Scintigraphic and Endoscopic Evaluation of Radiation-induced Acute Gastrointestinal Syndrome in Micro-pig Model

Seung-Sook Lee[1], Kyung-Min Kim[2], Jin Kim[3], Won-Suk Jang[1], Jung-Eun Lee[1], Noori Kim[1], Sun-Joo Lee[1], MiSook Kim[4], Young-Hoon Ji[4], Gi Jeong Cheon[2], Sang Moo Lim[2]
[1]*Laboratory of experimental pathology,* [2]*Laboratory of nuclear medicine research ,* [3]*Department of internal medicine,* [4]*Department of radiation oncology, Korea Institute of Radiological and Medical Sciences, Seoul 139-706, Korea*

1. Introduction

Micro-pig model can be served as a proper substitute for humans in studying acute radiation syndrome following radiation-exposure accidents, especially showing similar clinico-pathologic response of hemato-poietic and gastrointestinal (GI) syndrome to human. Among acute GI syndrome induced by radiation, GI motility disturbance has not been studied, however, it would be important in a viewpoint of affecting infectious progression from GI tract. Here, we employed scintigraphy of GI transit time and sequential endoscopic examination and tissue sampling in micro-pigs followed by abdominal radiation exposure. The specific aims of this study are to evaluate objective evidence of GI motility disturbance by scintigraphic evaluation and to find corresponding clinicoapthologic changes in radiation-induced acute GI syndrome.

2. Methods and Results

We tried both functional and pathological evaluation by motility test and histological analysis. To avoid inter-individual variability, we designed the experiment using internal normal control prior to scintigraphic and endo-scopic evaluation.

2.1 Local abdominal radiation-exposure model

Six PWG micro-pigs (6 month-old, body weight 25kg) were locally irradiated on whole abdomen in supine position with Co^{60} (δ-irradiation, 5Gy, 10Gy, and 15Gy). Local abdominal irradiation was designed to avoid fatal hematopoietic disturbances and to induce significant GI damage employing higher dose ranging from 5Gy to 15Gy which is critical to death by acute GI syndrome.

To avoid motility changes by anesthesia during experiments, we used extremely short-term inhalation anesthesia with seborane. The inhalation anesthesia worked for 2 minutes only during gamma camera working time, then the pigs were promptly recovered with normal motor function.

2.2 Scintigraphic evaluation of GI motility changes using gamma camera

We compared gastric emptying time and small bowel transit time using gamma camera (Scintron, MiE, Germany) with oral intake of ^{99m}Tc sulfur colloid (50mCi) and, twice before (individual control) and sequential changes after irradiation (3, 7, 10, 14, 21, 28, and 35 days after abdominal δ-irradiation of 5Gy, 10Gy, and 15Gy, respectively). Whole gut scintigraphy was performed by obtaining ROI (region of interest) drawn according to portions of stomach, small bowel and colon. In supine position, each anterior and posterior planar images were acquired for 1 or 2 minutes and the mean was used for calculating time-activity curves. Image acquisition was sequentially done during 30 min ~ 36 hours after feeding in each experiment.

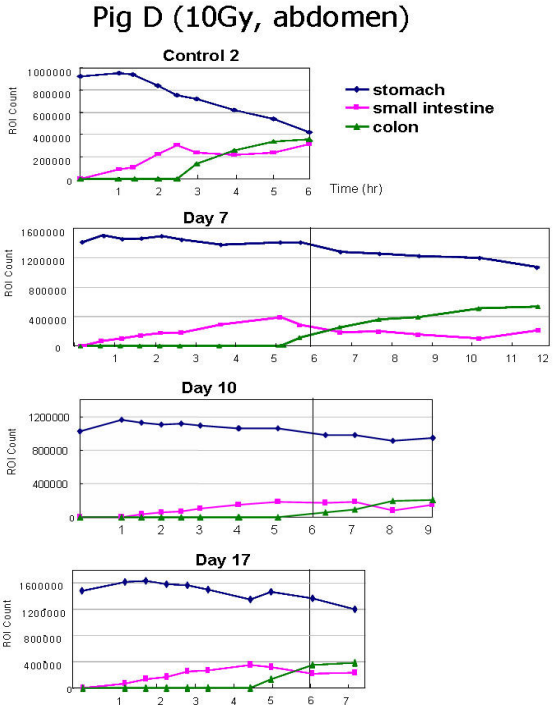

Figure 1. Scintigraphic evaluation in 10Gy-irradiated pig. Gastric emptying and small bowel transit are delayed.

