last patient in that group had a relatively mild BMS.

What turned out to be the most important observation was the similarity of the clinical picture and autopsy data in those victims with otherwise very different irradiation exposure. All these data indicated the presence of an obvious final toxaemia.

The terminal period in this group is shown in Table 5. It shows that all of the patients had nitrogenemia and almost all had jaundice. The majority of the patients died in a coma, and half of them had manifestations of ARDS and hypoxemia.

It is important to note that none of them had either severe diarrhoea or electrolytic disorders (patient Top. may be considered the only exception), or definite microbial tissue infection at autopsy. On the other hand, the last two patients with lower doses even showed blood recovery. While still alive, all of them had negative bacteriological tests or showed superficial (skin) microbial infection.

We believe that in this case, death is mainly determined by toxaemic MOF. Its clinical development may be schematically represented as follows: $\beta$-RSBS $\rightarrow$ nitrogenemia $\rightarrow$ liver failure $\rightarrow$ ARDS ($\pm$) $\rightarrow$ toxic encephalopathy. One may also say that this is MOF in its pure form.

Finally, on the basis of the material available to us on accidents with relatively uniform high dose irradiation, we can single out a late, possibly secondary, MOF. In this respect, the most representative is the well-known Nesvizh case of 1991 [7]. The clinical picture of the patient with all the main events is shown in Figure 1.

The victim is rather unique because he sustained a virtually uniform $\gamma$ irradiation with the dose of 15 Gy at the centre of the body. He suffered severe BMS and GIS with haemorrhage, septicaemia and viral infection. There was no stem cell transplantation. Growth factors were used, but full blood cell and immunity recovery never occurred.

After the 70th day, a peculiar syndrome started to develop with hepatitis, progressing to cachexia (or wasting), nitrogenemia and a very severe metabolic acidosis by the 100th day (pH 7.3, base excess (BE) basis deficit 13). Finally, on the 113th day, death due to hypoxaemia occurred against a background of mixed lung damage consisting of infection and pneumonitis.

On the 89th day after irradiation, he developed a wasting syndrome referred to above. In this observation, a syndrome very similar to MOF developed after the 70th day. Its genesis appears to be complex; it is a result of severe BMS and infection, and most probably, relatively

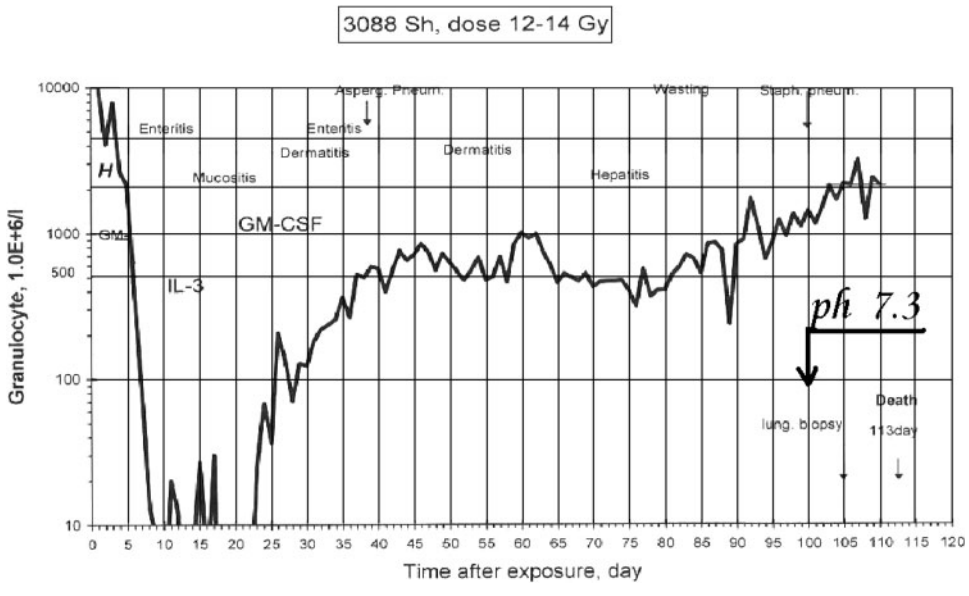


**Figure 1.** Clinical picture of patient Sh. (Nesvizh, 1991): total $\gamma$-irradiation 15 Gy.

late manifestations of radiation injury of internal organs from high dose irradiation.

## Conclusions

Based on the information considered, we can derive the following conclusions.

1. MOF is one of the main causes of death following high dose total irradiation (10 Gy and more) and severe LRI.
2. We can subdivide MOF into three types: leakage-associated; toxaemic (pure MOF); and secondary late MOF.
3. Management of these three types of MOF may be different and requires further investigation for the improvement of therapy.

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