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Effects of combined exposure to aluminum chloride and γ-radiation on histological and ultrastructure of intestinal Paneth cells

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ABSTRACT

Purpose: The use of aluminum chloride ($AlCl_3$) as in purification of water and the exposure to ionizing radiation (IR) in therapeutic treatments are believed to be relatively safe. However, their combined effects remain unclear. The aim of the present study is to investigate the effects of concomitant exposure to aluminum chloride and gamma radiation on the histological and ultra-structural pattern of the crypt Paneth cells (PC) of the small intestine in albino rats.

Materials and methods: Forty male albino rats were divided randomly into four groups (n = 10). Group 1: Control group, Group 2: Aluminum treated group (Rats received a daily a dose of 0.5 mg of $AlCl_3$ per kg of body weight/day), Group 3: γ-Radiation group (rats are exposed to a total dose of 8 Gy in 4 fractions of 2 Gy/week) and Group 4 Rats exposed to AlCl3 and exposed to γ-Radiation. Animals were sacrificed after 4 weeks, one day after the last radiation dose.

Results: Histological and ultra-structural studies in small intestine showed that exposure to γ-rays induced alterations in PC including apoptotic nuclei, presence of injury in secretory granules and completely damaged organelles at the sites of bacterial translocation in the crypt of lumens. Aluminum exposure during irradiation potentiate the damage notified by abnormal PC morphology, dilation the crypt's lumen and erosions of its villi with increased apoptosis in the crypt cells and appearance of homogenously electron-lucent granules.

Conclusions: It is concluded that concomitant exposure to aluminum and IR increased detrimental structural changes in PC of rat intestine due to their combined effect. It is thus recommended to limit the intake of aluminum when human are at risk of over exposure to ionizing radiation.

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1. Introduction

Aluminum is the third most prevalent element in the earth's crust, comprising approximately 8% of the earth's crust, exceeded only by oxygen (47%) and silicon (28%). It does not exist in its pure state but is always combined with other elements such as chloride, hydroxide, silicate, sulphate and phosphate. The wide distribution ensures the potential for causing human exposure and harm (Zhang & Zhou, 2005).

Evidence for contribution of aluminum to Alzheimer's disease (AD) remains contradictory (Flaten, 2001; Gupta et al., 2005). Epidemiological studies have indicated a link between aluminum in drinking water and AD. A variety learning and memory deficits (Buraimoh, Ojo, Hambolu, & Adebisi, 2011; Yokel, 2000). Aluminum chloride was implicated to have negative effects on anxiety-related behavior of rats as it increased the rate of anxiety, neurodegenerative effects of cerebral cortex of adult rats especially at higher dose, and detrimental effects on the integrity of the testes of rats (Buraimoh et al., 2011, 2012; Narahyana et al., 2014). Human exposure to aluminum occurs primarily through ingestion of food and water, utilization of personal care products and cookware, and consumption of medications and administered vaccines (Saiyed &Yokel, 2005; Seubert, Monaci, Pizza, O'hagan, & Wack, 2008). Experimental studies revealed that exposure of rats to aluminum have deleterious effects on lung tissues (Ojo & Buraimoh, 2013) as well as hippocampus (Çabuş, Oğuz, Tufan, & Adıgüzel, 2015).

Buraimoh and Ojo (2012) conclude that aluminum chloride exposure had negative and deleterious effects on the wall of the small intestine of Wistar rats as eminent in mucosa degeneration, few goblet cells and lymphocytes proliferation observed in the aluminum treated groups. While numerous studies have been conducted on aluminum toxicity, nearly all of them have investigated the effects of exposure to high concentrations. These concentrations are not representative of typical environmental exposure levels and cannot be associated with ordinary circumstances for people with normal renal function. Due to its abundance in nature and in man-made products, cumulative daily uptake of aluminum by humans is difficult to estimate. Study of aluminum is further complicated by the fact that a variety of complexes are formed in solution (Epstein, 1991) and these various forms may have different toxicities and biological effects. The European food and safety authority estimated the mean dietary exposure between 1.6 and 13 mg aluminum per day from food. This range corresponds to a dietary exposure from 0.2 to 1.5 mg/kg body weight/week in a 60 kg adult (EFSA, 2008). Satoh, Ishikawa, Oomori, Takeda, and Ono (1992) reported that bethanechol (2×10 (−4) mol/l) induced Paneth-cell secretion. Many Paneth cells massively exocytosed their secretory material into the crypt lumen; the enhanced secretion caused degranulation and vacuole formation. However, tetrodotoxin (2×10 (−6) mol/l) did not prevent the bethanechol-enhanced secretion by the Paneth cells. NaF (1×10 (−2) mol/l) and AlCl3 (1×10 (−5) mol/l) induced massive exocytosis of the Paneth cells of mouse intestine.