With whole abdominal δ-irradiation (5Gy) in micro-pigs (n=2), small bowel transit time prolonged at day 3 (2.06 and 1.97 times in each), gradually recovered and normalized at day 10 and at day 17, respectively. In 10Gy-irradiated animals (n=2), GI motility prolongation were exaggerated. Gastric emptying time ($T_{1/2}$) prolonged 4.7 times, 4.7 times, 2.4 times, and 1.2 times

compared to preirradiating control, at day 3, 10, 17, and 24, respectively [Figure 1]. In 15Gy-irradiated pigs, gastric emptying time was not measurable due to extreme delay. These results show that gastric emptying is delayed in correlation with exposure amount. This is a novel finding against the concept that stomach may be relatively safer than intestine from radiation damage. And it also suggests the possible role of motility-supporting management for patients with acute radiation syndrome.

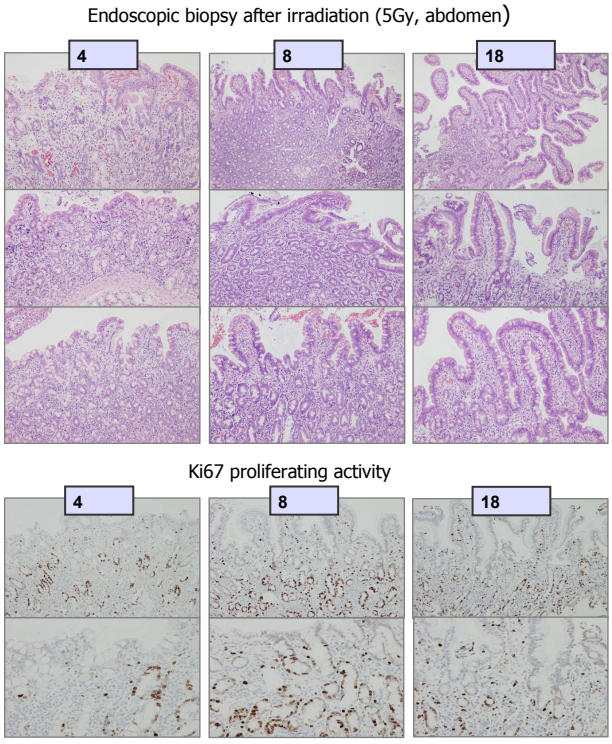

Figure 2. At 4th day after whole abdominal irradiation, shortening of mucosal villi, dilatation of microvessels, and reduced proliferating activity at crypts and mucosal glands. These radiation-induced mucosal changes has recovered with increased proliferating activity at 8th day.

2.3 Sequential clinico-pathological changes via endoscopic evaluation and tissue sampling

We grossly and microscopically evaluated GI mucosal changes via sequential endoscopy, at each day after gamma camera imaging. In 5Gy- and 10Gy-irradiated pigs, there were no grossly identifiable mucosal changes. In 15Gy-irradiated pigs, definite villi atrophy and multifocal erosion in small intestine were grossly noted from day 18. In contrast to minimal changes by endoscopic gross examination, microscopic mucosal changes were evident in earlier period. At 4th day after irradiation in 5Gy-irradiated pigs, we observed shortening of mucosal villi, dilatation of microvessels, reduced proliferating activities (Ki67 labeling index) and marked increase of apoptotic bodies (TUNEL assay) at crypts and mucosal glands. The radiation-induced mucosal changes progressed till day 8 and were recovered till day 22 [Figure 2]. These histologic changes were correlated with irradiating amount. Despite minimal grossly identifiable mucosal changes, severe diarrhea developed leading to death in 15Gy-irradiated pigs. From correlating symptomatic, gross, and microscopic findings, microscopical changes preceded clinical manifestation and grossly identifiable changes, which suggests that treatment should be started prior to symptomatic manifestation.

3. Conclusion

We confirmed GI motility disturbances occurring in victims of high-dose radiation exposure by objective experimental data employing whole gut scintigraphic evaluation. Serial endoscopic and pathologic examination suggest that pathologic changes precede clinical manifestations, which raises the necessity of initial active therapeutic approaches for managing patients with acute GI syndrome. Scintigraphic evaluation of gastric emptying and small bowel transit could be used as a useful biomarker for monitoring treatment effects in acute gastrointestinal syndrome after irradiation. Establishment of reliable biomarkers would allow further comprehensive clinicopathological studies and validation of newly developing therapeutics for acute radiation syndrome.

Acknowledgement

This study was supported by Ministry of Science & Technology (MOST) of the Korean government, through National Nuclear Technology Program (M20513005401-06A1300-40110).

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