Ionizing radiation generates free radicals from intracellular water, which in turn affect DNA synthesis. Cells with a high proliferation rate tend to be more susceptible to radiation injury. The gastrointestinal tract is radiosensitive. While the small bowel is more radiosensitive than the large bowel, it is injured less frequently because of its mobility within the peritoneal cavity. Ionizing radiation causes several typical changes in tissues in the bowel. These are characterized by inflammation or cell death including mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscess formation and swelling of the endothelial lining of arterioles (Theis, Sripadam, Ramani, & Lal, 2010). These may resolve but can develop into a more chronic change with persistent cytokine activation in the sub mucosa and fibrosis of connective tissue with arteriolar endarteritis (Wong et al., 2010). These changes result in tissue ischemia, leading to mucosal friability and revascularization as well as progressive fibrosis (Theis et al., 2010). This can lead to multiple areas of small bowel dysfunction plus stricture disease.

Roberts, Thomas, Willett, and Grover (2014) mentioned the injury to the intestines can occur following radiation therapy for cancer. It can affect both the large and small intestine, and may lead to a variety of clinical consequences (such as diarrhea, nausea, weight loss, abdominal pain, intestinal obstruction, and perforation) depend upon the extent of the injury. It usually develops six or more months after radiation therapy. This contrasts with the timing of acute radiation enteritis (characterized by diarrhea and abdominal pain), which develops during or shortly after radiation therapy and resolves within two to six weeks after completion of treatment.

Chronic radiation enteritis is due to an obliterate arteritis that leads to intestinal ischemia, which can result in stricture, ulceration, fibrosis, and occasionally fistula formation. The physiologic consequences can include altered intestinal transit, reduced bile acid absorption, increased intestinal permeability, bacterial overgrowth and lactose mal absorption. Clinical manifestations may include nausea, vomiting, lactose intolerance, obstructive symptoms, diarrhea, weight loss, malnutrition, and bleeding (Clevers & Bevins, 2013; Rhodri & John, 2014).

Acute radiation damage may occur within hours to days after radiation. Early radiation injuries result in edematous, thickened and hyperemic mucosa. Superficial ulceration or necrosis may be present. In the small bowel the villi become blunted, and in both the small and large bowel the crypts become shortened. The sub mucosa may show bizarre and enlarged fibroblasts with cytological atypia and is replaced with a hyaline-type substance. Infiltration by leucocytes is seen throughout the full thickness of the bowel wall. Spasm and thrombosis may affect arterioles. Hyaline thickening of the artery wall occurs.

The aim of this study was to evaluate the possible effects of concomitant administration of aluminum and exposure to gamma radiation on the histological and ultra-structure of the intestinal Paneth cells of adult male albino rats.

2. Material and methods

2.1. *Animals*

Male albino rats (120 ± 20 g) were purchased from the Egyptian Holding Company for Biological Products and Vaccines, Cairo,

Egypt. The animals were maintained under standard conditions of light, ventilation, temperature, and humidity and allowed to free access to standard pellet diet and tap water. Animals were acclimatized to laboratory conditions before starting the experiment. All animal procedures were carried out in accordance with the Ethics Committee of the National Research Centre conformed to the "Guide for the care and use of Laboratory Animals" published by the US National Institutes of Health (NIH publication No. 85–23, 1996).

2.2. Gamma irradiation

Rats were whole body gamma irradiated in at 10 ± 1 a.m. Animals received a total dose of 8 Gy (LD50/30) administered in 4 fractions of 2 Gy/week, at a dose rate 0.5 Gy/min to induce damage, the dose was calculated according to the Dosimeter Department in our institute (NCRRT). The radiation source was a Canadian Gamma Cell-40 (137Cs), (Atomic Energy of Canada Ltd, Ottawa, Ontario, Canada), located at the NCRRT, Nasr city, Cairo, Egypt. The Caesium-137 double encapsulated sources maintained by two cylindrical sliding drawers, above and below the sample cavity. A plastic sample tray with lid and supporters for use in the sample cavity is provided with the unit. The internal dimensions of the tray were 30.5 cm in diameter by 10.5 cm deep. The sample tray had ventilation holes in its side, which align with ventilation parts through the main shield and ensured a homogeneous dose distribution. Rats were placed in the plastic tray and irradiated in groups of 10 rats.

2.3. Aluminum chloride treatment

Aluminum chloride ($AlCl_3$) purchased as a powder by Oxford Laboratory Reagent, Mumbai, India was dissolved in distilled water just before administration. Rats received a daily a dose of 0.5 mg of $AlCl_3$ per kg of body weight/day for 28 days, as reported by Osman, Shayoub, Babiker, Osman, and Elhassan (2012). The dose is approximately 4 folds higher than the average daily dose 0.11 mg/kg body weight/day (EFSA, 2008).

2.4. Experimental design

Male albino rats were divided into four groups (n = 10):

1) Control group(C): normal healthy rats received 1 ml of distilled water daily by gavages.
2) $AlCl_3$ group (Al): rats received $AlCl_3$ at a dose of 0.5 mg/kg body weight daily for (28) days by gavages.
3) γ-Radiation group (IR): rats were exposed to whole body gamma irradiation as fractionated dose of 2 Gy/week up to 8 Gy.
4) $AlCl_3$+γ-Radiation group (Al + IR): rats were received the same dose of $AlCl_3$ daily by gavages within the irradiation period.

2.5. Preparation of samples

Rats were sacrificed 1 day post the last dose of irradiation. The intestine was stripped of mesenteric and vascular connections and removed from the peritoneum. The lumen was flushed with ice-cold saline to clear intestinal contents. The segments of ileums were collected sequentially at equivalent sites of each rat.

2.6. Light microscopy

Intestinal specimens were fixed in 10% neutral formalin buffer, and then embedded in paraffin wax. Specimens were dehydrated through graded alcohol, cleared in xylene and embedded in paraffin. Sections of 5 μm-thickness were cut and stained with Heamatoxylin and eosin (H&E) Drury and Wallington (1976) and examined under light microscope.

2.7. Transmission electron microscope

Intestine were dissected out carefully and very small pieces were fixed in 2.5% Glutaraldehyde overnight, post fixed in 1% osmium tetroxide, dehydrated in graduated series of ethanol and embedded in pure epoxy resin. Semi thin sections 1 μm thick were obtained, stained with 1% toluidine blue (Richardson, Jarret, & Finke, 1960) and examined by light microscope. Ultrathin sections (80–90 nm) were stained with uranyl acetate and lead citrate (Gluert & Lewis, 1998). The sections were examined with a JEOL electron microscope (JEM-100 CX) at 80 KV in E.M unit, National Center For Radiation Research and Technology (NCRRT), Atomic Energy Authority (AEA).

3. Results

3.1. Histological results

Histological examinations of sections of intestinal gland (crypts) of the control animals revealed the normal structure of intestinal tissues. These Crypts lie between adjacent villi and are surrounded by the same lamina propria that forms the villus cores (Fig. 1a).

The experimental animals that received aluminum chloride ($AlCl_3$) at a dose of 0.5 mg/kg body weight daily for (28) days have demonstrated variable changes. The crypt hyperplasia and increased numbers of goblet cells were observed (Fig. 1b).

Histological examination of sections in the intestinal tissue of gamma radiated animals (2 Gy/week up to 8 Gy fractionated), revealed certain histological changes appearing degeneration cryptal regions (Fig. 1c).

Animals receiving aluminum chloride along with irradiation revealed apoptosis in the crypt epithelium, and crypt atrophy and hyperplasia lamina propria that forms the villus cores (Fig. 1d).

Histological examinations of toluidine blue stained semithin sections of intestinal gland (crypts) of the control animals have revealed the normal structure of intestinal glands (crypt's, of Lieberkühn) illustrates the cross section through the base of the crypts of the small intestine (Fig. 2a). The experimental animals that received aluminum chloride ($AlCl_3$) at a dose of 0.5 mg/kg body weight daily for (28) days have revealed crypt hyperplasia and hyperplasia lamina propria that forms the villus cores (Fig. 2b and c).

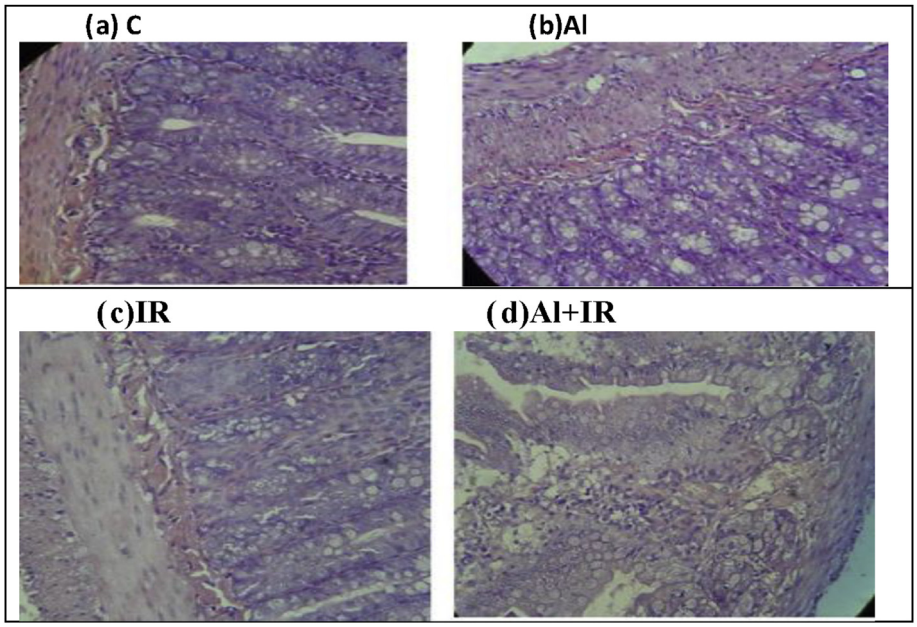

Fig. 1 – Histological sections of the small intestine of rats show the cross section through the base of the crypts of the small intestine.a) Control group. A normal intestinal gland (crypts) is found at the base of the mucosa. These crypts lie between adjacent villi and are surrounded by the same lamina propria that forms the villus cores. b) Aluminum-chloride ($AlCl_3$) treated group, revealed crypt hyperplasia and increased numbers of goblet cells. c) Irradiated-group, showing degeneration of some cryptal cells. d) Aluminum-Irradiated-group shows ongoing apoptosis in the crypt epithelium and the manifestation of crypt atrophy and hyperplasia lamina propria that forms the villus cores (H&E X-400).

Examined the sections of the intestinal tissue of the animals irradiated by gamma radiation at dose 2 Gy/week up to 8 Gy fractionated, showing reduction of the crypt glands and poorly differentiated columnar epithelial cells that lack secretory granules and atrophy villi were observed (Fig. 2d and e). The experimental animals which were treated with the same dose of aluminum chloride followed by irradiation showing ongoing apoptosis in the crypt epithelium and the manifestation of crypt atrophy and hyperplasia lamina propria that forms the villus cores (Fig. 2f and g).

3.2. *Ultrastrucutal results*

In control-group, the fine structure of the Paneth cells are distinguished by the secretory granules are the most prominent feature of the Paneth cells and fill the upper third of the cell. The nucleus is irregular in outline, the nucleolus is a dense sponge-like reticulum and rod-shaped mitochondria are scattered below the nucleus of the cell (Fig. 3).

In aluminum-treated group, we investigated the response of intestinal Paneth cells damage resulting from aluminum Chloride-treatment at a dose of 0.5 mg/kg body weight daily for (28) days, showed prominent changes in the Intestinal epithelial cells. Loss and abnormal Paneth cells morphology were found, dilated in the crypt's lumen and erosions of its villi following a single dose of aluminum were seen (Fig. 4a). In addition, apoptotic Paneth cells and homogenously electron-lucent granules were observed (Fig. 4b). Also, degeneration Paneth cells and abnormal nucleus was seen (Fig. 4c).

In irradiated-group, investigation of the response of Paneth cells damage resulting from irradiation. Abnormal Paneth cells morphology were found following fractionated dose 2 Gy/week up to 8 Gy of gamma radiation and degranulation of Paneth cells also occurred (Fig. 5a). Furthermore, appearance of bacteria in the crypt's lumen was observed after the 24 h post irradiation (Fig. 5b). Moreover, bacterial intrusions into the lysosomes of Paneth cells were observed (Fig. 5c).

In irradiated aluminum-treated group, investigation of the response of Paneth cells damage resulting from double treated of aluminum chloride and irradiated with the same dose in the previous group exhibited, poor ultra-structural detail of the Paneth cells but the granules of its were easily recognizable and always appeared very electron-dense (Fig. 6-a). In addition, data indicated that the epithelial cells were injured with associated expansion of intestinal crypt's lumen, notice the crypt cells of the irradiated-aluminum treated supplemented animals were distinguishable from those of the controls were associated with increased bacterial invasions of intestinal crypt's lumen were observed (Fig. 6-b & c).

4. Discussion

Environmental exposure to aluminum may play an important role in the study of causation of several diseases (Migliore & Coppedè, 2002). Human ingestion of aluminum from food and beverages represents the major source of intake (Becaria et al., 2002). It is estimated that the average dietary intake of aluminum in adults ranges from 2 to 3 mg per day. These

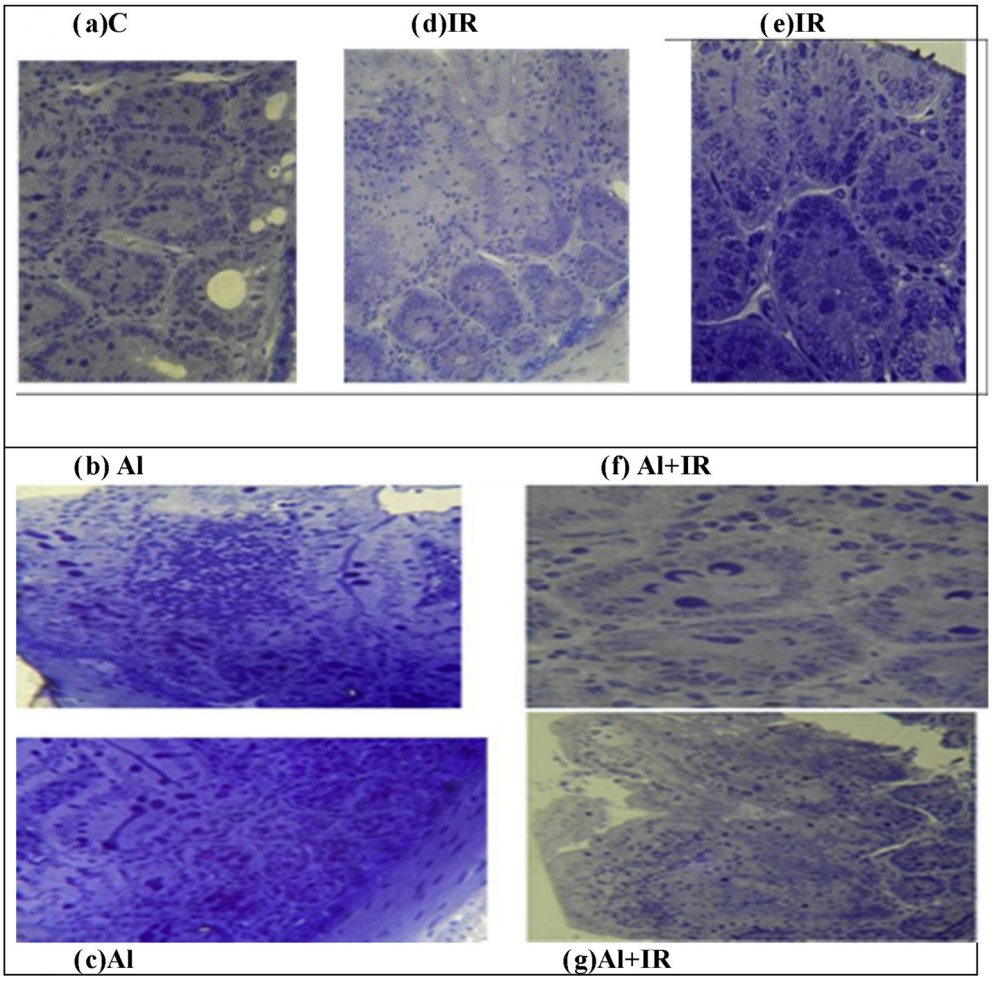

Fig. 2 – A high power view of the intestinal glands (crypt's of Lieberkühn) illustrates the cross section through the base of the crypts of the small intestine.a) Control group. b&c) Aluminum-chloride ($AlCl_3$) treated group, revealed crypt hyperplasia and hyperplasia lamina propria that forms the villus cores. d&e) Irradiated-group, showing reduction of the crypt glands and poorly differentiated columnar epithelial cells that lack secretory granules and atrophy villi was observed. f&g) Aluminum-Irradiated-group showing ongoing apoptosis in the crypt epithelium and the manifestation of crypt atrophy and hyperplasia lamina propria that forms the villus cores (toluidine blue, X-1000).

levels are not considered harmful to people with normal renal function (Klein, 2005). Dietary exposure is higher in young children and teenagers (Klein, 2005). However, these exposures do not include intakes associated with the use of personal care products, over-the-counter medication, inhalation of dust, and vaccines (Platt, Haas, & Busselberg, 1993). Thus, many people with underlying medical conditions are even more vulnerable to aluminum-induced toxicity due to their exposure to higher concentrations of this metal. In other words, total daily aluminum intake by the human body varies broadly and is presumably higher than the levels referenced above (Rogers & Simon, 1999).

In this study we attempted to estimate the effects of aluminum on the intestinal Paneth cells. Our results suggested that abundance of aluminum that would be expected in humans can result in subtle changes of intestinal Paneth cells. While the injury we have observed in acute studies, there may be long-term alterations in intestinal Paneth cells function as a consequence. The intestinal Paneth cells are more sensitive to aluminum toxicity. Our results have distinct different histological changes in intestine rat treated with aluminum. These changes varied from crypt hyperplasia and increased numbers of goblet. Moreover, the ultra-structural changes in intestinal Paneth exhibiting dilated in the crypt's lumen and erosions of its villi. In addition, apoptotic Paneth cells and homogenously electron-lucent granules almost immediately after exposure to aluminum. These results were in agreement with Buraimoh and Ojo (2012) conclude that aluminum chloride exposure had negative and deleterious effects on the histology of small intestine of Wistar rats as eminent in mucosa degeneration. Meanwhile, our study was designed to estimate the effects of double treatment of exposure to whole body gamma irradiation and aluminum supplemented on the intestinal Paneth cells. Most of the radiation effect results in immediate molecular events inside cell. Free radicals, produced from intercellular water interact

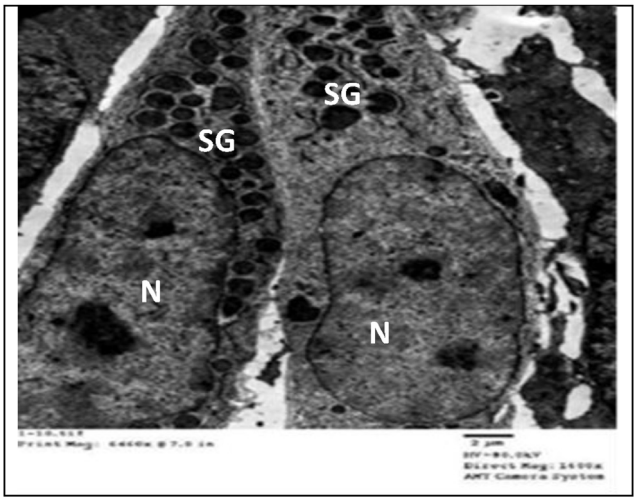

Fig. 3 – C. Electron micrograph of control rats shows two Paneth cells are distinguished by electron-dense secretory granules (SG), irregular nucleus (N), and darker cytoplasm. *Bar* = 2 *μm*.

with DNA to prevent replication, transcription and protein synthesis. Although damage energy dissipated from ionizing radiation generates a series of biochemical some injuries may be repaired by intracellular repair mechanisms, lethal injuries also occur. The relative sensitivity of various cells to ionizing radiation accounts for the wide range in timing of clinical manifestations. Rapidly proliferative cells such as intestinal mucosa are most sensitive to ionizing radiation and are, therefore, at greatest risk for injury. However, accompanying vascular and interstitial connective tissue may undergo radiation damage. The alterations in vascular and interstitial connective tissue are slowly progressive (David & Larson, 1986)

Our results suggest that the exposure of rats to fractionated dose (8 Gy) of gamma radiation has distinct different histological injury, showing reduction of the crypt glands and poorly differentiated columnar epithelial cells and atrophy villi. In consistence with the present findings, Joe et al. (2012) reported that the acute radiation damage may occur within hours to days after radiation. Early radiation injuries result in edematous, thickened and hyperemic mucosa. Superficial ulceration or necrosis may be present. In the small bowel the villi become blunted, and in both the small and large bowel the crypts become shortened. The sub mucosa may show bizarre and enlarged fibroblasts with cytological atypia and is replaced with a hyaline-type substance. In agreement with our results (Czito & Willett, 2010) reported that, Intestinal villi can be damaged by radiation therapy resulting in a reduction or loss of digestive enzymes leading to mal absorption of nutrients.

The small intestine displays numerous morphological and functional alterations after exposure to ionizing radiations appearing as sloughing villi, ruptured goblet cells, and shrinkage of sub mucosa layers (Saada, Rezk, & Eltahawy, 2010).

Ionizing radiation causes several typical changes in tissues in the bowel. These are characterized by inflammation or cell death including mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscess formation and swelling of the endothelial lining of arterioles (Theis et al., 2010; Rhodri & John, 2014).

The severe ultra-structural lesions that resulted in intestinal Paneth cells of rats following irradiation manifested as appearance increased of bacteria in dilated crypt's lumen was observed after the 24 h post irradiation and apoptotic Paneth cells with homogenously electron-lucent granules. In addition, macrophage activation lysosomes were prominent.

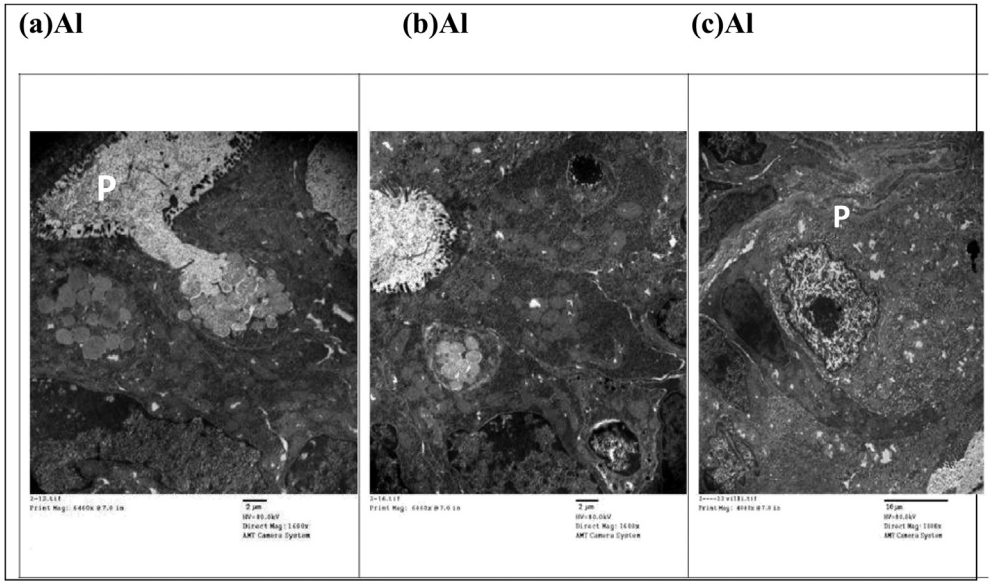

Fig. 4 – Aluminum-treated group (Al). Electron micrograph of Aluminum-chloride ($AlCl_3$)treated rats showing (a) transmission EM of crypt of small intestine showing dilated in the crypt's lumen (L) and erosions of its villi were observed. *Bar* = 2 *μm* (b) Apoptotic Paneth cells (P) and homogenously electron-lucent granules *Bar* = 2 *μm*. (c) Degeneration Paneth cells (P) and abnormal nucleus was seen (N). *Bar* = 10 *μm*.

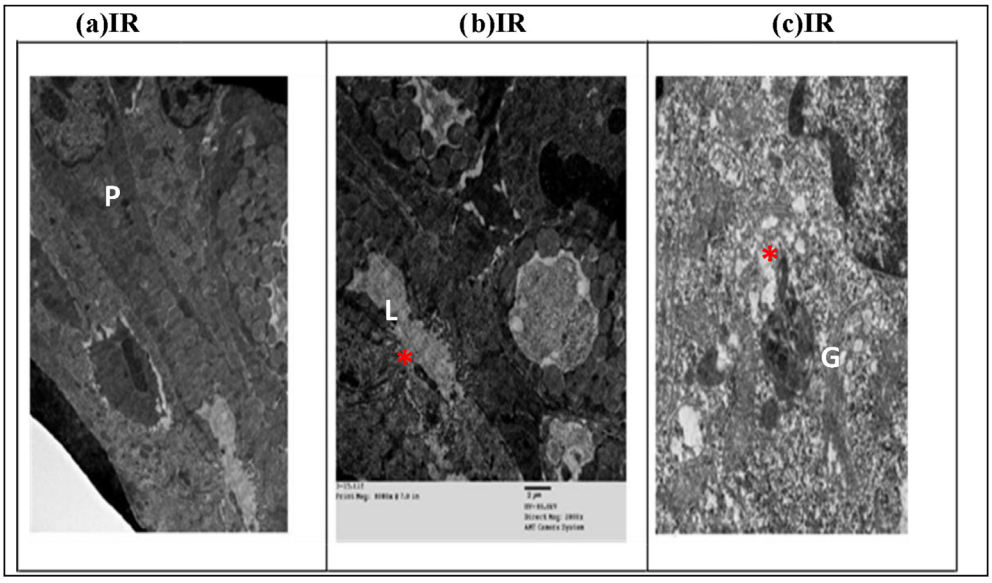

Fig. 5 – Irradiated group (IR). Electron micrograph of irradiated rats showed (a) transmission EM of crypt of small intestine showing apoptotic Paneth cells (P) homogenously electron-lucent granules. *Bar = 2 μm* (b) Bacterial translocation (*) in the crypt's lumen (L). *Bar = 2 μm* (c) Bacterial intrusion (*) into the lysosomes (ly) and prominent supra nuclear Golgi apparatus (G). *Bar = 500 nm.*

Though the mechanism responsible is not clear, the speed of the injury suggests to be related to oxidative stress of ionizing radiation on the plasma membrane. This action increases the permeability of the membrane of Paneth cells but does not result in total loss of membrane integrity over the period of time we have studied.

These results were in agreement with Shadad et al. (2013) who referred to the bacterial overgrowth contributes to radiation injuries to the small and large bowel.

Ionizing radiation kills crypt epithelial stem cells. As a result, crypts involute and epithelial barrier integrity is lost. This provides access of luminal microbes and their products to innate immune cells in the lamina propria, with activation of immune cells. An impaired recognition of bacterial translocation can further exacerbate the inflammatory process and promote stricture formation by two possible mechanisms. The bacterial wall antigens could cause a secondary excessive up regulation of pro-inflammatory transcription factors, such as nuclear

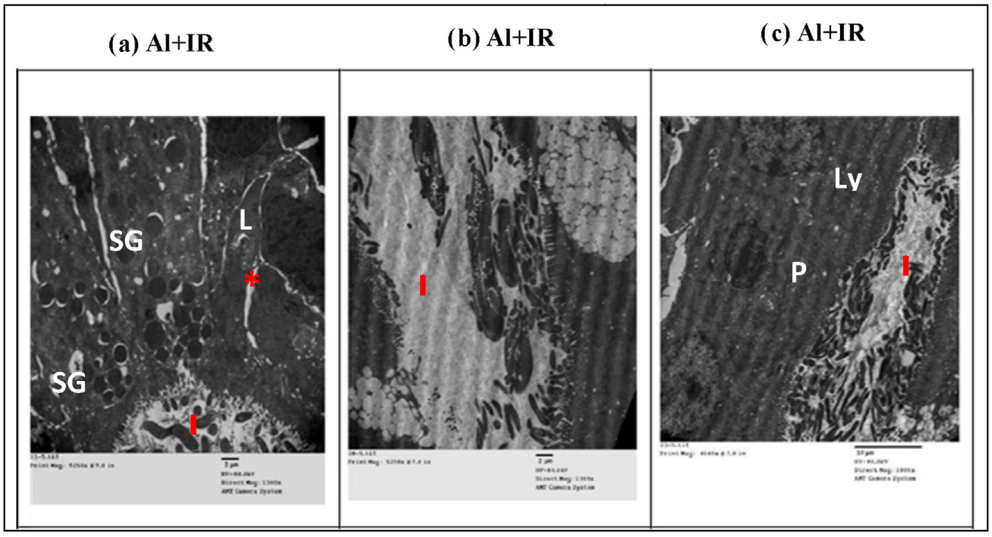

Fig. 6 – Irradiated& Aluminum-treated (Al+IR). Electron micrograph of Aluminum-Irradiated treated rats showed (a) transmission EM of crypt of small intestine exhibited poor ultrastructural detail while the granules of Paneth cells were easily recognizable and appeared very electron-dense granules *Bar = 2 μm* (b) Showing bacterial translocation in the crypts lumen (L). *Bar = 2 μm* (c) Showing dilated in the crypt's lumen (L) and increased bacterial invasions were observed. *Bar = 2 μm.*

factor kappaB Rogler et al. (1998). This might be followed by prolonged macrophage activation and induction of NADPH oxidase expression (Hausmann et al., 2001). Leading to a further increased in oxygen radical secretion to eradicate bacteria leading to further tissue destruction (Rieder, Brenmoehl, Leeb, Schölmerich, & Rogler, 2007). Meanwhile translocated bacteria could directly stimulate neighboring mesenchymal cells via pattern recognition receptors leading to increased activation of immune cells (Rogler et al., 1998, 2001).

Our results are in accordance with previous studies which have demonstrated an elevation in intestinal crypt epithelial cells are quite sensitive to radiation and the killing of these cells leads to mucosal injury (Merritt et al., 1994; Potten, Merritt, Hickman, Hall, & Faranda, 1994). Specifically, when the dose of radiation is sufficient to kill all of the epithelial stem cells in a crypt, then as the epithelial cells migrate up the crypt and are eventually shed into the intestinal lumen; the crypt cannot be repopulated with epithelial cells, and consequently involutes. When this happens to a large proportion of crypts in a region of intestine, normal barrier function is lost which leads to the exposure of the normally sterile lamina propria to luminal microbes. This triggers an acute inflammatory response associated with immune cellular infiltrates. Also Gorbunov, Garrison, and Kiang (2010) suggest that the changes in Paneth cells can contribute to small intestine inflammatory remodeling during the post-irradiation period. Paneth cell secretary activity was observed at the sites of bacterial translocation in the crypt lumens. Aluminum exposure during irradiation potentiate the damage notified by abnormal PC morphology, dilation the crypt's lumen and erosions of its villi with increased apoptosis in the crypt cells and appearance of homogenously electron-lucent granules. According to the results obtained in the current study, it could be concluded that the exposure to ionizing radiation combined to exposure to aluminum aggravate damage of Paneth cells in the ileum of rats. It is thus recommended to limit the intake of aluminum when human are at risk of over exposure to ionizing radiation.

Conflict of interest

The authors report no conflict of interest.

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